

# Systemic antibiotics in periodontal therapy

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## ABSTRACT

Periodontitis is a biofilm infection with a mixed microbial aetiology. Periodontitis is generally treated by non-surgical mechanical debridement and regular periodontal maintenance care. Periodontal surgery may be indicated for some patients to improve access to the root surface for mechanical debridement. A range of systemic antibiotics for treatment of periodontitis has been documented, with some studies showing superior clinical outcomes following adjunctive antibiotics while others do not. This has resulted in controversy as to the role of systemic antibiotics in the treatment of periodontal diseases. Recent systematic reviews have provided an evidence-based assessment of the possible benefits of adjunctive antibiotics in periodontal therapy. This review aims to provide an update on clinical issues of when and how to prescribe systemic antibiotics in periodontal therapy.

**Keywords:** Systemic antibiotics, periodontal disease, treatment, aggressive periodontitis, chronic periodontitis.

## INTRODUCTION

This review aims to provide the clinician with an update on the current literature regarding the use of systemic antibiotics in periodontal therapy. While the use of systemic antimicrobials for treatment of periodontitis has been controversial, the recent publication of two systematic reviews<sup>1,2</sup> has provided an unbiased evidence-based assessment of the possible benefits of systemic antibiotics. This paper will discuss some important clinical questions regarding when and how to use systemic antibiotics for the treatment of periodontal disease.

### **Understanding the principles of using antibiotics for treating periodontitis: what is the significance of the periodontal biofilm when prescribing systemic antibiotics?**

Periodontitis is an infection caused by bacteria residing in biofilms at or below the gingival margin (Fig 1). It is, therefore, not surprising that a wide range of systemic antibiotics have been used as part of periodontal treatment aimed at targeting potential pathogenic bacterial species within the periodontal biofilm.

The complex structure of the periodontal biofilm, consisting of multiple bacterial communities residing in a glycocalyx matrix, has been well described by Marsh *et al.*<sup>3</sup> It has been demonstrated that once bacteria attach to a tooth surface and reside within a mature

biofilm structure they have a reduced susceptibility to antimicrobials compared to planktonic or free floating bacteria.<sup>4</sup> Hence mechanical debridement is considered critical to disrupt the biofilm when using systemic antibiotics to treat periodontitis. The rationale for use of adjunctive systemic antimicrobials is to further reduce the bacterial load enabling resolution of the inflammation in the periodontal pocket.

### **Should antibiotics be used as a monotherapy in the treatment of periodontitis?**

The question as to whether antibiotics prescribed as a monotherapy, with no mechanical debridement, are efficacious in the treatment of periodontitis was addressed in a systematic review by Haffajee *et al.*<sup>2</sup> From the results of four studies evaluating metronidazole alone<sup>5,6</sup> or metronidazole combined with amoxicillin as monotherapy<sup>7,8</sup> it was concluded that the effect of the antibiotic alone was minimal and short term. The majority of studies do not support the concept of monotherapy with inferior results in terms of probing depth reduction, clinical attachment level gain and reduction in bleeding compared with scaling and root planing.<sup>9–11</sup> Furthermore, Topoll *et al.*<sup>12</sup> reported development of multiple periodontal abscesses in patients with advanced periodontal disease who had been prescribed systemic antibiotic therapy without subgingival debridement. The patients had received broad-spectrum oral antibiotics (penicillin and



**Fig 1.** Chronic periodontitis: deep probing depths, abundant supra- and subgingival biofilm.

tetracycline) one to three weeks prior to the development of abscesses. It was concluded that in patients with advanced periodontal disease, systemic antibiotic therapy without subgingival debridement might change the composition of the subgingival microbiota, resulting in multiple periodontal abscesses.

Two recent studies<sup>13,14</sup> created a great deal of discussion in the periodontal community when they showed similar clinical results for scaling and root planing as for antibiotics (amoxicillin plus metronidazole) prescribed as a monotherapy. Lopez and Gamonal<sup>14</sup> provided only short term, four month, microbiological and clinical results, and Lopez *et al.*<sup>13</sup> compared supragingival scaling and antibiotic with subgingival scaling and root planing and placebo. The authors suggested that this treatment approach could be used in populations with no or limited access to dental care. However, the results of these studies are not supported by the rest of the literature and should be interpreted with caution. Furthermore, the risks of side effects and development of antimicrobial resistance need to be considered. Thus, mechanical debridement ensuring adequate disruption of the biofilm continues to be regarded as the appropriate treatment approach when prescribing systemic antibiotics.

### **Do adjunctive systemic antibiotics offer an advantage over non-surgical mechanical therapy alone for the treatment of chronic periodontitis?**

It has been well documented that the majority of patients diagnosed with chronic periodontitis can be successfully treated following mechanical debridement, adequate oral hygiene and regular maintenance care.<sup>15,16</sup> At the fourth European Workshop, a systematic review by Herrera *et al.* concluded that systemic antibiotics used in conjunction with scaling and root planing can offer an additional benefit over scaling and

root planing alone in terms of probing depth reduction (0.4 mm, spiramycin) and clinical attachment level gain (0.5 mm, combination of amoxicillin and metronidazole) in pockets of 6 mm or deeper.<sup>1</sup> Similar findings were reported in the systematic review by Haffajee *et al.*<sup>2</sup>

### **Do adjunctive systemic antibiotics offer an advantage over surgical mechanical therapy alone?**

Periodontal surgery may be indicated where there is inadequate access for effective mechanical debridement. A systematic review by Haffajee *et al.* reported an additional clinical benefit in attachment level gain (weighted mean gain 0.6 mm) when systemic antibiotics were prescribed as an adjunct to surgical mechanical debridement in deep pockets.<sup>2</sup> In this meta-analysis the authors pooled results of three studies<sup>17-19</sup> using different antibiotics (penicillin, tetracycline, amoxicillin plus clavulanate) comparing periodontal surgery plus antibiotic versus periodontal surgery plus placebo. However, the most recent review of the literature by Herrera *et al.* concluded that there was insufficient data as to whether adjunctive antibiotics were beneficial when combined with periodontal surgery.<sup>20</sup>

### **Does operator experience influence the quality of debridement?**

If we recognize the importance of disruption of the periodontal biofilm, the quality of debridement is likely to have an influence on the treatment outcome. There is indirect evidence that when antibiotics are prescribed in conjunction with mechanical debridement the level of experience of the operator enhances clinical improvements. Periodontists taking three to four hours for treatment (using local anaesthesia where required) obtained significant clinical improvements following adjunctive antibiotics (amoxicillin and metronidazole) when compared with scaling and root planing without antibiotics.<sup>21,22</sup> In contrast, less experienced clinicians did not find significant differences.<sup>23</sup>

### **Choice of systemic antibiotic – which antibiotic is the best to use?**

Therapeutic success of an antimicrobial depends on the activity of the antimicrobial agent against the infecting organisms. Periodontitis is a mixed microbial infection making the choice of antibiotic regimen difficult. Certain antibiotics target specific parts of the subgingival biofilm. For example, metronidazole targets the gram-negative strict anaerobes from the red and orange Socransky complexes<sup>24</sup> such as *Fusobacterium nucleatum*, *Tanarella forsythia*, *Porphyromonas gingivalis*

and *Treponema denticola*, while members of the genera *Actinomyces*, *Streptococcus* and *Capnocytophaga* are minimally affected by metronidazole. Metronidazole also has a limited effect on the species *Aggregatibacter actinomycetemcomitans*, which is a facultative anaerobe rather than a strict anaerobe. Amoxicillin has a broader spectrum lowering counts of gram negative anaerobes as well as decreasing the counts and proportions of *Actinomyces* species during and after antibiotic therapy.<sup>25</sup> Micro-organisms can be intrinsically resistant to antimicrobials or can develop acquired resistance by emergence of resistant strains of bacteria that would otherwise be considered to be sensitive to the antimicrobial.

The literature reports a wide range of antibiotics used in conjunction with non-surgical and surgical mechanical debridement for the treatment of both chronic and aggressive periodontitis. The most commonly used antibiotics include tetracyclines, penicillins (amoxicillin), metronidazole, macrolides (spiramycin, erythromycin, azithromycin), clindamycin and ciprofloxacin. The most common combination antibiotic regimen reported is metronidazole and amoxicillin combined. Table 1 lists common antibiotic regimens documented in the literature for the treatment of periodontitis. It is apparent that the literature does not provide a clear indication of the superiority of one antibiotic regimen over another and the choice of antibiotic should be made on an individual basis.

### What is the ideal duration, dosage and timing of the antibiotic?

The dosage and duration of the antibiotic prescribed also varies widely among studies and there is no consensus on the ideal regimen. In principle it is important to prescribe an antibiotic in sufficient dose for adequate duration.

Another important clinical question is when to start the antibiotics in relation to the mechanical phase of treatment. Indirect evidence suggests that antibiotic intake should start on the day of debridement completion and debridement should be completed within a short period of time (< 1 week).<sup>20</sup>

### How critical is patient compliance when using adjunctive antibiotics?

The issue of patient compliance has been infrequently addressed in publications evaluating the effects of systemic antibiotics. Some studies have shown that as little as 20 per cent of patients comply with antibiotic regimens prescribed.<sup>26</sup>

One advantage of the antibiotic azithromycin may be that due to its pharmacologic properties and long half life, only one tablet (500 mg) per day during three consecutive days is required as opposed to one tablet three times a day for seven days with other antibiotic regimens.<sup>27</sup>

Compliance in terms of oral hygiene and maintenance care should also be addressed. It should be recognized that in studies where beneficial results following adjunctive antibiotics were reported, patients had received maintenance care and had good plaque control. If a patient was non-compliant with oral hygiene measures and maintenance protocols, then a favourable treatment outcome following adjunctive antibiotics was unlikely. Prescription of antibiotics is no substitute for adequate debridement, good oral hygiene and regular maintenance care.

### Are adjunctive systemic antibiotics useful for the treatment of aggressive periodontitis?

Aggressive periodontitis is a form of periodontitis where there is a rapid progression of disease in either a localized or generalized pattern affecting otherwise healthy individuals.<sup>28</sup> Aggressive periodontitis is frequently associated with the presence of high levels of subgingival *Aggregatibacter actinomycetemcomitans*, *A.a* (formerly *Actinobacillus actinomycetemcomitans*) and/or *Porphyromonas gingivalis*, *P.g*. It has been shown that adjunctive antibiotics may be required to eradicate or suppress these pathogens, which have the potential to invade the periodontal tissues. In the systematic review by Herrera *et al.* it was concluded that adjunctive systemic antibiotics should be considered in cases of aggressive periodontitis.<sup>1</sup> A recent randomized clinical trial found that the adjunctive use

**Table 1. Examples of antibiotic regimens documented for treatment of periodontitis**

Antibiotic	Antibiotic regimen	Periodontal disease as described by authors	First author/year
tetracycline	250 mg, 4 × day, 14 days	advanced chronic periodontitis	Al Joburi, 1989 <sup>38</sup>
doxycycline	200 mg, 1 × day, 8 days	generalized rapidly progressive periodontitis	Siguschi, 2001 <sup>39</sup>
spiramycin	1.5 UI, 2 × day, 14 days	advanced periodontal disease	Bain, 1994 <sup>40</sup>
azithromycin	500 mg, 1 × day, 3 days	aggressive periodontitis	Haas, 2008 <sup>29</sup>
metronidazole	250 mg, 3 × day, 7 days	periodontitis > 10% spirochetes	Loesche, 1984 <sup>41</sup>
clindamycin	150 mg, 4 × day, 10 days	refractory periodontitis	Walker, 1993 <sup>42</sup>
amoxicillin and metronidazole	375 mg, 3 × day, 8 days	chronic periodontitis	Flemmig, 1998 <sup>43</sup>
	250 mg, 3 × day, 8 days	presence of <i>A.a</i> , <i>P.g</i>	

of azithromycin has the potential to improve the treatment outcome in young patients with aggressive periodontitis compared to non-surgical debridement alone.<sup>29</sup> Due to the rapid progression of the disease it is advisable to refer patients diagnosed with aggressive periodontitis for specialist treatment.

### Should antibiotics be used when regenerative periodontal therapy is attempted?

Studies evaluating periodontal regenerative procedures using either barrier membrane technique (guided tissue regeneration) or enamel matrix proteins (Emdogain®) commonly use adjunctive systemic antibiotics. The rationale for use of the antibiotics is to prevent post-surgical infection, particularly if membrane exposure occurs and to optimize the potential for regeneration. There is, however, very limited evidence for the additional benefit of systemic antibiotics for the regenerative outcome. Studies investigating the regenerative outcomes with enamel matrix derivatives have found no added benefit when antibiotics were prescribed.<sup>30,31</sup>

### Periodontal abscess – should systemic antibiotics be prescribed?

The periodontal abscess is a lesion with extensive periodontal breakdown occurring during a short period of time with localized accumulation of pus.<sup>32</sup> This condition may cause systemic involvement and the lesion generally has a large bacterial mass with a high prevalence of well-recognized periodontal pathogens. The periodontal abscess may occur in untreated periodontitis patients or in treated patients in maintenance therapy. The role of systemic antibiotics in the treatment of the periodontal abscess is controversial. Some authors advocate use of systemic antibiotics in combination with mechanical debridement or drainage.<sup>33</sup> Others recommend systemic antibiotics only if a clear systemic involvement is present such as lymphadenopathy, fever or malaise or when the infection is not well localized.<sup>34</sup> Mechanical debridement and drainage through the periodontal pocket without antibiotics is usually effective in the management of the periodontal abscess (Figs 2 and 3).

### Necrotizing periodontal diseases – should systemic antibiotics be prescribed?

Necrotizing gingivitis and necrotising periodontitis are infections showing clinical signs of necrosis and ulceration of the gingival margin and interdental papilla. They are associated with pain, spontaneous gingival bleeding and halitosis. The predisposing factors associated with the onset and progression of necrotizing periodontal diseases include immunodeficiency, mal-

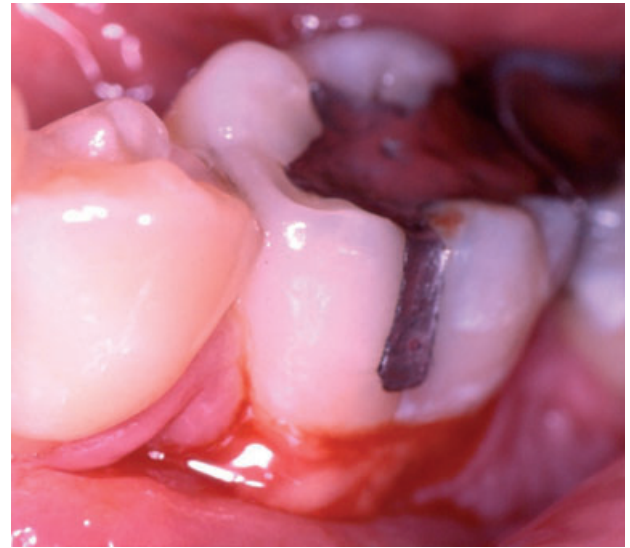


Fig 2. Periodontal abscess: 11 mm probing depth, suppuration and bleeding.



Fig 3. Healing following mechanical debridement without the use of adjunctive systemic antibiotics. Resolution of the deep probing depth, mesiobuccal gingival recession.

nutrition, stress, smoking and poor oral hygiene.<sup>28</sup> Treatment involves debridement, oral rinses, oral hygiene and management of pain. When there are systemic manifestations such as fever or malaise metronidazole, targeting the gram negative anaerobes, should be prescribed in conjunction with mechanical debridement.

### What are the common side effects following systemic antibiotics?

Within the literature there is a general lack of reporting on the presence or absence of adverse events following the adjunctive use of systemic antibiotics. Most adverse effects, which have been reported, are minor and related to gastrointestinal problems such as diarrhoea and nausea.

However, serious adverse events such as allergic and anaphylactic reaction and pseudomembranous colitis,

may occur and patients should be informed of the potential for adverse events both minor and major when prescribing systemic antibiotics. Anaphylactic responses to penicillin occur approximately once every 10 000 courses administered, with 10 per cent of these being fatal.<sup>35</sup> The use of antibiotics should be carefully considered choosing agents that maximize antimicrobial activity and minimize potential drug interactions and adverse reactions. A thorough medical history should be taken prior to antibiotic prescription.

An increase in microbial resistance following the use of systemic antibiotics has been evaluated in few studies. Feres *et al.*<sup>36</sup> identified antibiotic-resistant species in subgingival plaque and saliva samples from chronic periodontitis patients treated by scaling and root planing followed by orally administered amoxicillin or metronidazole. There was an increase in the percentage of resistant subgingival species following antibiotic administration. However, levels returned to baseline after a relatively short period of time (90 days).<sup>36</sup>

In Spain, where systemic antibiotics are readily available over the counter without prescription and widely used in the general population, it has been shown that there was an increase in the microbial resistance patterns of oral bacteria to commonly prescribed antibiotics compared to the Netherlands where antibiotics use is more restricted.<sup>37</sup> This underlines the importance of development of microbial resistance to antibiotics and the importance of responsible use to prevent the global spread of resistant strains of bacteria.

## CONCLUSIONS

Systemic antibiotics should not be prescribed as a monotherapy for the treatment of periodontitis. Systemic antibiotics are useful antimicrobial agents for the management of periodontal diseases when used in conjunction with adequate mechanical debridement for disruption of the subgingival biofilm. There is no consensus as to the ideal antibiotic, dose, duration and timing of antibiotics. Adjunctive systemic antibiotics should be considered in cases of aggressive periodontitis. While the literature shows an added clinical benefit following adjunctive systemic antibiotics for the treatment of chronic periodontitis in deep pockets, the decision to prescribe antibiotics should be made on an individual basis. The extent and severity of the periodontal disease as well as plaque control and patient compliance issues should be addressed.

The patients' medical history with respect to drug allergies and current medications must be considered. Patients should be well informed as to the possible side effects and drug interactions that may arise following systemic antibiotics.

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