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Oral inflammatory process and general health

Part 2: How does the periapical inflammatory process compromise general health?

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Abstract. – At present, the focal infection theory still has very controversial aspects. In spite of the great number of studies, there is no evidence that focal infections or even antigenic mimicry are responsible for anything other than sporadic abscesses/infections and possibly rare autoimmune disorders.

Inflammation of endodontic origin (i.e., apical periodontitis – AP) has not received the same attention as inflammation originating from the periodontium.

Endodontics is a microbiological problem, since the bacterial infection is the "prime mover" of pulp (before) and periapical (later) disease. The aims of endodontic treatment have to be considered from a microbiological viewpoint.

Considering these problems in this second part of their study, the Authors, after close examination of the virulence of microorganisms and of the host defense, analyze the endodontic infection and microbiological species. They emphasize the possibility of a relationship between periapical inflammatory lesions and bacterial endocarditis in preventing metafocal disease.

Bacterial endocarditis deserves special mention because despite involving specialists of two scientific fields, its prophylaxis is almost always assigned to medical practice, and especially, to dentistry. Given the dangers of the disease, antibiotic prophylaxis is both absolutely necessary and can be very effective, and it should be used especially in clinical situations with high risk individuals.

However, the ability of antibiotic therapy to prevent or reduce the frequency, magnitude or duration of bacteremia associated with a dental procedure is controversial.

Studies should also be undertaken to determine to compare the efficacy of endodontic treatment with alternative therapy such as implants, prosthetic replacements or no treatment other than extraction. To date, these studies have not been carried out, and there is no evidence to support the theory that modern endodontic therapy is not safe and effective.

Key Words:

Endodontic, Focal infection, Endocarditis.

Endodontics and Focal Infection

Although an infection produces a variety of local tissue responses, probably aiming to confine and limit the spread of pathogenic stimuli, apical periodontitis may not be an exclusively local phenomenon. Most research groups seeking to investigate the pathologic mechanisms focused on local immune-inflammatory reactions. The consequences of these reactions are on the one hand the confinement of invading microbiota, on the other certain extent of damage to the host's tissues[1].

Recent studies have emphasized the probable relationship between persistent inflammatory disorders of the oral cavity and pathologic conditions in several organs and systems. In this regard, acute and chronic apical periodontitis may have a major role.

Systemic conditions possibly associated with oral infections may include cardiovascular disease, atherosclerosis and thromboembolic events[2], which may all have fatal consequences, especially in the aging population. Various other pathologies such as cerebral abscesses[3], prosthetic joint infections, preterm low-birth weight, adverse pregnancy outcome[4,5], lung diseases, chronic obstructive pulmonary disease[6], diabetes mellitus[7] and osteoporosis[8-10] have all been linked to oral infections, mainly periodontal disease.

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In this regard, however, we must to say that, to date, inflammation of endodontic origin (i.e., apical periodontitis AP) has not received the same attention as inflammation of periodontal origin.

AP may be acute and painful; however, when chronic it is often asymptomatic. Although it may be preventable, or treatable with root canal therapy (RCT), it may still recur or persist after treatment is complete. Despite numerous differences between chronic inflammatory disease of periodontal and endodontic origins there are some notable similarities:

- Both conditions share common microbiota often Gram negative anaerobic bacteria;
- Elevated cytokine levels may be released systemically from acute and chronic forms of both disease processes (e.g., increased concentrations of inflammatory mediators have been detected both in the gingival crevicular fluid of subjects with periodontal disease and in the periapical tissues of endodontically involved teeth)[11].

If current investigations regarding the relationship between chronic periodontal inflammation and adverse general health outcomes ultimately suggest positive (or causal) associations, a similar attempt to link apical inflammatory lesions with general health outcomes may occur in the near future. At present, compared to the multitude of published research efforts involving cytokines and inflammatory mediators in periodontal disease[12-16], the study of these molecular markers in endodontic disease has not been as extensively documented.

Consequently, patients and practitioners currently lack important knowledge regarding the risks implied in maintaining teeth with chronic, asymptomatic apical periodontitis[17].

Root Canal Microbiology

"Endodontic treatment is basically the necessary solution to resolve or to prevent a bacterial problem"[18].

Therefore, endodontics is a question of microbiology, since the bacterial infection is the primary cause of pulp (earlier) and periapical (later) disease. Endodontic treatment has to be considered from a microbiological viewpoint[19-21].

After Miller[22] showed the presence of microorganisms within the root canal, various studies, including that of Henrici and Hartzell[23], characterized the different species of microorganisms within the endodontic system.

Microorganisms are capable of penetrating and infecting root canals from the oral environment. Robinson and Boling[24] demonstrated that systemic bacteria were able to enter inflamed dental pulps. This process is called anachoresis.

MacDonald et al[25] identified the presence of bacteria in the canals of non-vital, intact, traumatized teeth and suggested that bacteria were capable of entering the root canal system of these non-vital teeth via the individual's general circulation or the lymphatics and blood vessels of the periodontium.

Many researchers also emphasized the importance of improving anaerobic cultivation techniques to grow all the microorganisms inside the root canal[26]. A famous experiment by Kakehashi et al[27] revealed that exposed pulps in gnotobiotic rats did not develop periradicular lesions while pulp exposures in ordinary rats led to pulpal necrosis caused by oral microorganisms invading the pulp tissue. A decisive development of cultivation techniques occurred around the early 1970s when methods of growing anaerobic microorganisms present in the radicular canal were developed[28]. It has since become possible to cultivate anaerobes on specific media and identify the species[29,30]. Furthermore, the process of sampling the canalar microflora has been improved[31,32]. As these investigations have demonstrated, a predominance of anaerobic microorganisms exists in the root canal system[33] and that the ecology of the root canal flora is very diverse, containing complex bacterial interrelationships. An abundance of different bacterial species has been isolated within the root canal, (more than 100 different bacterial species) at a high concentration[34-37]. Since the mid-1980s, the Polymerase Chain Reaction (PCR), developed by Mullis et al, Mullis and Faloona[38,39], has been used and can isolate new microorganisms that are difficult or impossible to cultivate.

The systematical use of a rubber dam provided an aseptic technique used to perform the root canal treatment[40] and microbiological sampling[41].

Microorganism Virulence

Microorganism virulence is influenced by physical and biochemical factors (such as density, pH, temperature and oxygen availability), and periapical inflammatory processes may all be determined by micro-organisms inside the endodontic space. They usually have a low virulence, influenced by several factors:

1. Microorganism interaction: since a polimicrobial flora supports endodontic infection (42,43), a positive or negative interaction between different microbial species is really important. Several studies[44-46] show micro-organisms, alone or associated with different species and in different concentrations, inoculated inside endodontic space, cause extremely variable periapical inflammations.
2. Staying power against host defense.
3. Lipopolysaccharides (LPS) and other microbial products: the LPS (or endotoxins) are released during replication, growth and cellular death and are an important elements of Gram negative cellular walls. They interact with endothelial cells and activate macrophages that produce molecular mediators (TNF-α, several interleukins etc.). The LPS were found in many samples collected from the root canal[47] and also from teeth with endodontic periapical inflammations[48]. In addiction to the LPS, microorganisms produce different products (such as proteins, carbohydrates and lipids) determining cytokine formation and periapical damage[49,50].
4. Enzymes synthesis; microorganisms involved in endodontic infections produce enzymes (collagenases, ialuronidases, proteases etc.) damaging the host and his defensive molecules[51,52].

Infected root pulp causes the persistent microbiological irritation of periradicular tissue by either direct microbial action through their products such as enzymes, toxins, etc. (metabolites) or indirectly. Host reactions such as macrophages activations happen and are followed by a strong production of cytokine and prostaglandins able to activate osteoclasts and to reabsorb bone. Therefore endodontic apical parodontitis is more than just a mere consequence of pulp disease. It is a natural evolution. Pulpal pathogen moves towards an anatomic space. In fact, the pulp chamber can't expand and it has a terminal vascularization.

Host Defense

Normally, host defenses don't allow microorganisms of the canal system to reach the periapex[53]. They include:

Cellular Elements: mainly polymorphonuclear leukocytes (PMN), lymphocytes, plasmacells monocyte/macrophages and osteoclasts. PMN have an important role during inflammatory process, especially in the advance of periodontitis. In fact, several enzymes inside their intracellular granules destroy the host structural compounds[54,55]. Lymphocytes are very important in chronic apical periodontitis. It is impossible to understand the great defensive effort of immune system (IS) without mentioning the substantial deployment of lymphatic tissue in both the oral and extraoral environment: it is the great protagonist of the immuno-defensive system. The extraoral lymphoid organs include several lymph such as submental, submandibular and deep cervical, while the intraoral lymphoid organs include the palatine tonsils, lingual and pharyngeal (adenoids) and non-encapsulated clusters of lymphatic tissue, that are found in the context of gingival tissue, salivary glands, the mucosa and submucosa and oro-pharyngeal that form that barrier, also called lymphatic ring of Waldeyer. Finally, as regards the lymphatic tissue of the oral mucosa, we mention those cell clusters that are present above the basement membrane, called Langerhans cells. Their function is to engulf microbial antigens that penetrate the epithelial layer, and then to migrate to the local lymph where the activation of T lymphocytes in the paracortical area initiates a cell-mediated immune reaction. In the case of an increased virulence and aggressiveness of the germs of the oral cavity, the SI sends a large amount of locally PMN and macrophages. This stimulates B cells to produce antibodies against microbial antigens (*humoral immunity*). Simultaneously immuno- reactive mechanisms mediated by T lymphocytes are activated, and are capable of producing a large number of soluble factors, called cytokines (*cellular immunity*), such as IL-1, TNF-α and interferon, that have an important role in periapical inflammation. The plasma cells are important in chronic asymptomatic lesions. In periapical inflammations, macrophages are activated by bacterial LPS or by other mediators and produce cytokines such as IL-1, TNF-α and interferon. Finally, the osteoclasts activated by macrophages mediators provoke reabsorption and periapical bone and tooth mineralize tissue destruction.

Molecular Mediators: in the advance of apical periodontitis, cytokines are primary. Several studies[56-58] show the role and the presence of IL-1β e TNF-α during tooth periapical inflammation, as well as prostaglandins (PG) stimulating osteoclasts[59] and leucotriens (LT)[60,61]. However, some microorganisms may invade and survive inside inflammatory periradicular tissue such as those that belong to the *Actinomyces* and *Propionibacterium propionicum species*[62]. These species may provoke extraradicular infections commonly associated with an overstrumentation of root canal. This phenomenon leads to periapex diffusion of necrotic pulp and microorganisms[63-65].

Endodontic Infection and Microbiological Species

Studies suggest that more than 700 species of bacteria, including aerobic and anaerobic Gram positive and Gram negative microorganisms, may be identified in the human mouth, particularly on the teeth and in the gingival crevices[66,67].

Approximately 30 percent of the flora of the gingival crevice is *streptococci*, predominantly of the *viridans* group. Among 100 oral bacterial species recovered from blood cultures after dental procedures, the most viridans group are streptococci, they are the most common microbiological cause of community-acquired native valve infective endocarditis (IE) in non intravenous drug users[68]. Endodontic infections can be classified by the anatomic location (intra- or extra radicular), and by the time when the microorganisms colonize root canal spaces (primary, secondary and persistent)[19].

In the past, causes of these infections were studied using cultures, limiting the knowledge about microbiological population of endodontic infection. Several molecular techniques, such as Polymerase Chain Reaction (PCR), due to their specificity and sensibility, can isolate new microorganisms that are either difficult or impossible to grow. In that way, more data about etiopathogenesis of endodontic disease[38,39,43,62,69,70] have been obtained.

Intraradicular Primary Infections

Microorganisms involve in a primary endodontic infection are basically endodontic bacteria and consist mostly of a Gram negative *Fusobacterium, Porphyromonas, Prevotella* and *Campylobacter species*, but also of Gram positive, *Peptostreptococcus, Eubacterium* and *Pseudoramibacter* and facultative and *microaerophic Streptococcus* as well[42,71-73].

Several studies[74-77] using PCR, evaluated the correlation between bacteria and specific clinical signs in many endodontic infections. Their conclusions is that many bacterial species are responsible for both symptomatic and asymptomatic periapical lesions. This fact is justified by the existence of clones of the same microbiological species with different virulence[78]. Moreover, the virulence is influenced by the interaction between species responsible for endodontic infections, by the number of microorganisms important for beginning and supporting pathology, by environmental features (pH, temperature), and obviously by host susceptibility[79-82].

The endodontic infections are subdivided into: primary infections, which may show clinically asymptomatic or symptomatic periapical lesions (acute apical periodontitis or acute periradicular abscess), and persistent infections.

Asymptomatic Periapical Lesions

Several studies, using molecular techniques[62,74,83-93], show microorganisms are present in all samples, proving the infective etiology of pathology. The principal ones are: *Pseudoramibacter alactolyticus, Porphyromonas endodontalis, Treponema denticola, Dialister pneumosintes, Filifactor alocis, Tannerella forsythia* and *Treponema socranskii* species.

Fungi, principally *Candida albicans*, have been found only in a low percentage of endodontic primary infection cases.

Symptomatic Periapical Lesions

Acute apical periodontitis: the microbiological population is composed principally of: *Treponema denticola* (75%), *Peseudoramibacter alactolyticus* (60%), *Tannerella forsythia* (58%), *Porphiromonas gingivalis* (50%), *Porphyromonas endodontalis* (50%), *Propionibacterium propionicum* (50%), *Treponema maltophilum* (50%) and *Treponema socranskii* (42%). In this kind of endodontic infections, fungi are not present.

Acute apical abscess: microorganisms discovered in purulent exudates are: *Treponema denticola* (77%), *Porphyromonas endodontalis* (68%), *Dialister pneumosintes* (64%), *Tannerella for-*

sythia (64%), *Porphyromonas gingivalis* (59%), *Filifactor alocis* (42%), *Fusobacterium nucleatum* (41%), *Propionibacterium propionicum* (37%) and *Streptococcus* spp. (36%) (VGS, *viridans group streptococcus*). In this kind of endodontic infections, fungi are not present.

For VGS, classic purulence-producing microorganisms have been isolated from infections in virtually every body organ and many disease processes: pneumonia, pleural empyema, mediastinitis, pericarditis, endocarditis, septic thrombophlebitis, conjunctivitis, otitis media, meningitis, osteomyelitis, cellulitis, sinusitis, brain abscess, prosthetic joint infections, cholangitis and liver, lung and splenic abscesses[92]. These infections are similar to those that would occur in the oral cavity with the same microorganisms. VGS are classic purulence-producing microorganisms. Such infections are not unexpected as VGS are ubiquitous in the body (skin, conjunctiva, oral cavity, pharynx, gastrointestinal and genitourinary tracts), and possess adhesions that allow attachment to virtually any body surface, and are classically opportunistic bacteria that initiate infections only when host tissues are damaged, altered or diseased.

It is apparent from well-performed studies on the incidence and prevalence of metastatic infections with oral microorganisms that such bacteria are rarely a cause of systemic disease[93-96].

Pathogens that are present in the oral pulp diseases are *Dialister pneumosintes* and *Eubacterium*[97] and *Prevotella endodontalis*[87]. The importance of these pathogens in pulp infections, periapical and periodontal, or pericoronitis in periimplantitis infectious and their spread to nearby areas (orbital, submandibular, mediastinal) is mainly quantitative rather than qualitative.

Intraradicular Persistent Infection

It is important to stress that the microbial flora of already treated teeth, but with persistent periapical lesions, is markedly different from that of untreated teeth with necrotic pulp. While in untreated channels polymicrobial flora with a predominance of anaerobes is present and the ratio between Gram positive and Gram negative is approximately equal, in treated channels the microbial flora is characterized by a monoinfection, primarily by Gram positive species with an almost equal ratio of anaerobes and aerobic forms.

Microorganisms were found more frequently as clusters located in the small canals of the delta apex accessories or spaces between the filling and the canal wall. The organism most commonly associated with persistent endodontic infections is *Enterococcus faecalis*[21], facultative anaerobic Gram positive, which has the capacity to survive in an environment low in nutrients, like that of an endodontically treated tooth penetrating too deep into dentinal tubules. It is protected by chemo-mechanical preparation of the canal. This bacterium also survives in alkaline environments and resists the calcium hydroxide material commonly used as an intermediate medication in root canal treatment[98], but it is sensitive to iodoform and iodine derivatives[99,100].

Several studies[76,77,101] have evaluated its role in primary endodontic infections, demonstrating that it is more often related to those in the asymptomatic cases than in symptomatic cases. In one study, Siqueira Jr and Rocas[90] confirmed the prevalence of *Enterococcus faecalis* (77%) in persistent infections, and also showed the important role of another four species of anaerobes: *Pseudoramibacter alactolyticus* (52%), *Propionibacterium propionicum* (52%), *Dialister pneumosintes* (48%) and *Filifactor alocis* (48%). Fungi were also detected in persistent infections much more frequently than in primary infections (mostly asymptomatic). Among these microorganisms the presence of *Candida albicans*[102] has been found.

This fungus is able to use the opportunities created by the removal of other microbes and has the ability to grow in an environment poor in nutrients, such as the channels already covered. It also features the ability to invade dentinal tubules and is thus protected from the effects of procedures for cleaning and medications used in endodontics. The *Candida albicans* is more resistant than the *Enterococcus faecalis* to the action of sodium hypochlorite and chlorhexidine in the presence of the smear layer[103]. It manages to survive in an alkaline environment, so it is not susceptible to the effects of calcium hydroxide which, provides Ca^{++} ions needed for its growth[104,105]. It has a high susceptibility to the action of EDTA, however, which reduces the adhesive properties, metabolism and pathogenicity[105]. Finally, several studies[106-109] conducted on the correlation between *Cytomegalovirus* (HCMV), *Epstein-BarrVirus* (EBV), *Herpes Simplex* Virus (HSV) and periapical lesions of endodontic nature have shown that HCMV and HBV have an active role in determining, along with several bacterial species, a symptomatic periapical lesion.

Periapical Inflammatory Lesions and Systemic Diseases

Local Infections

A localized infection of alveolar bone or maxillary sinus may follow endodontic procedures. The reactivation of a periapical lesion or inoculation of bacteria by instruments into a previously uninfected site[110,111] may occur. These are thought to be one of the causes of root canal treatment failure and need to be managed surgically. In rare instances, the spread of infection of endodontic origin may cause inflammation of bone, i.e. osteomyelitis.

In this event, acute inflammatory processes and/or chronic inflammation of the maxillary sinus as a result of endodontic periapical lesions of upper premolars and molars, or because of an overextension shutter canal are frequently encountered.

Systemic Infection

Septicemic infections following endodontic therapies are rare, presumably due to effective host defenses, although a case of tetanus has been reported[112].

Infections of Articular Prostheses

There are some case reports on the infection of articular prostheses following an endodontic therapy. A retrospective review[113] of 3490 patient records treated with total knee arthroplasty between 1982 and 1993 showed 62 total knee arthroplasties with late infections (greater than 6 months after their procedure), of which seven were associated strongly with a dental procedure temporally and bacteriologically.

Curry and Phillips[114] recommended that according to current evidence, routine antibiotic prophylaxis should not be offered to all patients with artificial joints undergoing dental treatment.

In any case, serious consideration of antibiotic prophylaxis for all bacteremia-producing procedures, and prompt diagnosis and early treatment of all bacterial infections is essential.

Atherosclerosis and Cardiovascular Diseases (CVD) – Bacterial Endocarditis

The most disturbing association linked oral inflammatory processes with atherogenesis and atherothrombosis[2,115].

Investigating an association between acute cerebrovascular ischemia and chronic and recurrent infection, a research group from the University of Heidelberg has suggested that periapical lesions were more severe in the patient group than in the control group[116].

Beck et al.[117] have published an excellent review of the literature, considering the results of properly executed case-control and prospective studies that included thousands of individuals over many years and were conducted by different investigators from Europe and America. They concluded that there is an elevated risk of atherosclerosis and related cardiovascular diseases associated with oral inflammations.

A researcher from the Tokyo Dental College observed an association between immune responses to Heat shock proteins (Hsp) produced by oral bacteria, chronic marginal and periapical periodontitis, CMV infection, dental metal allergy, and their combinations[118]. This pathology a leading cause of human morbidity and mortality according to World Health Organization statistics[119].

Most recent studies of cases of infectious endocarditis secondary to dental therapy concerns exodontia maneuvers[120] and periodontal diseases[121], and devote little attention to potential links between inflammation of endodontic origin and cardiovascular disease. Moreover there is abundant evidence of the infective basis of pulpal and periradicular disease[122], and surgery or non-surgical endodontics in at-risk patients clearly predisposes them to bacterial endocarditis[123].

Moreover, the literature dealing with patients with root canal infections and apical periodontitis as only oral inflammatory lesions is extremely sparse.

We highlight two classic studies on the relationship of endodontic disease to systemic disease. In the first, Barnes and Langeland[124], the administration of antigen through the root canal of primates and rabbits caused both a local and systemic immunological response. In the second[12], the antigenic stimulation within the root canal determined a strong immune response, stimulating the production of circulating antibodies.

Marton et al[126] investigated 36 healthy young adults with apical periodontitis resulting in periapical radiolucencies of at least 3 mm in diameter. In this study, serum and whole blood immune and inflammatory parameters on referral and following root canal treatment and apicectomy were assessed. They measured the serum concentration of two strong acute phase proteins, CRP and α_2-macroglobulin (AMG), two moderate acute phase proteins, α_1-antitripsin (AAT) and hapto-

globin (HPT) and 2-week acute phase proteins, complement component C3 and ceruloplasmin (CER). The levels of AMG and AAT fell significantly as early as 7 days after treatment. All investigated acute phase proteins decreased significantly 3 months after treatment. Pretreatment CRP level (mean±SD: 6.6±4.2 mg/L) was comparable with elevated CRP levels found in patients with periodontal disease and it was high enough to consider it as a cardiovascular risk factor. The same Authors[127] found an elevated whole blood chemiluminescence, which decreased significantly in parallel with the treatment, indicating an activated metabolic and functional state of the peripheral blood neutrophil granulocytes. On the contrary, no significant changes were noticed with respect of serum immunoglobulin concentrations and complement activity, and peripheral blood lymphocyte subpopulations. Lim et al[128] found in human dental pulp and periapical lesions the production of local IL-1, -6 and GM-CSF production, as a cytokine source capable for inducing an acute phase reaction and systemic granulocyte activation.

It is not unreasonable to expect connections similar to those reported in the periodontal literature, given the predominance of Gram negative anaerobes associated with endodontic infections and the evidence of cytokine production in inflamed pulp and periapical granulomatous tissues.

A Scandinavian study[129], on the other hand, reported no statistically significant relationship between the number of apical periodontitis lesions and the presence of coronary heart disease in middle aged to elderly women.

On the basis of these studies, it is reasonable to expect similar links to those reported in the periodontal literature, given the predominance of anaerobic gram related endodontic infections and evidence of cytokine production in inflamed pulp tissue and periapical granuloma.

The eventual postulated biologic mechanism rests on the notion of an underlying hyperinflammatory response trait in the host that places the individual at risk for developing both periodontal disease and atherosclerosis. In the hypothesized chain of events, susceptible individuals produce a hyperinflammatory response to periodontal bacteria and their associated endotoxins. Once periodontal disease is established, bacterial endotoxins induce the host to overproduce cytokines such as interleukin (IL)-1β and tumor necrosis factor-α, which then are released systemically[56,57]. Production of the cytokine IL-6, among others, can lead to hepatic generation of acute phase reactants such as C-reactive protein, which has been linked to atherogenesis and thromboembolic events[130,131]. In conclusion, the hyperinflammatory response can lead to both more serious periodontal disease and greater risk for cardiovascular diseases.

Conclusions however, should be carefully considered since these studies did not employ uniform baselines. Most of these studies included more males than females. Different age groups were studied, and a large variety of indexes were used to characterize the oral state of health.

Focal Odontogenous Disease and its Prevention

In the case of focal disease odontogenous there is a "primary" and a "secondary" prevention strategy. The primary strategy is the early detection of dental foci of most dangerous diseases before they develop, followed by their elimination. The secondary strategy is to implement a timely therapeutic approach to the already developed disease metafocal incorporating a thorough cleaning of the oral cavity, in order to reduce the severity and duration of the disease. It is clear from the foregoing, that the bacteremia of dental origin play an important role in the possible genesis of a disease metafocal, and that their frequency is higher in the traumatic procedures and those which entail blood loss (extraction, mechanical and surgical periodontal therapy) than in less invasive treatments (sessions of endodontic treatment and prophylaxis)[132,133]. It is clear that bacteremia can be particularly dangerous for at risk patients (immuno-suppressed patients, such as the elderly, diabetics, subjects treated with corticosteroids or other immunosuppressive drugs, or holders of defects or prosthetic valves) for whom antibiotic prophylaxis is recommended[2].

Prevention Pulpo-Periapical Diseases

The importance of proper oral hygiene is obvious, as is the screening of all caries outbreaks and their timely treatment conducted with accuracy and precision. In the event of an established irreversible pulpal pathology or pulp necrosis with or without periapical disease (granulomas or radicular cysts), it should be stressed that a correct endodontic therapy will in most cases return

the so called "focal" teeth to complete and permanent cure, even though they previously would have been irretrievably lost.

Antibiotic prophylaxis in endodontic treatment of pulp-periapical diseases is normally not recommended[134,135], except for at risk patients, since in these cases the random leakage of material from top septic after an improper means channels can determine infectious complications[2].

Prevention of Periodontal Diseases

The prevention of these diseases is based on periodic cycles of oral hygiene training, and also on the control of home plate. In addition to traditional home care oral hygiene practices, the use of many antiseptic substances is also recommended for controlling bacterial plaque. Chlorhexidine, is considered the most effective agent in reducing the bacterial component in the oral cavity, especially in the presence of gingival inflammation or periodontal[136]. It can be used at various concentrations (0.12 or 0.20%). In the event that there is a pathological process, differentiate between chronic gingivitis and periodontitis. Gingivitis has little importance for the focal disease, and is only treated with oral hygiene and antiseptic substances. Periodontitis, however, is the most common foci of oral infection and dangerous. If mild (loss of attachment of 4-5 mm) it is treated only with scaling and root planning. If it is more severe, or there are deep pockets over 5 mm, in addition to the complete removal of tartar and tand careful polishing, a surgical approach should be considered[137].

Not all periodontal diseases require systemic prophylactic antibiotic therapy. More specifically, endogenous infections are caused by microorganisms that are part of the normal oral bacterial flora that are usually harmless, whereas exogenous infections are caused by germs coming from outside the oral cavity and are generally occur in individuals who are ill. They are almost always forms of prepubertal periodontitis, localized juvenile periodontitis, refractory adult periodontitis, or rapidly progressive periodontitis. In all of these, particular components of the bacterial disease are mainly represented by germs of exogenous origin, such as *Actinobacillus actinomycetem-comitans* and *Porphyromonas gingivalis*[138]. The use of systemic antibiotics, will be necessary eliminate or suppress these infections[139-141].

For details of these therapies refer to specialized texts, and here we simply point out that, at present, the most common antibiotics used in periodontal disease are: tetracycline, amoxicillin, metronidazole, clindamycin and ciprofloxacin[138,140,142-145]. It should also be borne in mind that the antibiotic therapy in periodontitis should not be considered an alternative to local treatment. Local treatment such as curettage and root planning should always be carried out before, because otherwise the use of antibiotics will be ineffective and will not be able to influence the healing process.

Recently, a genetic test, known as PST, a genetic Periodontal Susceptibility Test (PST), has become available to detect individuals with a genetic predisposition. It can detect a specific marker for identifying those at high risk of developing severe forms of periodontitis[146,147].

Prevention Endocarditis

In preventing metafocal disease, bacterial endocarditis deserves special mention because its prophylaxis is almost always assigned to medical practice and, especially, to dentists.

The development of infective endocarditis (IE) is the net result of the complex interaction between the bloodstream pathogen with matrix molecules and platelets at sites of endocardial cell damage. In addition, many of the clinical manifestations of IE emanate from the host's immune response to the infecting microorganism. The following sequence of events is thought to result in IE: formation of nonbacterial thrombotic endocarditis (NBTE) on the surface of a cardiac valve or elsewhere that endothelial damage occurs, bacteremia, adherence of the bacteria in the bloodstream to NBTE and proliferation of bacteria within a vegetation.

As we have seen, the dental maneuvers are commonly considered the most frequent cause of IE processes in subjects at risk[132], among which the most predisposed to the disease are those with congenital heart defects, and especially patients with valvular heart disease of rheumatic origin .. This phenomenon, as we know, is linked to high incidence of bacteremia, which may develop during the treatment of dental inflammation and periodontal diseases and especially during the surgery[133].

Given the dangers of the disease, its antibiotic prophylaxis in certain clinical conditions and especially in those at high risk is very effective[2,148,149].

However, the ability of antibiotic therapy to prevent or reduce the frequency, magnitude or duration of bacteremia associated with a dental procedure is controversial[150,151]. Some studies reported that antibiotics administered before a dental procedure reduced the frequency, nature or duration of bacteremia[152-154], while others did not[155].

Finally, results are contradictory regarding the efficacy of the use of topical antiseptics in reducing the frequency of bacteremia associated with dental procedures, but the preponderance of evidence suggests that there is no clear benefit[156,157].

Topical antiseptic rinses do not penetrate beyond 3 mm into the periodontal pocket and, therefore, do not reach areas of ulcerated tissue where bacteria most often gain entrance to the circulation. On the basis of these data, it is unlikely that topical antiseptics are effective to significantly reduce the frequency, magnitude and duration of bacteremia associated with a dental procedure.

Many Authors concluded that dental treatment was not a risk factor for IE even in patients with valvular heart disease and that few cases of IE could be prevented with prophylaxis[158-163].

The British Society for Antimicrobial Chemotherapy issued new IE prophylaxis recommendations[164]. This group now recommends prophylaxis before dental procedures only for patients who have a history of previous IE or who have had cardiac valve replacement or surgically constructed pulmonary shunts or conduits. Then the American Dental Association (ADA) Document on Infective endocarditis[165] recommends antibiotic prophylaxis for patients with conditions with underlying cardiac conditions associated with the highest risk of adverse outcome from IE, who undergo any dental procedure that involves the gingival tissues or periapical region of a tooth and for those procedures that perforate the oral mucosa.

This includes procedures such as biopsies, suture removal and placement of orthodontic bands, but does not include routine anesthetic injections through non-infected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, placement of orthodontic brackets or adjustment of orthodontic appliances.

Finally, there are other events that are not dental procedures and for which prophylaxis is not recommended, such as shedding of primary teeth and trauma to the lips and oral mucosa. In this limited patient population, prophylactic antimicrobial therapy should be directed against viridans group streptococci.

Amoxicillin is the preferred choice for oral therapy because it is well-absorbed in the GI tract and provides high and sustained serum concentrations. For patients who are allergic to penicillins or amoxicillin, the use of cephalexin or another first-generation oral cephalosporin, clindamycin, azithromycin or clarithromycin is recommended.

Because of possible cross-reactions, a cephalosporin should not be administered to patients with a history of anaphylaxis, angioedema or urticaria after treatment with any form of penicillin, including ampicillin or amoxicillin. Patients who are unable to tolerate an oral antibiotic may be treated with ampicillin, ceftriaxone or cefazolin administered intramuscularly or intravenously.

For patients who are allergic to ampicillin and are unable to tolerate an oral agent, therapy is recommended with parenteral cefazolin, ceftriaxone or clindamycin.

If a patient is already receiving chronic antibiotic therapy with an antibiotic that is also recommended for IE prophylaxis for a dental procedure, it is prudent to select an antibiotic from a different class rather than to increase the dosage of the current antibiotic.

Intramuscular injections for IE prophylaxis should be avoided in patients who are receiving anticoagulant therapy in these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

A careful dental evaluation is recommended so that required dental treatment may be completed whenever possible before cardiac valve surgery or replacement or repair of congenital heart disease. Such measures may decrease the incidence of late prosthetic valve endocarditis caused by viridans group streptococci.

There is no evidence that coronary artery bypass graft surgery is associated with a long-term risk for infection. Antibiotic prophylaxis for dental procedures is not recommended for patients with coronary artery stents[166].

There are insufficient data to support specific recommendations for patients who have undergone heart transplantation. Such patients are at risk of acquired valvular dysfunction, especially during episodes of rejection. Endocarditis that occurs in a heart transplant patient is associated with a high risk of adverse outcome[167].

As described in Table I, an antibiotic for prophylaxis should be administered in a single dose before the procedure. If the dosage of antibiotic is *inadvertently* not administered before the procedure, the dosage may be administered up to two hours after the procedure. Some patients who are scheduled for an invasive procedure may have a coincidental endocarditis. The presence of fever or other manifestations of systemic infection should alert the provider to the possibility of IE. In these circumstances, it is important to obtain blood cultures and other relevant tests before administration of antibiotics intended to prevent IE.

Conclusions

As of today the focal infection theory still has very controversial aspects: in spite of the great quantity of studies, there is no evidence that focal infections or even antigenic mimicry are responsible for anything other than sporadic abscesses/infections and possibly rare autoimmune disorders. Even infective endocarditis requires a very specific series of events beginning with susceptibility to infection (damaged cardiac valves), particular microorganisms (streptococci and staphylococci) possessing strong adherence properties, heightened microorganism virulence, platelet and fibrin deposition (non-bacterial thrombotic endocarditis), a suitable environment for the microorganisms to thrive and their ability to avoid the local host defenses.

Possibly this model explains why focal infections are not so frequent.

Natural events are commonly complex, secretive, multifactorial and mystifying. The current state of the literature into relationships between periodontal disease and certain adverse health outcomes shows that, in general, people with chronic periodontal disease tend to be more likely to experience these outcomes than people who do not. Whether these relationships are causal has yet to be agreed upon, and resolution of this point will have enormous impact on both the health of the public and relevant scientific research efforts.

If future investigations show that endodontic disease has a deleterious effect on systemic apparatus, public awareness of the importance of caries prevention would be seen in an entirely new light.

Although many people know that deep cavities can lead to toothaches, how much more attention would be paid to oral health maintenance if the scientific community showed that any systemic pathology could be avoided realizing fit prevention measures? Clearly there is much potential gain if this area of inquiry is explored thoroughly, especially if associations between endodontic disease and systemic outcomes are confirmed through consistent findings across epidemiological studies correctly performed. With this presupposition the endodontic community would occupy a position of great responsibility to contribute to improve the oral and general health of the population.

Table I. Antibiotic therapy for a dental procedure. (From J Am Dent Assoc 2008;139 Suppl: 3S-24S).

Situation	Agent	Regimen: single dose 30-60 minutes before procedure	
		Adults	*Children*
Oral	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 oral	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 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

Clinically the focus can be present without producing any clinical signs or symptoms (*latency state*), or it may demonstrate clinical symptoms (*demonstration state*), or it may create a secondary autonomous focus capable of sustaining itself efficiently even after the removal of the primary focus, or it can produce illnesses capable of evolving autonomously (*complication state*).

Not all odontoiatric and parodontal afflictions have a sure etiological origin, so active sites can exist without radiologic evidence. The metafocal illness, when present, sustains itself independently from the primary focus. Prevention and therapy of the dental elements and the parodontal structures assumes a priority importance, because they can develop the role of focus, before that illness is revealed clinically. In case of demonstration (states), it is important to search the oral focus potentially responsible, and their recognition leads to the elimination of the identified noxa by therapies of the conservative type (endodontic and parodontal) and the surgical type (mucus-gingival, apicectomies, cystectomies, extraction of elements seriously compromises and irrecoverable). Remission (*diagnosis ex adiuvantibus*) of the provoked pathology is sometimes present after following specific therapies. In these cases the focus plays the role of a primary eziopatogenetic factor. At other times, remission is absent and we are dealing with an aggravation of a preexisting pathology. In light of the impossibility to appraise aprioristically the causal connection, when very many people have a focus of infection, while those that have pathological demonstrations at a distance are relatively rare, a prudent therapeutic attitude, which should be on the whole conservative, is recommended Considering the mechanisms of correlation and the specific sites, it is by now in the clinical norm to require a stomatologic "*videat*" in case of demonstrations that is supposed to be of metafocal origin. The contribution offered by experts in the resolution of a diagnostic question, assumes a particular importance, above all in the evaluation of ocular pathology, articular pathology and in those cases characterized by absence of exact objective or symptomatic comparisons, especially when the state is marked by generic signs like prolonged fever state, diffuse pain, asthenia, anorexia. The focal hypothesis should always considered in the presence of a feverish prolonged and groundless state, expression of an infectious chronic process clinically little striking, and of a demonstration at distance without evident pathogenetic explanation.

Researches should be performed to determine what measures can be employed to reduce such harm, if it exists, and the risk and cost benefit analysis of any proposed remedies. Studies must also be performed to compare the efficacy of endodontic treatment with alternate treatments such as implants, prosthetic replacements or no treatment other than extraction. To date, these studies have not been performed and there is no evidence to support the theory that modern endodontic therapy is not safe and effective.

It is appropriate that those who investigate endodontically treated teeth as a focus of infection do so in a manner that is scientifically valid, using controlled clinical studies, and following the rules of epidemiological evidence, to determine the incidence/prevalence of diseases attributed to endodontic bacteremias[173].

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