# Chapter 6 Systemic and Local Drug Delivery of Antimicrobials

## INTRODUCTION

The recognition of the importance of bacteria as etiologic agents of periodontal disease and the seminal studies of previous decades which identified key pathogens have led to numerous investigations into the role of antibiotics in periodontal treatment. Unfortunately, due to differences of these studies in design, duration, antibiotic class and dosage, concomitant mechanical treatment, and disease classification, the extrapolation of concise conclusions is not easy, as several authors in the field have noted. In addition, during the last two decades, advances in laboratory technology have provided new insight about the structure and properties of the subgingival biofilm and its resistance to antimicrobials and raised questions about their efficacy. The above-mentioned parameters combined with the emerging global threat of antimicrobial resistance and the well known side effects or adverse reactions during antibiotic administration have developed a trend among clinicians for more cautious prescription of this class of drugs.

Knowledge of the disadvantages of systematic administration of antibiotics and difficulties in patient compliance (especially in long-term regimens) have also prompted researchers to develop several local delivery systems in periodontology, i.e., antimicrobial agents embodied in excipients for direct placement and action in periodontal pockets. Due to advanced material technology, several compounds are available for clinicians and a number of studies have evaluated their effects on periodontal conditions.



This chapter focuses on evidence-based systemic and local administration of antibiotics in periodontology and provides guidelines for their indications, according to current evidence and documentation.

## EVIDENCE-BASED OUTCOMES

Current major issues of concern among clinicians include the following: Can antibiotics be considered as a sole therapy for periodontal diseases? Are there adjunctive benefits to conventional mechanical treatment or periodontal surgery? Can antibiotics enhance periodontal regeneration or treat acute periodontal conditions? In this section, we review current evidence which should guide clinicians to indications and methods of delivery.

The issue of using antibiotics as monotherapy to treat periodontal disease has been addressed in several studies. Current data regarding biofilm structure and resistance to antimicrobials show that subgingival biofilms can be more effectively controlled when they are mechanically disrupted. When their dense structure has been altered and the huge number of bacteria diminished, the antimicrobials have the potential to better diffuse and eliminate the microbial target (Socransky and Haffajee, 2002). In addition, antimicrobial activity has been shown to be more effective in "young" and not well organized biofilms. In the Sixth European Workshop on Periodontology, in 2008, Herrera and coworkers addressed the question of whether systemic antimicrobials can be efficacious if the biofilm is not disrupted. The authors reviewed the existing literature and concluded, in agreement with previous position papers and systematic reviews (AAP, 1996; Haffajee et al., 2003), that clinicians should not consider antibiotics as a sole therapy for periodontal diseases and that antibiotics should be combined with mechanical means of disrupting or removing biofilms in gingival sulci and pockets. Therefore, currently, clinicians should act based on good medical practice and administer systemic antibiotics as adjuncts rather than as the main and sole therapy.



As mentioned above, although numerous studies have tested the role of systematic administration of antimicrobials in patients with chronic, aggressive, and refractory periodontitis, several discrepancies among them preclude the comparison and classification of their results and the extrapolation of guidelines. Although as many as 1,300 reports in the literature refer to systemic antibiotics in periodontology, fewer than 30 fulfilled the scientifically sound criteria set by Herrera et al. (2002) for the Fourth European Workshop and Haffajee et al. (2003) for the World Workshop to be included in meta-analysis.

For further comprehensive presentation and comparison of the various studies, the reader is referred to the above mentioned two recent reports, to excellent relevant reviews (Slots and Rams, 1990; van Winkelhoff et al., 1996, Slots and Ting, 2002; Slots 2002a,b, 2004), the previous reports of the American Academy of Periodontology (1996), and previous Workshops of the European Federation of Periodontology (van Winkelhoff et al., 1993).

Today, scientifically sound clinical studies should be designed as randomized clinical trials (RCTs) with the inclusion of controls, a duration of at least six months, and in accordance with strictly defined criteria and statistical analysis as described in the Consolidated Standards for Reporting Trials

(CONSORT) statement (Altman et al., 2001). Therefore, clinicians are encouraged to thoroughly examine the design of scientific trials on antibiotics before considering their conclusions.

Historically, clinical studies regarding the benefits of the systematic administration of antimicrobials in periodontology began in the late 1970s and initially referred to patients with localized juvenile periodontitis (LJP), a disease which partially coincides with localized aggressive periodontitis. In the classical studies of the 1980s and '90s, both in the U.S. and Scandinavia, it has been shown that in LJP patients, systemic administration of antibiotics (the tetracyclines and metronidazole) can improve clinical parameters and decrease the pathogenic subgingival microflora, especially *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans* (Slots and Rosling, 1983; Saxen et al., 1990; Saxen and Asikainen, 1993). The efficiency of the combined systemic administration of metronidazole and amoxicillin in LJP patients was investigated by van Winkelhoff et al. (1989), who have shown an improvement of clinical parameters and elimination of *A. actinomycetemcomitans* for at least nine months and therefore introduced this regimen in other classes of periodontal diseases.

For chronic periodontitis patients, who make up the majority in clinical practice, practitioners should currently comply with the most recent reports and meta-analyses, which generally and under confinements suggest benefits from the systematic administration of antimicrobials in chronic periodontitis, using as clinical evaluation the index probing attachment level (PAL). The Herrera et al. (2002) and Haffajee et al. (2003) reports concluded that the administration of antibiotics improves the mean attachment level in patients with chronic periodontitis when used as adjuncts to scaling and root planing. In both reports, at that time, it was stated that existing data precluded their ability to configure guidelines for clinicians concerning the most efficient antibiotic regimen and the appropriate time for administration (before, during, or after the initial treatment phase).

Current data concerning the impact of the quality of debridement and the sequence of antibiotic usage on clinical parameters were also analyzed in the recent report of the Sixth European Workshop on Periodontology (Herrera et al., 2008). After combining evidence in the literature, the authors suggest that if antibiotics are to be used as adjuncts, there is indirect evidence that they should be administered on the day of completion of debridement, which preferably should be performed in a short time and be of adequate quality to optimize clinical benefits for patients. Therefore, according to existing evidence, when treating chronic periodontitis patients, a meticulous debridement by a highly skilled operator should be performed in less than a week, preferably, and antibiotics—if administered—should be prescribed immediately afterward. Both strategies aim at avoiding the reorganization of the disrupted biofilm and achieving a shift in the subgingival microflora compatible with periodontal health. The results of this combined treatment include a reduction of prevalence, levels, and proportions of pathogenic species such as *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola*; members of the "red complex" and gram-negative anaerobic species; and members of the "orange complex" described by Socransky et al. (1998), as well as an increase of *Streptococcus* and *Actinomyces* spp.

The report by Haffajee et al. (2006) describes the effect of various periodontal therapies (including antibiotic use) on the subgingival microflora. Data from more than 400 periodontal patients who participated in longitudinal studies conducted over a decade by the Department of Periodontology at the Forsyth Institute were combined to evaluate clinical and microbiological effects of therapies adjunctive to scaling and root planing for up to 24 months. The analysis of more than 10,000 subgingival samples for 40 bacterial species by "checkerboard" DNA-DNA hybridization developed by Socransky and coworkers (1994) in the same department provides very significant insight into the changes of the subgingival habitat induced by various treatments, including periodontal surgery and antibiotic administration. Data from this important report have shown, among others, that the addition of various systemic antibiotics enhanced clinical and microbiological effects of mechanical treatment for up to 24 months. These benefits have been attributed by the authors to several factors, including the reduction of the total bacterial load in the oral cavity and thus the possibility of reinfection, as well as the reduction of specific periodontal pathogens in the pocket environment. Although the main microbiological outcome in this report appears to be the reduction of levels, proportions, and percentages of sites colonized by important periodontal pathogens, they are seldom eliminated and can regrow over time, especially without maintenance care.

After reviewing the literature, the evidence referring to antibiotic effects on patients diagnosed with early-onset or rapidly progressive periodontitis (earlier studies) or aggressive periodontitis (newer studies) is more solid. These patients generally seem to gain further clinical and/or microbiological benefits by the systematic administration of several antimicrobials (metronidazole, tetracyclines, clindamycin, a combination of metronidazole and amoxicillin). These conclusions have been shown in both the Herrera et al. (2002) and the Haffajee et al. (2003) reports after meta-analysis of well-designed studies and in newer RCTs (Guerrero et al., 2005; Xajigeorgiou et al., 2006).

Combining the above findings, it appears that in patients with a diagnosis of aggressive periodontitis, where the genetic background and immunity factors predispose for severe periodontal destruction, optimum control of the bacterial load

and periodontal pathogens is extremely important, and from this point of view administration of antimicrobials is indicated for patients in this category.

The results of clinical studies concerning the systematic administration of antimicrobials in combination with periodontal surgery to eliminate the pockets or to achieve periodontal regeneration are contradictory. It is known that antimicrobials can be useful for preventing post-surgical complications. In this case, antibiotic coverage usually targets bacteria that can cause transfections, although for periodontal surgery there are no studies confirming the necessity of antimicrobial administration. It is suggested that sterile conditions and antiseptic mouthwashes can be efficient in preventing complications (Newman and van Winkelhoff, 2001; Konstantinidis, 2007).

Findings concerning the clinical benefits of the combined use of antimicrobials with surgical periodontal treatment are controversial. Based on the limited data in the literature, both the Haffajee et al. (2003) and Herrera et al. (2008) reports suggest marginal or insufficient evidence for additional clinical benefits from periodontal surgery when combined with systemic antimicrobials.

The combination of guided tissue regeneration (GTR) with the administration of several antimicrobial regimens also does not appear to uniformly offer stable beneficial clinical outcomes, neither to efficiently prevent bacterial colonization nor to prevent complications (Demolon et al., 1993; Zuchelli et al., 1999; Vest et al., 1999; Loos et al., 2002). The recent relevant report of the Sixth European Workshop states that there is no sufficient evidence to support the administration of antibiotics during regenerative procedures.

At this point, it should be emphasized, the microflora of patients with deep periodontal pockets, especially after the repeated administration of antimicrobials, can include non-oral gram-negative species such as enteric rods and *Pseudomonas* spp., where the administration of other classes of antimicrobials such as the quinolones are indicated (Slots et al., 1990; Rams et al., 1992). In this group of patients the administration of a combination of metronidazole and ciprofloxacin appears to provide additional clinical improvement. Antimicrobials also have been administrated for acute inflammatory conditions of the periodontal tissues, such as periodontal abscess, necrotizing ulcerative gingivitis (NUG) or periodontitis (NUP), and peri-implantitis.

In the previous century, antiseptics were used for the treatment of NUG, while in the 1960s it was confirmed that the systematic administration of penicillin or metronidazole could contribute to the management of the acute phase of inflammation, especially when systemic manifestations such as fever, malaise, and lymphadenitis are present (Fletcher and Plant, 1966; Collins, 1970). Clinical cases without these symptoms can be adequately managed with no antimicrobials (Holmstrup and Westergaard, 2003).

The frequent occurrence of NUG in patients who are HIV-positive raised the question about the necessity of administration of antimicrobials in this patient category. According to the latest findings there is no need for antimicrobial coverage of this group if generalized symptoms are absent. In addition, the possibility of *Candida* spp. infection as a side effect of systemic antimicrobial administration suggests that antibiotics should be prescribed with caution and after consulting the physician (Konstantinidis, 2007).

There is insufficient or contradictory evidence in the literature to document the necessity of antimicrobial administration for treatment of acute periodontal abscess. Existing studies are usually case reports and there are no comparative studies that demonstrate adjunctive benefits from systemic antimicrobials. Generally, in the case of acute periodontal abscess, antimicrobials are considered necessary when the abscess is very extended, diffused, and accompanied by intense pain and/or coexisting compromising medical conditions and systemic manifestations. The combination of drainage with systemic administration of penicillin, hydrochloric tetracycline, or metronidazole was found efficient for the management of the acute conditions, while the combination of amoxicillin/clavulanic and the newer macrolide azithromycin resulted in recovery from acute symptoms without the simultaneous initial drainage of the abscess (Palmer, 1984; Smith and Davies, 1986; Genco, 1991; Herrera et al., 2000a). In any event, according to good medical practice, the initial drainage or surgical fission of the periodontal abscess is considered the necessary first step for managing its acute phase (AAP, 2000; Herrera, 2000b).

Limited documentation also exists about the use of antimicrobials in peri-implantitis, an infection in which there are no established treatment protocols. Existing data from animal and human studies support a positive contribution of the systemic administration of antimicrobials, especially nitroimidazoles or the combination of amoxicillin and metronidazole (Mombelli and Lang, 1998; Mombelli, 2002).

In addition, there is insufficient scientific documentation about administering antimicrobials to prevent complications during dental implant surgery. Two relative studies present controversial results. The Swedish study questions the need for antimicrobial use to prevent post-surgical complications (Gynther et al., 1998), while the American study indicates that the administration of antimicrobials is related to lower percentages of implant failures (Laskin et al., 2000). Nevertheless, because there are no RCTs on this issue, in everyday practice, clinicians usually prescribe antibiotics for implant placement based on the possibility of a complication and less on scientific documentation.

It should be pointed out that the above-mentioned data refer to systemically healthy individuals, whereas the approach for medically compromised subjects is modified. In addition, certain medical conditions require antimicrobial prophylaxis for all periodontal procedures, as will be described in the indications and technique sections below.

Data in the literature regarding evidence-based outcomes of local delivery systems in periodontology are far more limited. Most of the existing systems were originally tested in split-mouth models as monotherapy and compared to scaling and root-planing or no treatment and then as adjuncts to mechanical treatment, mainly in chronic periodontitis patients. These systems were usually applied at the initial treatment phase or during supportive treatment. A systematic review by Hanes and Purvis (2003) has evaluated existing evidence concerning pharmacological agents applied locally in chronic periodontitis patients. They reported that after meta-analysis of 19 studies, the adjunctive use of minocycline gel, minocycline in microspheres, chlorhexidine chip, and doxycycline gel results in significant probing depth reduction and probing attachment level gain compared to mechanical treatment alone, and therefore carefully concluded that in some populations these sustained-release systems, but not irrigations, can reduce probing depth and bleeding on probing equivalent to scaling and root planing.

## INDICATIONS

The indications for prescribing systemic antibiotics in periodontology are listed in Table 6.1 and are guided by combining current data and evidence in the literature and the current trend in the medical community to limit antibiotic use under the global threat of antimicrobial resistance. Clinicians are encouraged to constantly review the literature for updated information on this important aspect of periodontal therapy.



**Table 6.1.** Evidence-based indications for systemic antibiotics in periodontology.

| | |
|---|---|
| Chronic periodontitis | — Advanced chronic periodontitis<br>— Refractory<br>— Generalized recurrence during supportive treatment |
| Aggressive periodontitis | — Localized or generalized<br>— Refractory<br>— Generalized recurrence during supportive treatment |
| Acute periodontal abscess | When generalized symptoms are present |
| Necrotizing gingivitis | When generalized symptoms are present |
| Necrotizing periodontitis | |
| Peri-implantitis | |

For all periodontal procedures (including periodontal charting) in medically compromised individuals, clinicians should carefully review the subject's medical history and consult with the physician. Specific medical conditions require antibiotic prophylaxis and practitioners should comply with revised, periodically issued guidelines from scientific societies. The British Society for Antimicrobial Chemotherapy (2006) and the American Heart Association (2007) have revised their guidelines for antimicrobial chemoprophylaxis during dental procedures after carefully reviewing evidence about the correlation of dental procedures with infective endocarditis (Gould et al., 2006; Wilson et al., 2007). Both scientific societies have limited the cardiological conditions requiring chemoprophylaxis but increased the spectrum of dental procedures in which antibiotics should be prescribed. These indications, the dental procedures, and the recommended regimens are presented in Tables 6.2 and 6.3. Regarding local delivery systems, the main indication currently remains residual or recurrent pockets during supportive periodontal therapy, according to existing data in the literature.



## TECHNIQUES

The antibiotic regimens usually prescribed in periodontology for indications listed above are presented in Table 6.4. It should be noted that differences exist between various countries, according to the manufacturing company. Regarding local delivery systems, clinicians should be aware of advantages of their use as presented in Table 6.5.

Other factors to be considered by clinicians when choosing a local delivery system include the antimicrobial agent that it contains, the initial concentration and pharmacokinetics of this agent in the periodontal pocket environment, and the form, structure, and chemical properties of the excipient which regulate the time and rate of delivery of the antimicrobial (Goodson, 1996). It must remembered that the initial efforts to deliver antimicrobials by subgingival irrigations (Rams and Slots, 1996) had limited clinical results, while the incorporation of antimicrobial substances in polymers ensured a more stable rate of diffusion and release and therefore a more predictable presence of active concentration of the antimicrobials for efficient time in the subgingival environment. The anatomy of the pocket region and the restriction of antimicrobial activity in a confined area of the body are favorable for these systems but the continuous flow of the gingival crevicular fluid is a major challenge to be overcome by the biomaterials technology and, more recently, nanotechnology (Goodson, 2003).

The most widely known local delivery systems are presented in Table 6.6. Tetracycline fibers, the only system with zero

**Table 6.2.** Dental procedures and cardiac conditions for which antibiotic prophylaxis is required.

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**Table 6.3.** Regimens for a dental procedure.



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**Table 6.4.** Antibiotic regimens for periodontal conditions (when indicated).

**A. Periodontitis**

| Antimicrobial | Dosage |
|---|---|
| Metronidazole | 500 mgr/8 hours for 7 days |
| Tetracycline | 250 mgr/6 hours for 21 days |
| Doxycycline | 200 mgr the first day |
| | 100 mgr/24 hours for 21 days |
| Minocycline | 200 mgr the first day |
| | 100 mgr/24 hours for 21 days |
| Clindamycin | 100 mgr/12 hours for 21 days |
| Metronidazole and ciprofloxacin | 500 mgr each/8 hours for 7 days |
| Metronidazole and amoxicillin | 500 mgr each/8 hours for 7 days |

**B. Periodontal abscess (a), necrotic ulcerative gingivitis (b), peri-implantitis (c)**

| Antimicrobial | Dosage |
|---|---|
| Metronidazole (a, b, c) | 500 mgr/8 hours for 7 days |
| Amoxicillin (a) | 500 mgr/6 hours for 7 days |
| Amoxicillin and clavulanic acid (a) | 625 mgr/12 hours for 7 days |
| Clarithromycin (a) | 250 mgr/12 hours for 7 days |
| Metronidazole and amoxicillin (c) | 500 mgr each/8 hours for 7 days |

**Table 6.5.** Advantages of local delivery antimicrobial systems.

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|---|
| Release rate of antimicrobials that ensures therapeutic results |
| Reduction of toxicity and side effects of systematic delivery |
| Difficulty in antimicrobial agent decomposition |
| Patient compliance |
| (Possibly) lower cost and lower waste of antimicrobials |

order kinetics and thus with stable concentration of the antibiotic for the 10 days that they remain in the pocket environment, are not currently available on the market and they are the only system that requires physical removal of the system, since they are non-degradable. All of the other systems listed in the table are degradable and user-friendly because they are applied subgingivally either with a blunt needle that is provided or with a blunt instrument in the case of periochip.

## AUTHOR'S VIEWS/COMMENTS

Therapeutic planning in contemporary periodontology should be driven by scientific evidence. The use of antibiotics, especially systemic ones, has been a matter of debate and contradictory findings for several years. Clinicians should be aware that currently only results from well organized randomized clinical trials should be taken into consideration. Periodically issued systematic reviews and meta-analyses provide data and guidelines useful for clinical practice. The current trend in the medical and dental community to confine the use of antimicrobial agents should also apply to contemporary periodontology and therefore, they should be considered as adjuncts and not substitutes for proper mechanical treatment. Because specific clinical situations or certain microbiological profiles appear to benefit from adjunctive antimicrobials, in the future, a personalized antibiotic regimen, preferably after microbial analysis, could be a desirable target.



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**Table 6.6.** Local delivery systems in periodontology.

| System | Antimicrobial | Form | Initial concentration in GCF | Biodegradability |
|---|---|---|---|---|
| Actisite | Chlortetracycline | Fiber | 1,300 μgr/ml | – |
| Elyzol | Metronidazole | Gel | 461 μgr/ml | + |
| Periochip | Chlorhexidine | Chip | 500 ppm | + |
| Atridox | Doxycycline | Gel | 148 μgr/ml | + |
| Arestin | Minocycline | Microspheres | 340 μgr/ml | + |