Antimicrobial Treatment of Periodontal Diseases

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Summary

This paper presents a critical evaluation of the use of systemic antimicrobial treatment in periodontal disease. Recognizing specific types of periodontal infections can significantly influence the choice of antimicrobial treatment. Therapy should be tailored to differences in antibiotic susceptibility between various periodontal pathogens.

Many different antibiotic regimens have been described in the literature, making the choice in clinical practice difficult. Numerous studies have examined the impact of systemic antibiotic treatment in stopping the progression of periodontal diseases. Major candidates for antibiotic therapy are patients whose disease continues to progress despite conventional mechanical treatment. Antibiotics can also be used in patients with localized aggressive or other early developed forms of periodontitis, as well as in patients with systemic diseases affecting the course of periodontitis. They have proven to be beneficial as an adjunct to standard therapy. Serious side-effects of systemic antibiotic treatment, such as development of resistance and increase in opportunistic microorganisms, do not justify their use in the treatment of chronic, slowly-progressive forms of periodontal diseases.

Key words: *periodontitis, antimicrobial therapy, antibiotics, subgingival pathogens.*

Acta Stomat Croat
2004; 67-72

REVIEW
Received: May 10, 2003

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Introduction

Gingivitis and periodontitis are the two most common infectious periodontal diseases. Gingivitis occurs in almost all individuals. Advanced periodontitis is found in 10-20 % of the adult population. Both diseases are primarily caused by supra- and subgingival microbial plaque, possessing the properties of a biofilm. Microbial composition of pathogenic plaque has been studied over the last two to three decades. A higher percentage of certain microbial species in the subgingival plaque has been related to active destructive periodontal disease. Some of the periodontally pathogenic bacteria are: *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Peptostreptococcus micros, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Treponema denticola*, certain Enterobacteriaceae species and staphylococci (1-3).

Elimination or adequate suppression of periodontal pathogens in the subgingival microflora is essential for periodontal healing to take place. Antimicrobial therapy in periodontology includes mechani-

cal debridement of the root surfaces, oral hygiene measures and local and systemic antimicrobial chemotherapy.

Inflammatory periodontal diseases are primarily treated with supra- and subgingival scaling of the affected tooth surfaces. Clinical improvement is directly related to the reduction or removal of the subgingival pathogenic plaque (4-6). The majority of subgingival bacteria is sensitive to the antimicrobial effect of mechanical therapy (7). Mechanical and surgical treatment, combined with proper oral hygiene, in most cases arrests further periodontal attachment loss. However, despite well performed mechanical treatment, in some individuals the clinical attachment destruction cannot be stopped. Refractory periodontitis and diminished immune host response (8) can be related to residual subgingival pathogens (9, 10). Numerous studies have shown that mechanical debridement cannot effectively eliminate *A. actinomycetemcomitans, P. gingivalis, P. intermedia, B. forsythus, P. micros*, enterobacteria and some other bacterial species (5, 6, 11, 12-14). The reason is the ability of the mentioned bacterial species to invade gingival epithelial cells and subepithelial connective tissue (15-18). Certain periodontal pathogens possess the ability to recolonise the tooth surfaces from the tongue, tonsillae and buccal mucosa which act as reservoirs (19). Targeted antimicrobial therapy could perhaps suppress or eliminate residual periodontal pathogens, and thus serve as an adjunct to conventional mechanical therapy (20).

Microbial composition of subgingival plaque can differ greatly between individual patients (21, 22). Recent studies have shown that some subgingival bacteria, including *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*, relatively rarely occur in healthy periodontium, and are able to stimulate production of specific antibodies in patients with periodontitis. These bacteria are exogenous microorganisms and could represent true periodontal infections (23). Atypical (non-oral) pathogenic enteric bacteria were isolated from some periodontal lesions, and present superinfections. Periodontal infections caused by oral microorganisms can be considered endogenous periodontal infections. Knowing the type of periodontal infections is important when choosing appropriate antimicrobial periodontal therapy (24). Antibiotic therapy of severe periodontitis forms should be adapted to the differential antimicrobial susceptibility of the periodontal pathogens present (23, 25).

Microbiological analysis revealed that subjects with the same clinical form of the disease have different bacterial composition of subgingival plaque, and that the same bacteria can be found in different clinical forms of the disease. Consequently, it is not possible to relate specific bacteria to specific clinical appearance, or discern between periodontitis forms on the basis of microbiological isolates. This conclusion is in accordance with modern understanding of periodontal disease as a result of the interaction between microorganisms and different host factors. The same microorganisms can lead to different clinical forms of the disease (26).

Starting with the first investigations in the late 1970s, the use of antibiotics in periodontal therapy has been controversial. The value of antibiotic therapy has often been misinterpreted, overestimated or over-simplified. In this article we will survey modern concepts of systemic antimicrobial therapy in the treatment of periodontal diseases.

History

Microscopic studies at the beginning of the last century revealed the presence of large numbers of spirochetes and amoebas in subgingival plaque (27, 28). These microorganisms were held responsible for the initiation of periodontal disease, and subsequently neo-salvarsan and ementin were used as treatment. These anorganic arsenic drugs had very dangerous side effects. After them appeared prontosil, chemotherapeutic derived from artificial dyes, one of its metabolites being sulfonamide. Sulfonamides are still being used in medicine. The beginning of the antibiotic era was Flemming's discovery of Penicillium notatum mould producing a substance which inhibits *Staphylococcus aureus* growth. Since then numerous antibiotics have been discovered, which are used in medical or dental practice. Although the advantages of antibiotic use in fighting bacterial infection are huge, unwanted effects such as resistance, toxicity, sensitivity and interaction with other medications are often encountered.

Traditionally, in periodontics antibiotics were prescribed to patients not responding to conventional mechanical treatment, or as an adjunct for periodontal surgical procedures. Initially, the choice of antibiotics was based on clinical experience and mostly penicillins were used. Tetracycline hidrochloride became widely used during the 1970s, and the advantages of its usage were its broad antimicrobial spectrum and low systemic toxicity. First controlled clinical studies testing the effectiveness of antibiotic therapy started in the late 1970s. Despite numerous investigations, it is still not clear which is the most effective antibiotic in periodontology. In the literature, many different forms of antibiotic therapy have been described, making the choice of antibiotics very difficult.

The concept of antimicrobial therapy

The aim of antimicrobial therapy is to stop periodontal attachment loss, and as far as possible, to maintain the soft tissue esthetics. This includes removal of bacterial plaque and calculus from the root surfaces, surgical access if needed, and oral hygiene instructions and removal of local plaque retention factors.

Systemic antimicrobial therapy in periodontology is based on the fact that specific bacterial species cause periodontal destruction and that it is possible to achieve bactericidal or bacteriostatic concentrations of the antimicrobial substance in the periodontal pocket (29). In comparison with mechanical treatment or local delivery, systemically administered antibiotics have several advantages. Through serum it is possible to influence microorganisms (Table 1) in the furcation area, or at the bottom of a deep periodontal pocket, perhaps even bacteria present in the epithelial or connective tissue of the gingiva (30), or bacteria colonising oral mucosa or extraoral locations (31, 32). Disadvantages of antibiotic therapy are possible adverse effects (Table 2) (33, 34).

Since periodontal disease is not caused by one microorganism, antibiotic usage for elimination of one pathogenic species is not possible. In the best case, antibiotics will suppress some subgingival bacteria over a limited period of time (35).

Most of the clinical studies only tested one antibiotic, instead of comparing different kinds of antibiotics. Therefore it is very difficult to give one-sided, on scientific evidence-based recommendation for the choice of antibiotic treatment of certain periodontal clinical conditions (26).

Antibiotics in periodontal therapy

Tetracyclines

Tetracyclines are a group of broad-spectrum, bacteriostatic antibiotics. They are the first antimicrobial drugs which have been scientifically investigated in periodontology. This group includes tetracycline hydrochloride, minocycline and doxycycline.

In their double-blind clinical studies, Rams and Keyes (36) and McCulloch et al. (37), showed that systemic intake of tetracyclines statistically significantly reduced probing pocket depth. The risk of the occurrence of periodontal destruction after 7 months was decreased by 43%, and destruction was not stopped in more than one third of the patients. Some authors described the reappearance of the disease after systemic tetracycline therapy (38, 39). Possible cause of further disease progression are microorganisms inadequately suppressed by tetracycline, such as *A. actinomycetemcomitans* (40). Tetracycline therapy could lead to superinfection with enteric bacteria, staphylococci or with *Candida albicans* (41-43).

It seems that the older studies showed beneficial effect against *A. actinomycetemcomitans*, while newer studies do not support this. This can partly be explained by the higher resistance to these antibiotics. Besides this, positive effects were observed in studies conducted in North america, where different *A. actinomycetemcomitans* serotypes are present with different virulence factors, than in Europe. We did not find studies in the literature by European authors showing beneficial effect of tetracyclines against *A. actinomycetemcomitans.*

Concerning the choice of tetracyclines, the advantages of doxycycline are one daily dosage, rare gastrointestinal adverse effects, as well as normal calcium absorption. Especially interesting is the usage of low-dosage doxycycline (20-30 mg) during 6-9

months. Clinical attachment gain has been proved, without resistance occurrence or changes in normal periodontal microflora (44). Besides the antimicrobial effect, doxycycline inhibits collagenase and other matrix metalloproteinases, enzymes responsible for collagen degradation during periodontal infection, so its efficacy is partly due to this mechanism (45).

Minocycline, as an adjunct to mechanical therapy failed to eliminate *A. actinomycetemcomitans* in all patients, and the disease reoccurred in 25% of the test subjects, despite regular check-ups every 3 months (46).

It seems that the effect of tetracyclines is optimal in patients with 'refractory' chronic periodontitis, while it is not the best choice for treatment of localised aggressive periodontitis, due to the weak effect on *A. actinomycetemcomitans* the antibiotics from this group have.

Metronidazole

Metronidazole is a synthetic nitroimidazole. Its action is bactericidal, acting on anaerobic bacteria, including gram-negative rods and spirochetes, through DNA synthesis blocking. Due to the susceptibility of the spirochetes, it is effective in cases of necrotising periodontal diseases. It seems relatively ineffective in the suppression of *A. actinomycetemcomitans*. Periodontal abscesses can be successfuly treated with metronidazole, while for aggressive periodontitis treatment its antimicrobial spectrum is not wide enough (47).

Penicillins

Penicillins inhibit bacterial cell-wall synthesis, and the antimicrobial spectrum of natural penicillins is narrow. Amoxicillin is a semi-synthetic penicillin with broadened antimicrobial spectrum, and is used in periodontology because it is effective against some subgingival bacterial species such as *P. micros* and *A. actinomycetemcomitans* as well. It can be used in cases of acute infections, although it is most commonly used in combination with metronidazole. Amoxicillin in combination with clavulonic acid is indicated in the presence of oral bacteria capable of producing β-lactamase (48).

Ciprofloxacin

A member of the fluorquinolones, it is used in the therapy of urinary infections. Ciprofloxacin is also effective in the treatment of periodontal superinfections caused by enteric bacteria, pseudomonas or staphylococci. Clinical isolates of *A. actinomycetemcomitans* are highly sensitive to ciprofloxacin (49). Another positive aspect is its inactivity towards streptococci, whose presence in the subgingival area is associated with periodontal health. Heightened streptococcal counts can postpone recolonisation of the pathogenic bacterial species (50).

Azithromycin

Azithromycin is an antibiotic from the macrolide group, it exerts bacteriostatic activity by blocking of bacterial proteins synthesis. The spectrum is broad and covers gram-negative bacteria, including enteric bacteria. Assessment of availability in periodontal tissues showed extremely high values in periodontal tissues, crevicular fluid and saliva. Periodontally inflamed tissues exhibit concentrations significantly higher than healthy periodontal tissues, which is a very convenient characteristic of this antibiotic (51). Data from clinical investigations support the use of azithromycin in the treatment of advanced chronic, or aggressive periodontitis (52).

Clindamycin

Clindamycin is a pyranoside antibiotic similar to macrolides, with a broad antimicrobial spectrum. Efficacy of clindamycin has been tested in several clinical studies (53, 54). This drug has stopped attachment loss in a high number of patients and increased the number of sites with the attachment gain, even in patients who had already undertaken unsuccessful antibiotic therapy. Resistance to clindamycin of certain *A. actinomycetemcomitans* and *P. gingivalis* serotypes was described (55). Because of the possibility of dangerous side-effects, as well as the occurrence of resistance of certain subgingival microorganisms to this medicaton, it is not the first-choice antibiotic used in the treatment of periodontal diseases.

It can be concluded that antibiotic monotherapy, with one medication as an adjunct to the mechanical therapy, has a favourable influence on the com-

position of bacterial microflora and reduction in the number of active periodontal pockets. Clinical improvement is a result of the total bacterial load suppression, and the changes in the composition of the subginigival bacterial microflora. Due to the complex composition of the subgingival bacterial microflora, such a form of antibiotic therapy is often ineffective in eliminating exogenous bacterial pathogens.

Combined and serial antibiotic therapy

Subgingival microflora in periodontal diseases includes different pathogenic bacteria possessing differential sensitivity to antimicrobials, so the use of two or more antibiotics presents a useful option in the treatment of these diseases. The advantages of combined antibiotic therapy are broadened spectrum of antimicrobial activity, occurence od synergistic activity (Table 3) (56) and prevention of bacterial resistance development. Disadvantages of such a treatment are elevated incidence of adverse effects.

Metronidazole in combination with amoxicillin or ciprofloxacin has been successfuly used in the treatment of advanced periodontitis, especially infections with *A. actinomycetemcomitans* (9, 39, 57, 58). Metronidazole and amoxicillin *in vitro* act synergistically on *A. actinomycetemcomitans.* Combination of metronidazole with amoxicillin or amoxicillin and clavulonic acid can eliminate *A. actinomyctemcomitans* and other periodontal pathogens from the periodontal pockets for at least two years (57, 59). Metronidazole and ciprofloxacin can be effective in mixed periodontal infections, such as the presence of anaerobes, *A. actinomycetemcomitans*, enteric bacteria and pseudomonades (58, 59). As this combination is ineffective against most gram-positive, facultative anaerobic bacteria, it can facilitate streptococcal colonisation of the pockets which have no periodontally pathogenic potential (60).

Serial use of antibiotics is indicated for a combination of antibiotics, in which one has bactericidal and the other bacteriostatic activity. Combined administration would lead to antagonistic effects and therapeutical failure. This form of systemic antimicrobial therapy should be used in especially severe cases of recurrent or refractory periodontitis, where attachment loss was not arrested despite careful initial therapy, or in cases of disease reactivation during the supportive phase of therapy, occurring despite good oral hygiene and repeated mechanical subgingival instrumentation. One of the combinations effective in the prevention of recurrent periodontitis in high-risk individuals is doxycycline and metronidazole (61).

Systemic antimicrobial therapy in periodontal practice

The main candidates for antibiotic therapy are periodontal patients, in which conventional mechanical therapy does not arrest further disease progression. The use of antibiotics is also indicated in patients with localised aggressive periodontitis or other forms of early-onset disease, as well as in patients with systemic disease influencing the periodontitis. In patients with acute or recurrent periodontal infections, like periodontal abscesses, acute necrotizing gingivitis or periodontitis (62) or periimplantitis (63), systemic medication of antibiotics can lead to clinical improvement. Patients with stable periodontitis can profit from antimicrobial therapy minimally or for a short period.

Microbiological analysis should be performed after conventional mechanical therapy has been finished, in order to assess the need for antibiotic therapy. It should include antimicrobial susceptibility testing on specific antimicrobials. The microbial testing should be repeated 1-3 months after the antibiotic administration, not only to check if elimination or marked suppression of the pathogens occurred, but also to monitor for possible superinfections (23, 64, 65).

Microbial sampling of individual or several combined active pockets is conducted. The sample combined from more pockets gives a better insight in the spectrum of periodontal pathogens that need to be acted upon through antimicrobial therapy. Representative subgingival sample is obtained by combining samples from the deepest pocket bleeding or showing suppuration, from each quadrant (66). The samples can be taken by means of sterile curettes or paper points, and the samples should immediately be put into the reduced transport media (67).

Conclusion

The value of systemic antibiotic use in arresting disease progression has been investigated in numerous studies. It was shown that it can improve the treatment outcome, as an adjunct to therapy. Serious adverse effects such as the development of antibiotic resistance and growth of opportunistic microorganisms do not support the concept of routine use of antibiotics in the treatment of chronic, adult forms of the disease. Systemic antimicrobial therapy is indicated in cases of disease where the periodontal destruction continued, despite thoroughly performed mechanical therapy. In patients from high-risk groups, such as aggressive forms of periodontitis or periodontitis as a manifestation of systemic disease, the use of antibiotics is indicated as an adjunct to scaling and root planing. Antibiotics are never indicated in the treatment of chronic gingivitis.