Review article ∎

Antibiotics in the Management of Periodontal Disease

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SUMMARY

Systemic antibiotics are increasingly used in the treatment of periodontal infections. Whilst these drugs are used mostly on an empirical basis, some physicians contend that rational use of antibiotics should be the norm due to their wide abuse and global emergence of antibiotic-resistant organisms.

This is a review of the principles and rational antimicrobial therapy, treatment goals, drug delivery routes and various antibiotics used in the management of periodontal diseases. The available data indicate, in general, that mechanical periodontal treatment alone is adequate to ameliorate or resolve the clinical condition in most cases, but adjunctive antimicrobial agents, delivered systemically, can enhance the effect of therapy in specific situations. This is particularly true for aggressive periodontitis in patients with generalised systemic disease that may affect host resistance, and in case of poor response to conventional mechanical therapy.

This article provides an update on systemic antibiotic therapy for the treatment of periodontitis.

Key words: antibiotics, periodontitis, therapy, metronidazole, tetracycline, clindamycin

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INTRODUCTION

Antibiotics are typically used in medicine to eliminate infections caused by the invasion of the host by a foreign, pathogenic microorganism. The microbial etiology of inflammatory periodontal disease has provided the basis for the introduction of antibiotics in their overall management.

This review will assess the ability of specific antibiotics to reduce the pathogenicity of the subgingival microflora and subsequently affect the clinical signs of disease, primarily the aetiology of periodontal disease. However, consideration must also be given both to the rationale for the use of antibiotics in periodontal treatment and also to the possible routes of administration.

ETIOLOGY OF PERIODONTAL DISEASE

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 two major types of periodontal disease: gingivitis and periodontitis. Gingivitis involves a limited inflammation of the unattached gingiva, and is a relatively common and reversible condition. In contrast, periodontitis is characterized by general inflammation of the periodontal tissues, which leads to the apical migration of the junctional epithelium along the root surface and progressive destruction of the periodontal ligament and the alveolar bone (1). Periodontitis progresses in cyclical phases of exacerbation, remission and latency, a phenomenon that is closely linked to the effectiveness of the host immune response.

Experts now distinguish among generalized and localized chronic periodontitis, generalized and localized aggressive periodontitis (AP), periodontitis associated with systemic diseases, periodontitis associated with endodontic lesions and necrotizing ulcerative periodontitis (2). Of these, chronic periodontitis is the most frequently encountered in the adult population. In addition, certain conditions may be predisposing or aggravating factors for periodontitis, including accumulation of subgingival plaque, smoking and conditions associated with some immune disorder (e.g., diabetes mellitus, AIDS) (3).

More than 500 microbial species have been identified in subgingival plaque, which can thus be considered to represent a complex ecological niche (4). 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. Among these species, the most important are *Aggregatibacter actinomycetemcomitans (A.a.)*, *Porphyromonas gingivalis (P.g.)*, *Tannerella forsythia (T.f.)*, *Treponema denticola (T.d.)*, *Fusobacterium nucleatum (F.n.)*, *Prevotella intermedia (P.i.)*, *Campylobacter rectus (C.r.),* and *Eikenella corrodens*

(E.c.) (5,6). Although *A. actinomycetemcomitans* is associated with localized aggressive periodontitis, *P. gingivalis* is considered the major etiologic agent of chronic periodontitis (5,7).

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 immune response modulates progression of the disease toward destruction or healing (8). However, overproduction of certain mediators, such as interleukin-1β, tumor necrosis factor alpha and prostaglandins, lead to the chronic, persistent inflammation which is in the origin of tissue destruction (9,10). In fact, these mediators can activate one or more tissue degradation factors, notably matrix metalloproteinases, plasminogen and polymorphonuclear serine proteases, which cause bone resorption (11,12).

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 oral hygiene practices and regular follow-up to eliminate new deposits (13,14). The effectiveness of this treatment is reflected by the disappearance of clinical symptoms, reduction or elimination of periodontal pathogens and regeneration of beneficial bacterial flora. Not all patients or all sites respond uniformly and favorably to conventional mechanical therapy. 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.

RATIONALE FOR THE USE OF ANTIBIOTICS

The academic argument over the importance of a specific or non-specific bacterial etiology for periodontal diseases may never be totally resolved. However, there is little doubt that certain specific organisms are closely associated with some forms of periodontal disease (15). Unlike the majority of general infections, all the suspected periodontal pathogens are indigenous to the oral flora (16,17). Consequently, the long-term and total elimination of these organisms with antibiotics will be very difficult to achieve as immediate repopulation with the indigenous bacteria will occur when the therapy is completed (18). Nevertheless, in certain forms of periodontitis the loss of connective tissue attachment is rapid. Extremely virulent, gram - negative organisms populate the deep pockets, and bacteria can actually invade the connective tissue (19, 20). Under these circumstances, antibiotics provide a useful adjunct to root planing, which by itself may not remove all subgingival deposits and certainly would not affect any invading organisms that had already penetrated the soft tissue.

ROUTES OF ADMINISTRATION

The singular aim of using antibiotics as a part of the treatment regimen is to achieve, within the periodontal environment, a concentration of the drug that is sufficient either to kill or arrest growth of the pathogenic microorganisms. The most effective and reliable method of achieving these concentrations is by systemic administration, whereby the drug is able to bathe the subgingival flora by passing into the ginival crevicular fluid (21). Indeed, certain drugs such as tetracycline have been found to concentrate in crevicular fluid at higher levels than those found in serum after the same oral dose (22). The drug can then bind to the tooth surface, from which it is released in active form (23).

Antibiotics can be administered locally (immediate or controlled release) or systemically. Systemically administered antibiotics penetrate the periodontal tissues and the pocket via serum. There they can reach the microorganisms which 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 non-diseased sites that could potentially cause chronic reinfection (24). Systemic antibiotic therapy is therefore advantageous for the eradication and prevention of infections by periodontal pathogenic bacteria that invade the sub-epithelial 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 (25, 26).

Several studies have evaluated the use of antibiotics to stop or reduce the progression of periodontitis (27-30). 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).

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 (31). Patients who smoke can also benefit from systemic antibiotic therapy

in conjunction with conventional mechanical treatment (27). Furthermore, periodontitis caused by *A. actinomycetemcomitans* often requires antibiotic treatment because this bacterium is found on all mucous membrane surfaces of the oral cavity (32), and is capable of invading all soft tissues (33). This bacterium can therefore quickly recolonize the periodontal pocket after mechanical therapy without antibiotics (34).

CHOICE OF ANTIBIOTICS

The choice of antibiotic in clinical practice may be based on microbiological analysis of the samples obtained from affected sites (31). More often, therefore, the choice of antibiotic is empirical and based on the clinical signs. Systemic antibiotic therapy for periodontal treatment usually involves monotherapy based on metronidazole, tetracyclines (tetracycline, doxycycline, minocycline), clindamycin, ciprofloxacin and the β-lactams (amoxicillin with or without clavulanic acid) (30).

Metronidazole

Metronidazole is a nitroimidazole compound with a broad spectrum of activity against protozoa and anaerobic bacteria (35). In medicine, it is used in the treatment of trichomonal genital infections, as a prophylactic agent before abdominal surgery, and in the management of severe anaerobic infections (36, 37). The antibacterial activity against anaerobic cocci, anaerobic Gram - negative bacilli, and anaerobic Gram - positive bacilli had led to its use in the treatment of periodontal diseases (38).

In periodontal treatment, metronidazole has been used both in tablet forms, and less commonly, as a topical application. The drugs is well-absorbed after oral administration and the peak plasma level is usually reached in about one hour (39). The half-time of metronidazole is about 8 hours and the principal site of metabolism is the liver. Metronidazole is excreted in the urine.

Metronidazole is widely distributed throughout the body and, after an oral dose, can be detected in saliva and crevicular fluid (40). After five days, oral dosing with 250mg thrice daily, the levels of metronidazole in crevicular fluid show a much greater range and can be nearly 50% higher than the concurrent serum concentrations (41).

The rationale use of metronidazole in the treatment of periodontal diseases and other oral infections has revolved around the drug's specificity for anaerobes and the apparent inability of susceptible organisms to develop resistance (42,43).

In one of the first studies on metronidazole and periodontal disease (44), a dose of 250mg, thrice daily for one week was administered to five patients. This resulted in significant reductions in bleeding scores and

pockets depths, as well as gains in attachment levels, and these improvements were sustained six months after therapy. In three of the patients, mechanical debridement was undertaken and this contributed to the improvement of the periodontal condition.

The clinical, histopathological, and bacteriological benefit of metronidazole therapy is more pronounced when concurrent scaling, root planing, and oral hygiene instruction are undertaken (45). The severity of the periodontal destruction may therefore be an important consideration in the use of metronidazole. Advanced and refractory periodontitis respond well to the drug when it is used as an adjunct to traditional therapeutic measures (46, 47).

A problematical group of periodontal patients are those with advanced disease but who do not respond to oral hygiene instruction. The study of 10 such patients (48) showed that a week's course of metronidazole resulted in significant improvements in pockets depths and attachment levels. They concluded, however, that these changes, which occurred in the absence of improvement in either plaque indices or inflamed gingival units, were not of sufficient clinical magnitude to warrant administration of a medically important drug.

Finally, metronidazole has also been found to be very effective, when combined with amoxicillin, in eliminating A. a. in patients suffering from AP (49). This lead to almost total elimination of the aggregatibacter for up to 11 months after therapy (50). In a recent study, Guerrero and others (51) clearly demonstrated that the systemic administration of a combination of metronidazole and amoxicillin, in conjunction with nonsurgical treatment of aggressive periodontitis, significantly improved clinical results for a period of six months.

The oral dose for metronidazole is 750mg/day, which is administrated as 250mg tablets at eight-hourly intervals for eight days adjunct to both non-surgical and surgical treatment. The oral dose for metronidazole in combination with amoxicillin is 750 mg/day (for each drug) for eight days.

Tetracyclines (doxycycline, minocycline)

The tetracyclines are a group of closely related, bacteriostatic antibiotics that provide a "broad spectrum" of activity against both Gram-positive and Gram-negative species, although more suitable antibiotics are usually preferred for Gram-positive infections. 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 (52-54).

Tetracyclines are usually given orally, although topical application have been used in periodontal treatment regimensn (55, 56). Tetracyclines are absor-

bed from the gastrointestinal tract and absorption is reduced when the drugs are taken with milk products or with substances containing calcium, magnesium, iron, or aluminium. However, even when the drugs are taken on an empty stomach, a certain amount remains in the bowels.

All tetracyclines are distributed widely in the tissues and are localized in developing dental structures and bone. Tetracycline, minocycline and doxycycline are detectable in crevicular fluid after oral dosing and their respective concentrations can reach levels 10 times and five times in the serum (57, 58).

Tetracycline is excreted in the urine and should not be given to patients whose renal function is compromised. Doxycycline is excreted predominantly in the faeces and consequently does not accumulate in the blood of patients with renal disease. Excretion of minocycline is also unaffected by the state of renal function as the drug appears to be metabolized in the liver and then excreted in the faeces.

Tetracycline has been shown to be considerable benefit in the treatment of aggressive periodontitis (AP) in which the prime pathogen, Aggregatibacter actinomycetemcomitans, is very susceptible to the antibiotic (59). This capnophilic, Gram-negative rod is difficult to eliminate from AP patients by mechanical debridment alone (60, 61), presumably because of its ability to invade the soft tissue. Systemic administration of 1g/day tetracycline for 3-6 weeks in conjuction with supragingival plaque control can halt the progression of the AP lesions (62, 63).

In addition to the antimicrobial effects of tetracyclines, a further mechanism has been proposed to explain their efficacy in the treatment of periodontal disease. In a series of laboratory experiments and clinical trials on diabetic humans, Golub et al. have shown that tetracycline, doxycycline, and minocycline can all suppress the activity of the tissue enzyme collagenase as determined by its presence in crevicular fluid (64, 65).

The oral dose for tetracycline is 1g/day, which is administrated as 250mg tablets at six-hourly intervals for two weeks adjunct to both non-surgical and surgical treatment. The oral dose for the doxycycline and minocycline is 100-200mg/day, for 21 days.

Clindamycin

Clindamycin is a derivate of lincomycin that is more active and has fewer side-effects than the parent drug. Clindamycin is effective against gram-positive cocci and gram-negative anaerobic rods, but has very little impact on *A.a.* (66).

Clindamycin is almost completely absorbed after oral administration to produce a peak blood concentration in about 60 min. The half-life of the drug is about 3 hous and it is well distributed throughout the tissues including bone. Clindamycin also accumulates in poly-

morphonuclear leukocytes. Most of the drug is metabolized and excreted in the urine and bile.

Due to the potential severity of side-effects that can accompany the use of these drugs, their use in the treatment of periodontal disease has been limited. Short-term, clinical and microbiological studies have shown that clindamycin is beneficial in controlling advanced periodontal infections (67, 68). 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 (31).

The oral dose for clindamycine is 900mg/day, which is administrated as 300mg tablets at eight-hourly intervals for eight days adjunct to both non-surgical and surgical treatment.

Other antibiotics

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 and are found in the crevicular fluid (69).

Ciprofloxacin is effective against several periodontal pathogens, including *A. a.* (70). This antibiotic effectively penetrates the diseased periodontal tissues and can reach higher concentrations in the crevicular fluid than in the serum.

Systemic phenoxymethylpenicillin has apparently been used successfully as a part of a surgical regimen in the treatment of AP (71). However, later results from a controlled clinical trial indicated that the adjunctive use of phenoxymethylpenicillin does not enhance the treatment of AP by root planing and flap surgery (72).

Several studies have been devoted to the systemic use of host - response modulator agents such as nonsteroidal anti-inflammatory drugs (73, 74) and sub-antimicrobial doses of doxycycline (75, 76).

INDICATIONS FOR ANTIBIOTICS IN PERIODONTAL THERAPY

The results of the clinical trials discussed above suggest that there is an important role for antibiotic therapy as an adjunct to periodontal treatment. In accordance with the general principles of prescribing antibiotics, however, it is essential that the drugs are administered only after careful case selection, and antibiotic therapy should be a substitute for the routine and time-honored treatment regimens.

The following periodontal disease states would justify the adjunctive use of antibiotics:

1. In severe cases both of acute necrotizing ulcerative gingivitis and periodontitis, especially if there are signs of systemic involvement, metronidazole can quickly alleviate the symptoms, which then permits through mechanical debridement to be carried out.
2. Occasionally, the local infection of a periodontal abscess can spread within tissue planes to cause marked facial swelling and systemic involvement. In these cases, broad-spectrum antibiotics should be prescribed to control the infection. Careful clinical and radiographic examinations must be done to establish whether the lesion is wholly periodontal in origin or whether there is pulpal involvement of the associated teeth.
3. Multiple abscess formation and gross periodontal infection would necessitate the administration of antibiotics (metronidazole and tetracycline). A number of medical conditions (e.g. Diabetes mellitus) can predispose to advanced periodontal destruction with abscess formation.
4. Antibiotic therapy is warranted in cases of periodontal disease, which, despite through non-surgical management and good plaque control, continue to show breakdown and loss of attachment. These so-called refractory cases can benefit from a short course of antibiotic therapy. The drug of choice should be determined from sampling the cultivable pocket flora from which the predominant populating organisms can be identified.
5. Antibiotic therapy is recommended in the management of cases of AP either in combination with flap surgery or a non-surgical treatment programme.

CONTRAINDICATIONS AND UNWANTED EFFECTS

Antibiotics are amongst the most widely prescribed pharmaceutical agents in modern medicine. Although only a small number of these drugs have been used in the treatment of periodontal diseases, it is essential that the main contraindications for their use and their possible unwanted effects are known to the periodontist.

Generally, the contraindications for use are related to the impaired metabolism and excretion of the drugs. Consequently, disease or impaired function of the hepatic or renal tracts should warrant caution in prescribing systemic antibiotics. When penicillins are prescribed it is vitally important to determine whether or not there is a history of hypersensitivity to the drug. The unwanted effects of penicillin are often mild and characterized by rashes, urticaria, joint pains, and dermatitis, although severe anaphylactic reactions have been reported and can be fatal.

CONCLUSIONS

Literature has shown long-term benefits of non-surgical therapy in maintaining clinical attachment levels, with and without systemic antibiotics. However,

those long-term successes depend on optimal oral hygiene and regular maintenance visits for monitoring the status of periodontium and reinforcement of daily plaque removal by the patient. If the patient does not take adequate responsibility for home care and other compliance issues, relapse is likely to occur. In those cases, the situation justifies the use of antibiotics as a therapeutic strategy.

Systemically administered antibiotics can reach microorganisms that are inaccessible to scaling instruments or local antibiotic therapy. 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.

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ANTIBIOTICI U TERAPIJI PARODONTALNOG OBOLJENJA

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Sažetak

Sistemski antibiotici se učestalo koriste u terapiji parodontalnih infekcija. Dok se ovi lekovi uglavnom koriste na empirijskoj osnovi, neki lekari se bore za to da, racionalna upotreba antibiotika treba biti normatirana zbog njihove široke zloupotrebe i globalnog pojavljivanja rezistencije organizama na antibiotike.

Ovo je revijalni članak o principima i racionalnoj antimikrobnoj terapiji, ciljevima terapije, načinu davanja lekova i raznim antibioticima koji se daju u terapiji parodontalnog oboljenja. Dostupni podaci generalno pokazuju da je dovoljan samo mehanički tretman parodontopatije za poboljšanje ili rešavanje kliničkih stanja u najvećem broju slučajeva, ali i da sistemski primenjeni antimikrobni lekovi mogu dodatno poboljšati efekat terapije u specifičnim slučajevima. Ovo je naročito važno za agresivnu parodontopatiju, kako kod bolesnika sa nekim opštim sistemskim oboljenjem, koje može uticati na domaćinovu otpornost, tako i u slučajevima smanjenog odgovora domaćina na konvencionalnu mehaničku terapiju.

Ovaj članak pruža novine u terapiji parodontopatije, koje se ogledaju u sistemskoj primeni antibiotika.

Ključne reči: antibiotici, parodontopatija, terapija, metronidazol, tetraciklini, klindamicin