Systemic Antibiotic Therapy in the Treatment of Periodontitis

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ABSTRACT

Periodontitis is characterized by a general inflammation of the tooth-supporting tissues, which leads to apical migration of the junctional epithelium along the root surface and progressive destruction of the periodontal ligament and the alveolar bone. Although the bacteria present within the subgingival dental biofilm constitute the primary etiologic agents of periodontitis, the host's immune response modulates development of the condition toward either destruction or healing. Given the infectious nature of periodontal diseases and the limited results with conventional mechanical therapies for the treatment of certain forms of periodontitis (aggressive and refractory), the use of antibiotics is warranted in certain cases. This article provides an update on systemic antibiotic therapy for the treatment of periodontitis.

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Periodontal disease is one of the most common microbial infections in adults. It is an inflammatory disease of bacterial origin that affects the tooth-supporting tissues. There are 2 major types of periodontal disease: gingivitis and periodontitis. Gingivitis involves limited inflammation of the unattached gingiva and is a relatively common and reversible condition. In contrast, periodontitis is characterized by a general inflammation of the periodontal tissues, which leads to apical migration of the junctional epithelium along the root surface and progressive destruction of the periodontal ligament and the alveolar bone. Periodontitis progresses in cyclical phases of exacerbation, remission and latency, a phenomenon that is closely linked to the effectiveness of the host's immune response.

The classification of periodontal diseases has evolved a great deal over the years. In the most recent report of the American Academy of Periodontology, published in 1999, the various forms of periodontal disease were classified on the basis of cause, severity and site of disease.[1] Experts now distinguish among generalized and localized chronic periodontitis, generalized and localized aggressive periodontitis, periodontitis associated with systemic diseases, periodontitis associated with endodontic lesions and necrotizing ulcerative periodontitis. Of these, chronic periodontitis is the most frequently encountered in the adult population.

Epidemiologic studies have shown that 5% to 20% of the North American population suffers from a severe and generalized form of periodontitis.[2] The prevalence of the disease varies with sex, ethnic background, geographic region and socioeconomic status. In addition, certain conditions may be predisposing or aggravating factors for periodontitis, including accumulation of subgingival plaque, smoking

and conditions associated with an immune disorder (e.g., diabetes mellitus, AIDS).[3] In particular, the risk of periodontitis is 2.5 to 6.0 times higher for smokers than for nonsmokers.[4] Furthermore, periodontal treatments often prove less effective among patients who smoke.[5] Finally, numerous studies have demonstrated that periodontitis may constitute a significant risk factor for other systemic disorders, including atherosclerosis, aspiration pneumonia and preterm births.[6,7]

Etiology of Periodontal Disease

More than 500 microbial species have been identified in subgingival plaque, which can thus be considered to represent a complex ecological niche.[8] Under the influence of local and systemic factors, some of these bacterial species in the subgingival dental biofilm constitute the primary etiologic agents of periodontal disease. The accumulation and proliferation of these bacterial species in the periodontal pocket are the initiating steps in the onset and progression of periodontal lesions. These polymicrobial infections involve bacteria called periodontal pathogens, most of them gram-negative and strictly anaerobic, which act in synergy. Among these species, the most important are *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Prevotella nigrescens*, *Campylobacter rectus, Eikenella corrodens* and *Peptostreptococcus micros*.[9,10] These bacteria produce a wide variety of virulence factors that enable them to colonize subgingival sites, resist the host's defence mechanisms and cause destruction of the periodontal tissues (**Fig. 1**).[11] Although *A. actinomycetemcomitans* is associated with localized aggressive periodontitis (**Figs. 2a** and **2b**), *P. gingivalis* is considered the major etiologic agent of chronic periodontitis.[9,12] Recent studies have demonstrated specific associations among periodontal pathogenic bacteria involved in the onset and progression of the disease. For example, a highly significant association between *T. forsythia* and *C. rectus* was reported in cases of aggressive periodontitis.[13] Socransky and others[14] demonstrated that the bacterial complex composed of *P. gingivalis, T. denticola* and *T. forsythia*, called "Red Complex," is strongly associated with the active destruction phases of chronic periodontitis.

Although the presence of periodontal pathogens is essential for the onset of periodontitis, these organisms are not sufficient for the disease to progress. In fact, the host's immune response modulates progression of the disease toward destruction or healing.[15] Various inflammatory mediators produced by the immune cells normally contribute to tissue homeostasis. However, overproduction of certain mediators, such as interleukin-1β, tumour necrosis factor alpha and prostaglandins, lead to the chronic, persistent inflammation that is at the origin of tissue destruction.[16,17] In fact, these mediators can activate one or more tissue degradation factors, notably matrix metalloproteinases, plasminogen and polymorphonuclear serine proteases, which cause bone resorption[18,19]

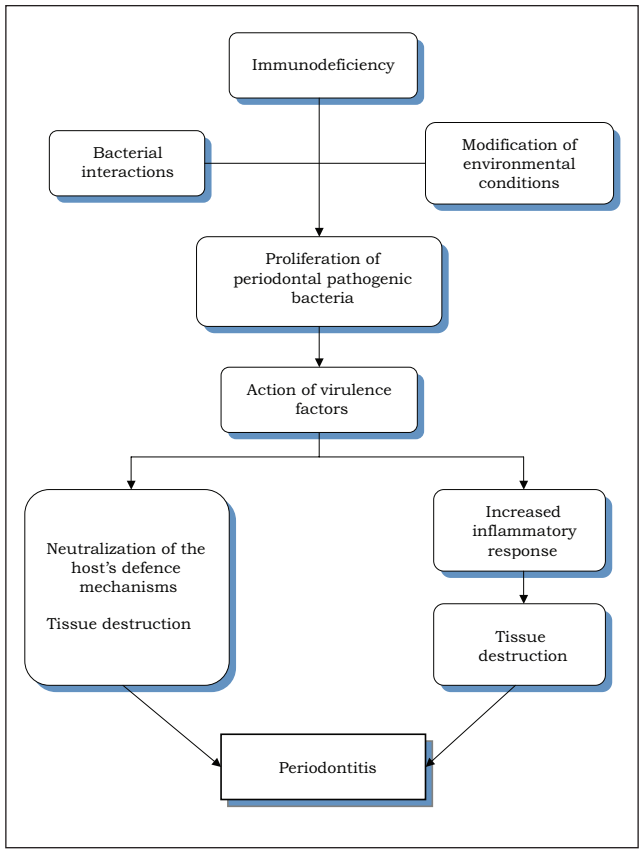

Figure 1: Pathogenesis of periodontitis.

It has recently been suggested that certain viruses of the family Herpesviridae, including cytomegalovirus, Epstein-Barr virus and the herpes simplex virus, could have a causative role in periodontal disease.[20] The presence of these viruses in periodontal lesions may contribute to tissue destruction through their lytic activity directed against structural and immune cells. However, additional studies will be required to confirm the participation of these viruses in the pathogenesis of periodontal disease.

Mechanical Therapy

Mechanical debridement of the dental biofilm and elimination of local irritating factors are the basis of initial periodontal therapies. Longitudinal studies have demonstrated the effectiveness of this approach, which is based on scaling and root planing, reinforcement of the patient's oral hygiene practices and regular follow-up to eliminate new deposits.[21,22] The effectiveness of this treatment is reflected by the disappearance of clinical

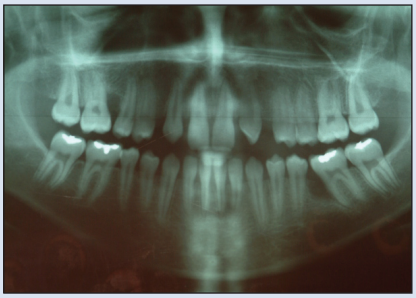

Figure 2a: Panoramic radiograph showing localized aggressive periodontitis in a 13-year-old patient.

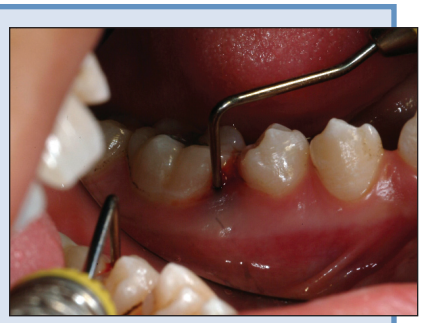

Figure 2b: Localized deep probing on the same patient reveals little plaque or calculus.

symptoms, the reduction or elimination of periodontal pathogens and the return of beneficial bacterial flora. However, this treatment protocol does have limitations. Not all patients or all sites respond uniformly and favourably to conventional mechanical therapy. Reduced effectiveness of the therapy may be explained by a series of patient-related factors (local or generalized), the extent and nature of attachment loss, local anatomic variations, the form of the periodontal disease and the composition of the biofilm. Given the infectious nature of periodontal disease and the limited results that can be achieved with conventional mechanical therapies, the use of antibiotics is warranted for certain forms of periodontitis.

General Considerations for Antibiotic Therapy

Antibiotics can be administered locally (immediate or controlled release) or systemically. Although controlled-release local antibiotic therapy provides for a significant reduction in the undesirable side effects associated with systemic administration, the major disadvantage of this form of therapy is the often-temporary nature of the clinical improvement; with controlled-release therapy, reservoirs of periodontal pathogens are not totally eliminated, and recolonization of the treated sites can occur. This article focuses on the indications for systemic antibiotic treatment. Systemically administered antibiotics penetrate the periodontal tissues and the pocket via the serum. There, they can reach microorganisms that are inaccessible to scaling instruments and local antibiotic therapy. Systemic antibiotic therapy also has the potential to suppress any periodontal pathogenic bacteria colonizing the deep crevices of the tongue as well as clinically nondiseased sites that could potentially cause chronic re-infection. Systemic antibiotic therapy is therefore advantageous for the eradication and prevention of infections by periodontal pathogenic bacteria that invade the subepithelial periodontal tissues or that colonize extradental areas.

In deciding whether to use curative systemic antibiotic therapy, it is important to consider the potential benefits and side effects. The benefits may allow treatment of patients who have had limited response to conventional mechanical therapy and those with multiple diseased sites presenting refractory periodontitis. The potential risks include development of resistant bacterial species, emergence of fungal opportunistic infections or *Pseudomonas* infection, and allergic reactions.[23,24]

Several studies have evaluated the use of antibiotics to stop or reduce the progression of periodontitis.[25–29] Systemically administered antibiotics show a statistically significantly greater gain in attachment and reduction in depth of periodontal pockets, regardless of initial probing methods or therapeutic modalities (antibiotic therapy alone, in conjunction with scaling and root planing, or in conjunction with scaling and root planing plus surgical therapy). However, the therapeutic benefits observed are clinically significant in only a limited number of situations. For example, attachment gain is greater among patients with aggressive periodontitis than among those with chronic periodontitis. The wide variations in dosages and protocols that have been studied mean that it is difficult to clearly specify which types of molecule and which dosages are most successful. Given the lack of highly probative data, practitioners should refer to existing professional recommendations defining indications and appropriate protocols.

According to the American Academy of Periodontology, patients who are likely to benefit from antibiotics are those for whom conventional mechanical treatment has proven ineffective (i.e., those with refractory periodontitis), those suffering from acute periodontal infections (necrotizing periodontal disease and periodontal abscesses) or aggressive periodontitis, and certain medically compromised patients.[30] Patients who smoke can also benefit from systemic antibiotic therapy in conjunction with conventional mechanical treatment.[25] Furthermore, periodontitis caused by *A. actinomycetemcomitans* often requires antibiotic treatment because this bacterium is found on all mucous membrane surfaces of the oral cavity[31] and is capable of invading all soft tissues.[32] This bacterium can therefore quickly recolonize the periodontal pocket after mechanical therapy without antibiotics.[33] These recommendations are in line with those of the French Health Products Safety Agency.[34] However, it should be remembered that the effectiveness of an antibiotic treatment cannot be guaranteed. This may be related to the fact that the same clinical form of

periodontitis may be caused by different microorganisms in different patients.

Choice of Antibiotics

The choice of antibiotic in clinical practice may be based on a microbiological analysis of samples obtained from affected sites.[30] However, this approach is often limited to cases that have proven difficult to treat, because such analyses can be expensive and technically difficult. More often, therefore, the choice of antibiotic is empirical and based on the clinical signs. The most commonly prescribed antibiotic treatments for periodontitis are presented in **Table 1**. Systemic antibiotic therapy for periodontal treatment usually involves monotherapy based on the β-lactams (amoxicillin with or without clavulanic acid), metronidazole, tetracyclines (tetracycline, doxycycline, minocycline), clindamycin and ciprofloxacin.[29]

The β-lactams, including amoxicillin, are broad-spectrum drugs that are frequently prescribed by periodontists for treating periodontal abscesses. These antibiotics show excellent tissue distribution but relatively low concentrations are found in the crevicular fluid. Given that several periodontal pathogens produce β-lactamases that can inactivate β-lactams,[35] the combination of amoxicillin and clavulanic acid should be carefully considered.

Metronidazole, with its narrow spectrum of activity mainly targeting strictly anaerobic bacteria, has been reported in several studies as an effective agent for treating refractory periodontitis involving *P. gingivalis* and/or *P. intermedia*.[36] It allows for the attainment of effective antibacterial concentrations in gingival tissues and the crevicular fluid. Oral administration of metronidazole seems to have little impact on indigenous oral and intestinal microflora.[37]

The tetracyclines, including doxycycline and minocycline, are active against important periodontal pathogens such as *A. actinomycetemcomitans*; they also have anti-collagenase properties and can reduce tissue destruction and bone resorption.[38] Although systemically administered tetracyclines reach relatively high concentrations in the crevicular fluid, wide variation has been observed among different patients.[39] These differences may explain the observed differences in clinical response to the systemic administration of tetracyclines. Tetracyclines are particularly indicated for periodontal infections in which *A. actinomycetemcomitans* is the predominant pathogen; their effectiveness is more limited in dealing with periodontal destruction caused by mixed infections.

Clindamycin is effective against gram-positive cocci and gram-negative anaerobic rods, but has very little impact on *A. actinomycetemcomitans*.[40] This antibiotic is also effective in the treatment of refractory periodontitis. However, clindamycin should be prescribed with caution because of the risk of overgrowth of *Clostridium difficile*, which could result in pseudomembranous colitis.[30]

Table 1 Frequently prescribed antibiotic therapies for the treatment of aggressive and refractory periodontitis

Antibiotic	Dosage (adult)[a]
Metronidazole	500 mg t.i.d. for 8 days
Doxycycline or minocycline	100–200 mg q.d. for 21 days
Clindamycine	300 mg t.i.d. for 8 days
Ciprofloxacine	500 mg b.i.d. for 8 days
Metronidazole + amoxicillin	250 mg t.i.d. for 8 days (each)
Metronidazole + ciprofloxacin	500 mg b.i.d. for 8 days (each)

[a] *q.d.: once a day; b.i.d.: twice a day; t.i.d.: 3 times a day*

Ciprofloxacin is effective against several periodontal pathogens, including *A. actinomycetemcomitans*.[41] This antibiotic effectively penetrates the diseased periodontal tissues and can reach higher concentrations in the crevicular fluid than in the serum.

Because periodontal lesions host a variety of periodontal pathogenic bacteria, it has become increasingly common to treat aggressive periodontitis with a combination of antibiotics.[26] The acknowledged advantage of antibiotic mixtures lies in the expanded spectrum of activity and, in some cases, the synergistic effects. Such combinations include metronidazole and amoxicillin for *A. actinomycetemcomitans* infections and metronidazole and ciprofloxacin for mixed periodontal infections or for patients who are allergic to amoxicillin. In a recent study, Guerrero and others[42] clearly demonstrated that the systemic administration of a combination of metronidazole and amoxicillin, in conjunction with non-surgical treatment of aggressive periodontitis, significantly improved clinical results for a period of 6 months. In vitro, metronidazole combined with amoxicillin or ciprofloxacin demonstrated a synergistic effect against *A. actinomycetemcomitans*.[43] Conversely, antagonistic effects are observed between certain antibiotics, for example, tetracyclines and certain β-lactams.[44]

Other Therapies

Several studies have been devoted to the systemic use of host–response modulator agents such as non-steroidal anti-inflammatory drugs[45,46] and subantimicrobial doses of doxycycline.[47,48] The U.S. Food and Drug Administration recently approved the systemic use of capsules of doxycycline hyclate (Periostat; CollaGenex Pharmaceuticals, Inc., Newton, Penn.), an inhibitor of matrix metalloproteinases, as an adjunct therapy to

scaling and root planing in the treatment of periodontitis. Several studies[47,48] have demonstrated some benefits associated with the use of subantimicrobial doses of doxycycline, but questions remain, and large-scale use of this therapy for the treatment of chronic periodontitis is not yet warranted.

In addition to the curative approach, prophylactic antibiotic therapy is recommended for patients who are undergoing a periodontal procedure and who have a risk of local or general infection (e.g., transplant or graft patients, immunocompromised patients, those with a systemic pathology such as diabetes or arthritis), as well as patients at risk for focal infection (e.g., patients at risk for endocarditis or patients with articular prostheses). These recommendations apply for all types of periodontal surgery, the placing of implants, scaling and root planing, probing of the periodontal pocket, insertion of a fibre or thread containing antibiotics into the periodontal pocket, and any prophylactic cleaning expected to cause bleeding.[49] Among healthy patients, there is insufficient evidence to support the hypothesis that prophylactic antibiotic therapy will reduce the risk of postoperative infection.

Conclusions

In certain cases, the infectious nature of periodontal disease justifies the use of antibiotics as a therapeutic strategy. Patients likely to benefit from antibiotics are those with limited response to conventional mechanical treatment, those suffering from acute periodontal infections or aggressive periodontitis, and those who are medically compromised. Systemically administered antibiotics can reach microorganisms that are inaccessible to scaling instruments or local antibiotic therapy. The main approaches to systemic antibiotic therapy for periodontal treatment are based on monotherapy, although combinations of antibiotics are becoming more common. The most frequently used antibiotics are metronidazole, the tetracyclines, clindamycin, ciprofloxacin and amoxicillin. When deciding whether to use curative systemic antibiotic therapy, however, it is important to consider both the benefits and the undesirable effects. The potential risks associated with systemic antibiotic therapy are well known, particularly those involving the emergence of opportunistic mycetic infections and selection of resistant bacterial strains. The development of resistance to antibiotics by oral bacteria will be discussed in a future article.

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