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The use of systemic antibiotics in the treatment of aggressive periodontal disease

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General dentists frequently encounter patients with aggressive periodontal disease and should be able to diagnose and manage this disease properly. Periodontal care in the absence of a comprehensive treatment plan and proper therapy can result in the rapid progression of the disease and, ultimately, tooth loss. It is important for the general dentist to diagnose, inform, and treat the periodontal patient accurately, using referral and nonsurgical, surgical, and antimicrobial/antibiotic therapy.

This article provides a brief history of the classification of aggressive periodontal disease, describes the microorganisms associated with aggressive periodontal disease, discusses the selection and use of systemic antibiotics in therapy, and lists the various antibiotic regimens for treating aggressive periodontal disease.

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During the International Workshop for a Classification of Periodontal Disease and Conditions in 1999, a new classification of disease was introduced. The committee recommended discarding the term *early onset periodontitis* (EOP) as its age-dependent criteria, required knowledge of rates of progression, and temporal knowledge of when the disease started made the classification too restrictive.[1,2] EOP was used by the 1989 American Academy of Periodontology (AAP) and 1993 European Classifications as a generic term to describe a group of dissimilar destructive disease processes that affected young patients (prepubertal, juvenile, and rapidly progressive periodontal disease).[1]

The name *aggressive periodontitis* (AP) was chosen because the disease progresses rapidly and has a destructive nature regardless of the patient's age.

The workshop suggested that "any classification system for the various forms of Periodontitis should not be based on the age of the patient at the time of presentation, but should instead be based on clinical, radiographic, historical, and laboratory findings."[1]

According to the Parameters of Care Supplement, AP is defined as encompassing distinct types of periodontitis that affect people who, in most cases, appear healthy otherwise. It tends to have a familial aggregation and rapid rate of disease progression.[3]

AP can be further classified into the localized and generalized categories based on specific features of this disease process.

Localized form

The localized form of aggressive periodontal disease has a circumpubertal onset.[1,3] Intraoral/radiographic examination reveals that the disease process is limited to the first molars and incisors with interproximal attachment loss on at least two permanent teeth, one of which is a permanent molar, and involving no more than two teeth other than the first molars and incisors.[1,3] Several species of bacteria are detected in the localized form; however, *Actinobacillus actinomycetemcomitans* produces several virulence factors that help it evade the host's defense mechanisms. Following the initial assault, the host's defense mechanisms produce a robust serum antibody response to the infecting agents, overcoming the neutrophil function abnormalities and localizing the disease process as a result.[1,3,4]

Generalized form

The generalized form of aggressive periodontal disease usually affects men and women over the age of 30, although patients may be older.[1,3] In contrast to the localized form, generalized aggressive periodontitis has a poor serum antibody response to the initial assault. This response, along with the periodontal pathogen's virulence factors, produces a disease process in which intraoral/radiographic examination reveals that the disease process has generalized interproximal bone loss affecting at least three permanent teeth other than the first molars and incisors.[1,3] This attachment loss is episodic in nature and has periods of quiescence of variable lengths.[1,3] This form of the disease frequently is associated primarily with *A. actinomycetemcomitans* and *Porphyromonas gingivalis*.[1,3,5]

It is important to note that not all of the features of AP need to be present or will be present in all cases.

Pathogenesis

The periodontal pathogens primarily associated with aggressive periodontal disease are *A. actinomycetemcomitans* and *P. gingivalis*.[1,3] The microbe must meet several criteria before it is considered a periodontal pathogen. First, the microbe must be present in high numbers in the diseased site but not in healthy sites.[6] Second, the microbe should elicit high antibody titers in the patient's serum, gingival crevicular fluid, and saliva.[6] Finally, the microbe should have an arsenal of virulence factors and should cause disease in an animal model.[6]

The aggressive nature of this disease process is due in part to *A. actinomycetemcomitans*, which is regarded as the key etiological agent based on studies reporting a frequency rate of nearly 90% in periodontal lesions.[5,7-9] *A. actinomycetemcomitans* demonstrates virulence by producing several pathogenic substances; in addition, studies have shown that *A. actinomycetemcomitans* flora increases with the progression of disease and can cross epithelial membranes.[6,8,9] Mandell et al reported that only *A. actinomycetemcomitans* was associated with clinical attachment loss among eight juvenile periodontal patients with progressing disease.[10]

Table 1. Virulence factors of *A. actinomycetemcomitans*.[6]

Factors that promote colonization and persistence in the oral cavity
Adhesions
Invasions
Bacteriocins
Antibiotic resistance
Factors that interfere with the host's defenses
Leukotoxin
Chemotactic inhibitors
Immunosuppressive proteins
Fc-binding proteins
Factors that destroy host tissues
Cytotoxins
Collagenase
Bone resorption agents
Stimulators of inflammatory mediators
Factors that inhibit host repair of tissues
Inhibitors of fibroblast proliferation
Inhibitors of bone formation

Table 2. Common antibiotic therapies for treatment of aggressive periodontitis.[20-22,24-35]

Drug	Adult dosage
Tetracycline–HCL	250 mg four times a day for 12–14 days
Metronidazole	500 mg three times a day for 7 days
Doxycycline	200 mg for one day, followed by 100 mg per day for 14 days
Metronidazole and amoxicillin	250 mg metronidazole plus 375 mg of amoxicillin three times daily for 7 days*
Metronidazole and ciprofloxin	500 mg of each drug twice a day for 8 days

* 375 mg amoxicillin is a European dosage

To produce aggressive periodontal disease, *A. actinomycetemcomitans* must be able to infect periodontal sites by adhering to the cells (particularly epithelial cells) or surface of the tooth, by competing effectively with the large resident microbial population, and by overcoming cellular and humoral defense mechanisms.[11] *A. actinomycetemcomitans* has an arsenal of virulence factors (see Table 1) that attack the host and compromise the periodontium. Because this periodontal pathogen has a high virulence and destructive nature, the dental practitioner needs to employ systemic antibiotics in addition to surgical and/or nonsurgical therapy (see Table 2).

Treatment considerations

Once aggressive periodontal disease has been diagnosed, a comprehensive periodontal treatment plan must be developed. The treatment of periodontal diseases may be divided into four phases: systemic, hygienic, corrective, and maintenance/supportive therapy.[5] Pihlstrom described the systemic phase as the appropriate consideration of systemic diseases and their impact on the etiology or treatment of the disease.[5] The focus of therapy in the hygienic phase is to eliminate as many of the local factors of periodontal disease (bacterial plaque and calculus) as possible.[5] The corrective phase focuses on procedures designed to correct the effects of periodontal disease.[12] In the maintenance/supportive phase, recall and therapy outcomes are assessed.[5] Systemic antibiotics are employed in the hygienic and/or corrective phases.

As treatment progresses through the four phases, the dentist uses both surgical and nonsurgical therapy to remove biofilm created by the bacterial pathogens; this procedure is in agreement with good medical practice because the bacterial load should be reduced as much as possible prior to the use of antibiotics.[13] This practice supports the AAP's position paper on systemic antibiotics in that such systemic antibiotics are considered only for those who exhibit continued loss of periodontal attachment despite conventional mechanical periodontal therapy.[12]

Systemic versus topical antibiotic use

There are several advantages to using systemic antibiotics instead of topical ones. Systemic antibiotics reach the periodontal pathogens via serum at the base of deep pockets, in furcation areas, and within gingival epithelial and connective tissues.[12] The antibiotic's diffusion into the connective tissue and epithelium is important because *A. actinomycetemcomitans* invades these areas where topical agents are less effective at achieving high concentrations; however, topical agents can achieve higher gingival crevicular fluid concentration than systemic agents.[14] Systemic antibiotics also inhibit periodontal pathogens from colonizing other periodontal sites.[15] Disadvantages include adverse drug reactions and uncertain patient compliance in following the prescribed antibiotic regimen.[16,17]

Selection of appropriate antibiotic(s)

It is important to reiterate the importance of initial therapy, which removes plaque and calculus and decreases the bacterial load in the periodontal sites. Some periodontal pathogens, including *A. actinomycetemcomitans*, are able to use their virulence factors to escape the effects of mechanical debridement and invade the periodontal tissues (see Table 1). Systemic antibiotic therapy reinforces mechanical periodontal treatment and supports host defense systems by killing subgingival pathogens that are not affected by mechanical therapy.[12,18] Table 2 lists common antibiotic therapies used in conjunction with mechanical therapies for treating aggressive periodontal disease.

Culture and sensitivity testing are strongly recommended to select the most beneficial antibiotic regimen. Several laboratories across the country offer this service. When culture and sensitivity testing are not available, Walker and Karpinia have suggested that patients with no previous history of antibiotic therapy might respond well to tetracycline/doxycycline.[19] They also have suggested combination therapy when the disease process is considered aggressive.

Tetracycline

Tetracycline is a broad-spectrum, bacteriostatic antibiotic that has anticollagenase properties; it was one of the first systemic antibiotics used for the treatment

of periodontitis associated with *A. actinomycetemcomitans*.[20-22] In a split-mouth study design, Listergarten et al tested the clinical efficacy of using 250 mg tetracycline four times a day for 14 days.[20] The therapy included oral hygiene instructions and scaling and root planing in half the mouth. One group received antibiotic therapy; the other received a placebo. No statistically significant differences were measured in favor of the tetracycline group, although the mean attachment level and probing depth improved more in the test group. In 1983, Slots and Rosling showed that 1.0 g/day of tetracycline HCl enhanced the resolution of gingivitis and supported clinical attachment gain, concluding that although tetracycline is indicated in monoinfections of *A. actinomycetemcomitans*, it may not provide adequate suppression of periodontal mixed infections.[21]

Tetracycline inhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria.[23] Adverse effects on dental treatment can include opportunistic "super infection" with *Candida albicans*; therapy is not recommended during pregnancy or in children who are 8 years of age or younger due to enamel hypoplasia and permanent tooth discoloration. In some individuals, total elimination of *A. actinomycetemcomitans* did not occur and a superinfection of the organism resulted.[20]

Metronidazole

Metronidazole is a bacteriocidal antibiotic that can be used for treating periodontitis associated with *A. actinomycetemcomitans*.[24,25] Wynn et al stated that metronidazole could be used in the treatment of oral soft tissue infections caused by anaerobic bacteria.[23] In 1997, Winkel et al reported that scaling and root planing, followed by systemic metronidazole, could improve the periodontal status of patients who previously responded poorly to periodontal therapy.[25]

Mechanism of action

Metronidazole is reduced to a product that interacts with DNA to cause the loss of helical DNA structure and strand breakage, resulting in inhibition of protein synthesis and cell death in susceptible organisms.[23]

Adverse effects on dental treatment

Less than 1% of patients report xerostomia and a metallic taste. Patients should avoid alcohol-containing food or drinks during therapy and for 72 hours following discontinuation; metronidazole inhibits ethanol's usual metabolism and may cause a disulfiram-like reaction.[23]

Doxycycline

Doxycycline can be used in the treatment of periodontitis associated with *A. actinomycetemcomitans*.[26,27] In a 1999 study, Feres et al sought to evaluate changes in subgingival plaque composition during and after a 14-day doxycycline administration.[28] Using scaling and root planing as its original therapy, the study found that administering 100mg/day of doxycycline for 14 days had minimal effects on the composition of the subgingival microbiota, which rapidly returned to a pretreatment equilibrium.[28] In a subsequent study, Feres et al offered an explanation for the pathogenic species in the subgingival microbiota by investigating the proportion and prevelance of doxycycline-resistant species in subgingival plaque samples taken during and after doxycycline administration.[29] They proposed that the subgingival biofilms were not removed completely. As a result, the organisms growing in or near the biofilms became more resistant to the antibiotic.[28,29] Feres et al also confirmed literature that showed resistant species can be found in subgingival plaque prior to and after doxycycline administration.[29]

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Metronidazole–amoxicillin

In a prospective controlled clinical trial, Berglungh et al distributed 16 subjects randomly into two groups; one group received antibiotic therapy and the other received a placebo.[30] Each subject received initial therapy and two quadrants were scaled and root planed (one in the maxilla; the other in the mandible). This resulted in four groups: those who had received antibiotic therapy but no scaling, antibiotic therapy with scaling, placebo with no scaling, and placebo with scaling. The researchers found that mechanical instrumentation plus combination metronidazole and amoxicillin therapy was more effective than mechanical therapy alone in terms of eliminating probing depths greater than 6.0 mm and in gaining clinical attachment in those areas.

In a double-blind placebo-controlled study, Winkel et al reported similar results, that systemic usage of combination metronidazole and amoxicillin as an adjunct to initial therapy achieved better clinical and microbiological results than conventional therapy alone.[31,32] During a five-year follow-up for this regimen, Buchmann et al reported that the clinical attachment levels ranged from –0.04–0.29 mm with no further statistically significant periodontal breakdown; in addition, periodontal disease progression was arrested successfully in 95% of the initially compromised lesions.[33]

Several studies have reported that metronidazole and amoxicillin suppressed *A. actinomycetemcomitans* below detection level after periodontal therapy.[31,32] Winkel et al also analyzed the effects of this periodontal therapy on patients who smoke and reported that smokers showed similar improvements in bleeding index, probing depth, and gain in clinical attachment.[31] The evidence presented in these articles suggests that amoxicillin plus metronidazole, in combination with nonsurgical therapy, may represent the sole approach to resolving periodontal infections.

Mechanism of action

The mechanism of action for metronidazole is listed above. Amoxicillin inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins. This binding inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, inhibiting cell wall biosynthesis.[23]

Adverse effects on dental treatment

Adverse effects include a disulfiram-like reaction, gastrointestinal disturbances, and antibiotic resistance.[23,32] Prolonged use of amoxicillin may lead to development of oral candidiasis.[23]

Metronidazole–ciprofloxacin

Ciprofloxacin can be used in combination with metronidazole for the treatment of a mixed anaerobic periodontal infection (such as aggressive periodontal disease) when the patient has an allergy to beta-lactam drugs. According to two studies by Slots et al, ciprofloxacin is effective against enteric rods, pseudomonads, staphylococci, and *A. actinomycetemcomitans.*[34,35] These studies revealed that periodontal infections are comprised of several opportunistic pathogens such as *Enterobacteriaceae*, *Pseudomonadaeae*, and *A. actinomycetemcomitans.* The authors concluded that systemic ciprofloxacin administration, when used in conjunction with nonsurgical therapy, can help to eradicate the periodontal pathogens.[34,35]

Ciprofloxacin inhibits DNA-gyrase in susceptible organisms.[23] Among patients who use ciprofloxacin, 1.0–5.0% report headaches, restlessness, nausea, diarrhea, and vomiting.

Summary

When treating aggressive periodontitis, it is imperative that the dentist employ several treatment modalities to halt further loss of periodontal attachment. According to the Parameter of Care Supplement on AP, these modalities should include oral hygiene instruction/reinforcement and evaluation of the patient's plaque control, supra- and subgingival scaling and root planing to remove the bacterial biofilms, implementation of antimicrobials, and periodontal maintenance.

Antibiotics are always an adjunct to conventional treatments. Conventional surgical and nonsurgical therapy reduces the subgingival deposits and disrupts the subgingival biofilms. Patients who continue to lose clinical attachment despite initial therapy are prime candidates for the use of systemic antibiotic therapy. Systemic antibiotic therapy in aggressive periodontitis should be used to eliminate or suppress specific pathogens that are capable of causing the periodontal attachment apparatus to break down. Comprehensive mechanical and antimicrobial therapy is an appropriate treatment regimen for long-term stabilization of periodontal health.[33]

Antibiotic therapy aims to reinforce mechanical periodontal modalities and support the patient's immune system. Ultimately, it is the dentist's decision as to what type of therapy should be implemented. Culture and sensitivity testing is recommended to aid in selecting the most efficacious antibiotic.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of Defense or the U.S. Government.

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