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Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm

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Abstract

Objectives: The aim was to answer three relevant questions: can systemic antimicrobials be efficacious if the biofilm is not disrupted? Can the type of debridement of the subgingival biofilm impact upon the clinical outcomes of the adjunctive antimicrobial therapy? Is the efficacy of the adjunctive systemic antimicrobial therapy dependent on the quality of the debridement of the subgingival biofilm and the sequence debridement–antibiotic usage?

Material and Methods: Relevant papers were searched, critically analysed and their data were extracted.

Results: For the first question, studies assessing susceptibility of bacteria in biofilms, and clinical studies evaluating systemic antimicrobials as monotherapy, were reviewed. For the second question, clinical studies comparing systemic antimicrobials as adjuncts to non-surgical debridement or to periodontal surgery and clinical trials using systemic antibiotics with periodontal surgery were evaluated. For the third question, a previous systematic review was updated.

Conclusion: If systemic antimicrobials are indicated in periodontal therapy, they should be adjunctive to mechanical debridement. There is not enough evidence to support their use with periodontal surgery. Indirect evidence suggests that antibiotic intake should start on the day of debridement completion, debridement should be completed within a short time (preferably <1 week) and with an adequate quality, to optimize the results.

Key words: biofilm; non-surgical; periodontitis; surgical therapy; systemic antimicrobials

Periodontal diseases, specifically periodontitis, are caused by pathogenic bacterial species located in the subgingival niche. These bacterial species adhere to the tooth surfaces and are organized in a complex structure, the dental plaque, which has been considered recently as an example of a biofilm (Marsh 2005). The presence of these pathogenic bacteria within complex bacterial communities may have important implications in the use of antimicrobial therapies aimed to fight against them. In fact, at the 5th European Workshop of Periodontology, it was concluded that ''dental plaque displays properties that are typical of biofilms and microbial communities in general, a clinical consequence of which is a reduced susceptibility to antimicrobial agents as well as pathogenic synergism'' (Marsh 2005).

The use of systemic antimicrobials as part of the therapy in the management of periodontal diseases has been debated for decades. The adjunctive benefits of using systemic antimicrobials in the treatment of periodontitis have been reported in two systematic reviews presented at European (Herrera et al. 2002) and World (Haffajee et al. 2003) Workshops. At the European Workshop, Herrera et al. (2002) concluded that in specific clinical situations, such as with patients with deep pockets, patients with

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progressive or ''active'' disease, or with specific microbiological profiles, this antimicrobial therapy adjunctive to scaling and root planing (SRP) could be clinically relevant. However, Haffajee et al. (2003) concluded that, although there are sufficient data to suggest that antibiotics might help in the treatment of periodontitis, the optimum protocol of use has not been clearly defined. This lack of clear protocols of use may be due in part to the specific properties of biofilms, which make subgingival periodontal pathogens more difficult to target, and, therefore, the development of strategies specifically designed to treat the subgingival microflora, as a biofilm, is highly desirable. In the mean time, treatment strategies based on conventional therapies should be adapted to the present knowledge on biofilms.

Among the factors related to systemic antimicrobial usage in the treatment of periodontal diseases, adverse effects should be taken into account: in particular, side effects for individual patients, as well as the increase in bacterial resistance, which is a major global public health problem. These factors should be considered when prescribing systemic antimicrobials, and they should not be used routinely but rather in certain patients and under defined periodontal conditions (Herrera et al. 2002, Lindhe & Palmer 2002).

One of the key issues related to the use of systemic antimicrobials in the treatment of periodontitis has been the importance of biofilm disruption. Specifically, three questions can be raised, which are very relevant clinically and still somehow controversial:

1. Can systemic antimicrobials be efficacious if the biofilm is not disrupted? This question may also be formulated at a more clinician level: if a systemic antimicrobial will be prescribed for the treatment of periodontitis, is there a need for adjunctive root debridement or will it be efficient as sole therapy?
2. Can the type of debridement (non-surgical *versus* surgical) of the subgingival biofilm impact upon the clinical outcomes of the adjunctive antimicrobial therapy? This question may also be formulated at a more clinician level: if a systemic antimicrobial is prescribed as an adjunctive to the treatment of severe periodontitis, should it be used as an adjunctive to SRP or to surgical debridement?
3. Is the efficacy of the adjunctive systemic antimicrobial therapy dependent on the quality of the debridement of the subgingival biofilm and the sequence debridement–antibiotic usage? This question may also be formulated at a more clinician level: if a systemic antimicrobial is going to be used as an adjunctive therapy to debridement, at which moment of the treatment should the antimicrobial be prescribed and how that debridement should be performed (chronology, sessions, quality, etc.)?

   In addition, the reported adverse effects of the adjunctive use of systemic antimicrobials were assessed.

The aim of the present review is to carry out a critical evaluation of the available literature with the objective of defining the best therapeutic protocol of systemic antimicrobial use in the treatment of periodontitis, by answering the three questions raised above.

Can Systemic Antimicrobials be Efficacious if the Biofilm is Not Disrupted?

Methods

Two different aspects were assessed to answer this question: the biofilm characteristics that prove that bacteria arranged in organized communities demonstrate a higher level of resistance against antimicrobials, and clinical studies evaluating the outcomes of the use of systemic antimicrobials as monotherapy, both compared with the use of antimicrobials plus debridement, debridement alone and no therapy.

Biofilm resistance against antimicrobials

Different explanations have been suggested to explain the resistance of biofilms against antimicrobial agents:

- The biofilm extra-cellular matrix (Mah & O'Toole 2001).
- Different physiological phases of the microorganisms within a biofilm (Dibdin et al. 1996, Anderl et al. 2003, Walters et al. 2003).
- Horizontal gene transfer (Roberts et al. 1999, Roberts & Stewart 2004).
- Molecular mechanism of communication among bacterial cells, Quorum Sensing (Roberts & Mullany 2000).

Biofilm resistance against antimicrobials in dental biofilms

The dental biofilm share most of the features of other currently known biofilms (Costerton & Lewandowski 1997, Darveau et al. 2000, Bjarnsholt et al. 2005), with antimicrobial resistance being of special relevance (Haffajee & Socransky 2000). A number of publications have studied dental biofilms in vitro, showing an increase in resistance against amoxicillin, metronidazole and doxycycline (Larsen 2002), in *Porphyromonas gingivalis* biofilms, and also for *Streptococcus constellatus*, *Aggregatibacter actinomycetemcomitans* and *P. gingivalis*, always as single-species biofilms, for antibiotics such as clindamycin, doxycycline, metronidazole and moxifloxacin (Noiri et al. 2003). With more complex biofilms (higher number of species), using saliva samples from different patients, most of the bacterial species growing in a biofilm, demonstrated high levels of resistance against tetracycline, minocycline, amoxicillin, doxycycline and amoxicillin/clavulanate. Moreover, mature biofilms showed a higher degree of tolerance for antimicrobial agents (Eick et al. 2004).

Because of this, different authors have suggested that minimum inhibitory concentration (MIC) profiles should be determined for bacteria as part of a biofilm and not in the planktonic state. We currently lack, however, a standardized method to perform this type of test. Although considerable efforts have been made to assess bacterial resistance in biofilms, many different methodologies have been used, which makes it difficult to effectively compare the results among studies and thus provide guidelines of therapeutic value (Domingue et al. 1994, Sedlacek & Walker 2007).

Very recently, the first description of resistance in the oral biofilm, due to horizontal gene transference, was reported in vivo, when *Streptococcus cristaceus* acquired a transposon that conferred doxycyline resistance from a strain of *Streptococcus oralis*. Both strains were isolated from the subgingival biofilm in patients undergoing doxycycline therapy as part of their periodontal treatment (Warburton et al. 2007). This transfer had been observed previously in non-oral strains, such as two strains of *Staphylococcus aureus*

that acquired an operon associated with vancomycin resistance (vanA operon) from *Enterococcus faecalis* strains (Weigel et al. 2003).

Clinical and microbiological outcomes of the use of systemic antimicrobials as monotherapy in the treatment of periodontitis

Two systematic reviews have recently addressed the question of the efficacy of using systemic antimicrobials in the treatment of periodontitis. One of these reviews focused on the use of systemic antimicrobials as an adjunctive to SRP therapy (Herrera et al. 2002); the other review assessed its adjunctive use both to SRP and to periodontal surgery and when used as a monotherapy (Haffajee et al. 2003). As monotherapy, four studies were included evaluating either metronidazole alone (Clark et al. 1983, Lindhe et al. 1983a) or metronizadole combined with amoxicillin (Lopez et al. 2000, Winkel et al. 2001). From the three meta-analyses performed (one for adjunctive therapy to SRP, other to surgery and as monotherapy), the use as monotherapy was the only one not reaching significant results (mean effect of 0.849 mm, $p = 0.083$) and, therefore, the conclusion in the consensus report was that ''there was insufficient evidence to support the use of systemic antibiotics as a monotherapy in periodontitis patients''.

When reviewing the studies selected in the systematic review presented at the fourth European Workshop (Herrera et al. 2002), some of the studies had split-mouth design (see Table 1), and therefore in these studies half of the mouth was not scaled, and their results could also be assessed comparing the use of the antibiotic as monotherapy with either no treatment, SRP alone or SRP plus adjunctive antimicrobial. The administration of tetracycline as monotherapy (Hellden et al. 1979) had only a minor effect on the clinical and microbiological parameters examined, and this effect was transient, being noticeable at the 8-week interval, but not after 25 weeks. This was especially clear for the microbiological outcomes (Listgarten et al. 1978). In another study using tetracycline for 50 weeks (Lindhe et al. 1983b), the clinical effect in a group of patients with ''excellent plaque control'' was similar to that obtained with SRP in the control group, although a rebound to a more pathogenic microflora was observed after the end of the antibiotic therapy. When doxycycline was studied (Ng & Bissada 1998), and although a statistical analysis between scaled and non-scaled sites was only provided for the placebo group, the figures showed a limited or null impact when doxycycline was used as monotherapy. With metronidazole (Lindhe et al. 1983a), the repeated subgingival debridement in the SRP and SRP plus antimicrobial groups resulted in more pronounced reduction of the inflammatory infiltrates than in the monotherapy group. Finally, the combination of metronidazole and amoxicillin has also been evaluated in a split-mouth design (Berglundh et al. 1998), concluding that the antibiotic regimen alone was less effective than mechanical therapy in the reduction of sites with bleeding on probing (BOP), probing pocket depth (PPD) and gain in clinical attachment levels (CALs). However, in the monotherapy group there was a microbiological impact observed at 2 months that lasted for at least 12 months, when combined with a meticulous supragingival plaque control.

These split-mouth studies were not designed to evaluate systemic antimicrobials as monotherapy, but there is another group of split-mouth and parallel studies specifically designed to evaluate this issue. These studies are not very numerous and most of the available literature has evaluated metronidazole. When a single dose of 2 g of metronidazole was compared with SRP and no treatment in a parallel study of 3 months, a similar clinical and microbiological outcome was observed in both metronidazole and in SRP groups at 1 month. These benefits, however, were only maintained at 3 months in the SRP group (Walsh et al. 1986). This positive clinical and microbiological outcome on a short-term basis (4 weeks) was also observed in a split-mouth study in women using metronidazole 250 mg, q.i.d., for 7 days (Lekovic et al. 1983). In another split-mouth study, SRP plus metronidazole demonstrated a significant clinical benefit in terms of PPD and BOP reductions at 3 months, while metronidazole alone showed only minor improvements (van Oosten et al. 1987). No improvements were observed, after 3 months, in a study with a similar design, for SRP plus metronidazole or metronidazole alone, in patients with inadequate oral hygiene and previous SRP 3 months earlier (Jenkins et al. 1989). When the effect of metronidazole was compared with a placebo in a double-blind design, differences between groups were evident, but the impact of the monotherapy was very limited, leading the authors to recommend adjunctive therapy (Watts et al. 1986). In summary, monotherapy with metronidazole can result in PPD reductions ranging 0–2.4 mm, but with limited CAL gain and reduction in bleeding. The results are inferior or equivalent at most, in a short-term basis, to the results achieved by SRP. When compared with the results obtained with the use of adjunctive metronidazole, monotherapy results are significantly lower (Greenstein 1993).

Recently, two studies from the same research group have reported on the use of antimicrobials as monotherapy in moderate to advanced periodontitis (Lopez & Gamonal 1998, Lopez et al. 2006). The first is a double-blind clinical study comparing amoxicillin plus metronidazole *versus* placebo during 4 months. The authors concluded that antibiotics were able to change the proportions of periodontal pathogens in the subgingival flora and to significantly improve the clinical outcomes assessed. In the second publication, also reporting on a double-blind study, comparing amoxicillin plus metronidazole and supragingival scaling *versus* SRP and two placebos for 12 months, similar clinical results were observed in both groups, and the microbiological results were maintained for up to 12 months.

With the exception of these two studies (Lopez & Gamonal 1998, Lopez et al. 2006), the rest of the reviewed literature does not support the use of systemic antimicrobials as monotherapy in periodontitis. This conclusion was already published in 1993 when Greenstein (1993) reviewed the role of metronidazole in the treatment of periodontal diseases and concluded that its usage as sole therapy should not be recommended, because only its adjunctive use to SRP had demonstrated clinical efficacy. Later, the 1996 position paper on systemic antibiotics by the American Academy of Periodontology also suggested that systemic drugs should only be used as adjunctive therapy, based on the concept of ''good medical practice'' (debridement should precede medication), and the results of the reviewed studies (AAP 1996). This conclusion was later confirmed by Slots (2004), and the results of a systematic review and the following consensus report

Table 1. Study design, patients and periodontitis characteristics of the 32 selected papers to assess the quality of debridement

Author and year	Antibiotics	Country	Study			Patients						Periodontitis	
			design	groups	length	baseline	final	percnt; smokers	male/female	age range	source	as described	Ag.P./Ch.P.
Listgarten et al. (1978)	TET	Sweden	CCT	2 × 2	25 w	12	12	NA	7/5	27–42	Hospital	Severe P.	Ch.P.
Hellden et al. (1979)	TET	Sweden	CCT	2 × 2	25 w	12	12	NA	7/5	27–42	Hospital	Severe P.	Ch.P.
Lindhe et al. (1983b)	MET	Sweden	CCT	2 × 2	50 w	16	16	NA	7/9	32–48	University	Advanced PD	Ch.P.
Lindhe et al. (1983a)	TET	Sweden	RCT	2 × 2	50 w	14	14	NA	6/8	37–52	University	Advanced PD	Ch.P.
Joyston-Bechal et al. (1984)	MET	UK	CCT	2	22 w	47	45	NA	NA	NA	Hospital	Chronic PD	Ch.P.
Loesche et al. (1984)	MET	USA	RCT	2(+1)	15–30 w	40	NA	NA	NA	NA	University	>10% spiros P.	unclear
Joyston-Bechal et al. (1986)	MET 3 y, MET 22 w	UK	CCT	2	22 w, 3 y	45	28	NA	NA	NA	Hospital	Chronic PD	Ch.P.
Chin et al. (1988)	SPI/MET	Canada	RCT	2	6 m	56	50	NA	NA	>34	NA	Advanced PD	Ch.P.
Al Joburi et al. (1989)	TET, SPI	Canada	RCT	3	24 w	96	79	NA	NA	>34	NA	Chronic Adult P.	Ch.P.
McCulloch et al. (1990)	DOX	Canada	RCT	2	7 m	82(55)	48	NA	26/29	32–73	Private and university	Active P.	Ch.P.
Soder et al. (1990)	MET	Sweden	RCT	2	6 m	98	92	NA	52/46	31–40	Residents	P.	Ch.P.
Kulkarni et al. (1991)	DOX	Canada	RCT	2	7 m	27	27	NA	NA	NA	NA	Active P.	Ch.P.
Saxen & Asikainen (1993)	MET, TET	Finland	RCT	3	6, 18 m	27	18	NA	8/19	14–26	University	LPJ with *Aa*	Ag.P.
Walker et al. (1993)	AUG, CLIN	USA	CCT	3	24 m	30	NA	NA	NA	NA	University	Refractory+active	Ch.P.
Bain et al. (1994)	SPI	Canada	RCT	2	24 w	193	189	NA	NA	>34	University	Advanced PD	Ch.P.
Magnusson et al. (1994)	AUG, CLIN	USA	RCT	3	2 y	21(17)	16	NA	NA	35–62	University	Refractory+active	Ch.P.
Berglundh et al. (1998)	AMO/MET	Sweden	RCT	2 × 2	24 m	16	16	NA	6/10	35–58	University	Advanced PD	Ch.P.
Flemmig et al. (1998)	AMO/MET	Germany	CCT	2	12 m	48	38	NA	NA	>29	University	*Aa* and/or *Pg* P.	Ch.P.
Ng & Bissada (1998)	DOX	USA	CCT	4 × 2	24 w	32	32	47%	18/14	32–72	Not stated	P.	Ch.P.
Palmer et al. (1998)	MET	UK	RCT	3	24 w	90	84 (58)	33%	43/47	35–65	Referred to P.Gr. clinic	mod–sev adult P.	Ch.P.
Palmer et al. (1999)	MET–smoker, MET–non	UK	RCT	3	6 m	90	57(39)	NA	43/47	35–65	Referred to P.Gr. clinic	mod–sev adult P.	Ch.P.
Winkel et al. (1999)	AUG	Holland	RCT	2	12 m	21	21	NA	6/15	NA	University	Adult P.	Ch.P.
Sigusch et al. (2001)	DOX, MET, CLIN	Germany	CCT	4	24 m	48	48	NA	20/28	NA	University	gen. RPP	Ag.P.
Rooney et al. (2002)	AMO/MET, MET, AMO	UK	RCT	4	6 m	66	NA	NA	NA	20–45	Referred to university	Advanced P.	Ag.P. and Ch.P.
Smith et al. (2002)	AZI	UK	RCT	2	22 w	46	44	22%	21/23	>18	Referred to hospital	P.	Ag.P. and Ch.P.
Guerrero et al. (2005)	AMO/MET	UK	RCT	2	6 m	41	40	22%	28/13	16–35	P.Gr. clinic	gen. Ag.P.	Ag.P.
Mascarenhas et al. (2005)	AZI	USA	RCT	2	6 m	31	30	100%	19/11	31–66	University	mod–sev Ch. P.	Ch.P.
Mombelli et al. (2005)	AMO/MET	Switzerland	RCT	2 × 2	12 m	16	14	38%	10/6	25–65	University	mod–sev P. (*Pg*+)	Ag.P. and Ch.P.
Ehmke et al. (2005)	AMO/MET	Germany	CCT	2	24 m	48	35	9%	NA	>30	University	*Aa* and/or *Pg* Ch.P.	Ch.P.
Xajigeorgiou et al. (2006)	AMO/MET, DOX, MET	Greece	RCT	4	6 m	47	43	33%	22/21	22–49	University	gen. Ag.P.	Ag.P.
Haffajee et al. (2007)	AZI, MET	USA	RCT	4	12 m	98	92	10%	59/33	22–77	Forsyth Institute	P.	Ag.P. and Ch.P.
Gomi et al. (2007)	AZI	Japan	RCT	2	25 w	34	34	0%	16/18	>25	Referred to hospital	Severe Ch.P.	Ch.P.

AZI, azithromycin; SPI, spiramycin; TET, tetracycline; DOX; doxycycline; MET, metronidazole; CLIN, clindamycin; AMO, amoxicillin; AUG, amoxillin plus clavulanate; RCT, randomized clinical trial; CCT, controlled clinical trial; NA, not available; w, weeks; m, months; y, years; Ag.P., aggressive periodontitis; *Aa*, *A. actinomyctemcomitans*; Ch.P., chronic periodontitis; P.Gr., post-graduate; P., periodontitis; PD, periodontal disease; spiros, spirochaetes; LPJ, localized juvenile periodontitis; mod–sev; moderate and severe; RPP, rapidly progressive periodontitis; gen., generalized.

(Haffajee et al. 2003). However, the methodology of the reviewed papers on monotherapy was, in most cases, of low quality. This should be taken into account when interpreting the data.

Can the Type of Debridement (Non-Surgical *versus* Surgical) of the Subgingival Biofilm Impact Upon the Clinical Outcomes of the Adjunctive Antimicrobial Therapy?

As discussed previously, the use of systemic antimicrobials can improve the clinical and microbiological outcomes of periodontal mechanical therapy. Systemic antimicrobials have been used mainly as an adjunct to basic periodontal therapy (SRP) and enough evidence exists to support this combined therapy (Herrera et al. 2002, Haffajee et al. 2003). However, in certain situations, periodontal surgery may be necessary and in these cases there is controversy with regard to when it is more effective to prescribe the systemic antimicrobial: either in conjunction with basic periodontal therapy or together with the surgical phase.

In order to answer this question, we have reviewed the efficacy of the adjunctive systemic antimicrobial use to periodontal surgery.

Methods

A search was performed in PubMed, with the following strategy: (*periodontitis* OR *periodontal*) AND (*surgery* OR *surgical*) AND (*antibiotic* OR *antimicrobial*). The search was restricted to papers published in English language, in humans, clinical trials, randomized clinical trials (RCT), meta-analysis and reviews.

In addition, we carried out a hand search of the most relevant scientific journals in Periodontology, such as *Journal of Clinical Periodontology* and *Journal of Periodontology*, together with the evaluation of secondary references from relevant papers and review articles in order to supplement the search. Most of the included papers were obtained by hand search.

Results

In the literature, there are many studies describing the added effect of administering systemically antibiotics as an adjunct to periodontal surgery, ranging from case reports to RCT. The number of RCTs available is, however, limited. Therefore, we have also considered case reports and cohort studies in the evaluation. The available literature was classified into three levels, according to the level of evidence provided to answer the proposed question.

Comparative studies between SRP plus antibiotics versus periodontal surgery plus antibiotics

There is not one single clinical trial in the searched literature with this design. Only a study by Palmer et al. (1996) may provide some evidence to answer this question. This study was an RCT that evaluated the efficacy of adjunctive systemic tetracycline in the non-surgical and surgical management of 38 patients with aggressive periodontitis (early-onset periodontitis, as defined in the paper), and they concluded that tetracycline was a useful adjunct, especially to non-surgical treatment. Firstly, patients were instructed in oral hygiene, followed by SRP and the prescription of either tetracycline 250 mg, q.i.d., for 14 days, or a placebo, in a randomized, double-blind basis. After 3 months, a modified Widman flap was recommended at teeth with PPD $\geqslant$ 5 mm and BOP. The same course of tetracycline or placebo was repeated, with an adjunctive 0.12% chlorhexidine mouthwash. Clinical evaluations were performed at baseline, 3, 6 and 12 months, and so 3-month results were available after both the non-surgical and the surgical phase. Thirty-eight patients completed the non-surgical phase and 26 completed the surgical phase. There was a reduction in PPD at 3 months, which was significantly greater in the test group. Both groups demonstrated CAL gains, with slightly more in the antibiotic group (statistically significant). There were further reductions in mean PPD after surgery, which were maintained at 12 months. No further statistically significant gain in CAL was observed following surgery. The differences between groups (tetracycline *versus* placebo) were not statistically significant. The comparison of mean PDD and CAL changes following surgery suggests that no further advantage was obtained by the antibiotic in the surgical phase, although this may also be a result of the smaller number of subjects and fewer sites treated in the surgical phase.

RCTs comparing periodontal surgery plus antibiotic versus periodontal surgery plus placebo

This group of studies has evaluated antimicrobials as adjuncts to the surgical treatment of periodontitis, aiming to enhance both clinical and microbiological outcomes (see Table 2).

A meta-analysis by Haffajee et al. (2003) reviewed three studies and included four comparisons (Kunihira et al. 1985, Haffajee et al. 1995, Palmer et al. 1996). They reported that systemically administered antimicrobial agents provide a significant clinical benefit in terms of mean CAL gain (weighted mean 0.609, $p = 0.007$). Individually, the included comparisons suggested benefits of the adjunctive antimicrobial, although often not statistically significant. In addition, different drugs (penicillin, tetracycline, amoxicillin plus clavulanate) were pooled in the meta-analyses.

Another group of RCTs has evaluated the adjunctive effect of selected antimicrobial agents, such as ofloxacin (Kleinfelder et al. 2000) or azithromycin (Dastoor et al. 2007), combined with periodontal surgery, in the treatment of chronic periodontitis in *A. actinomycetemcomitans*-positive patients (Kleinfelder et al. 2000) or in chronic periodontitis in smokers (Dastoor et al. 2007). Ofloxacin plus surgery resulted in a significant CAL gain and in the suppression of *A. actinomycetemcomitans* below detectable levels for at least 12 months (Kleinfelder et al. 2000). Conversely, in heavy smokers, adjunctive azithromycin with periodontal surgery in one quadrant did not significantly enhance PDD reduction or CAL gain, although they observed faster wound healing, and less gingival inflammation at the short-term evaluation (Dastoor et al. 2007).

Case reports, cohorts studies and other clinical trials

The rationale of using systemic antibiotics as part of a surgical protocol may also be based on other reasons, such as:

- As an adjunct in the treatment of specific disease profiles (''active'' or refractory diseases, severe diseases, smokers, etc.), with periodontitis that could require a more ''aggressive'' treatment.

Table 2. Study design, patients and treatment features of selected papers assessing systemic antimicrobials as adjuncts to periodontal surgery

Author and year	AB	Country	Study design	Groups	Follow-up	Patients	Age	Disease description
Palmer et al. (1996)	TET, placebo	UK	RCT	2	12 m	38	12–24	EOP (30 L./8 G.)
Kunihira et al. (1985)	PEN, placebo	USA	RCT	2	62 m	16	<30y	L.JP
Haffajee et al. (1995)	TET, AUG, placebo	USA	RCT	4	10 m	40	48 ± 12	Active, pockets >4 mm
Kleinfelder et al. (2000)	OFLO	Germany	CCT	2	12 m	35		*Aa*-adv. P.
Dastoor et al. (2007)	AZI, placebo	USA	RCT (pilot study)	2	6 m	30	ne	mod–adv Ch.P, heavy smokers
Lindhe & Liljenberg (1984)	TET	Sweden	Cohort study	2	5 y	28	14–18/ 39–48	JP *versus* adult P.
Kornman & Robertson (1985)	TET	USA	Case series	1	Staged	8	12–23	JP
Mandell et al. (1984)	DOX, TET local	USA	Case series	1	264 d	4	13–18	Active JP
Jaffin et al. (1984)	TET	USA	Case series	1	4 y	4		JP
Mahmood & Dolby (1987)	MET, placebo	UK	RCT (cross-over)	2	6 m	15	29–52	mod–adv P.
Söder et al. (1999)	MET, placebo	Sweden	RCT	8	5 y	98	36.5 ± 2.8	Ch.P. (smokers *versus* non-smokers)
Haffajee et al. (1988)	TET	USA	Case series	2	6 m	33	17–42	Active PD.
Müller et al. (1993b)	MIN	Germany	Case series	1	24 m	33	13–63	*Aa*-P.
Müller et al. (1993a)	MIN	Germany	Case series	1	24 m	33		*Aa*-P.

Author and year	Treatment sequence	Type of SURG	AB dosage
Palmer et al. (1996)	OHI+SRP+(TET *versus* placebo) followed by SURG+CHX+(TET *versus* placebo)	Modified Widman flap	TET 250, 4 ×, 14 d
Kunihira et al. (1985)	OHI+SRP followed by SURG+(PEN *versus* placebo) then SPT	Open curettage	PEN 250, 4 ×, 10 d
Haffajee et al. (1995)	SRP+SURG+CHX+(TET *versus* AUG *versus* placebo *versus* IBU) then SPT	Modified Widman flap	TET 250, 3 ×, 30 d; AUG 375/125, 3 ×, 30 d
Kleinfelder et al. (2000)	OHI+supra+SURG+(OFLO *versus* nothing) then SPT	Open flap surgery	OFLO 200, 2 ×, 5 d
Dastoor et al. (2007)	SRP followed by SURG+CHX+Ibuprofen+(AZI *versus* placebo)	Apically positioned flap	AZI 500, 1 ×, 3 d
Lindhe & Liljenberg (1984)	SUR+CHX+TET then SPT	Modified Widman flap	TET 250, 4 ×, 14 d
Kornman & Robertson (1985)	SRP followed by (TET+SRP *versus* SPT) followed by SURG+TET	Modified Widman flap	TET 250, 4 ×, 28 d
Mandell et al. (1984)	Local TET followed by DOX+(SURG *versus* nothing)	Flap without osseous re-countouring	DOX 100, 1 ×, 14 d
Jaffin et al. (1984)	OHI+TET followed by SURG+TET	Prichard's technique	TET 250, 4 ×, 28 d
Mahmood & Dolby (1987)	OHI+SRP followed by SURG+CHX+(MET *versus* placebo)	Modified Widman flap	MET 200, 3 ×, 7 d
Söder et al. (1999)	SRP+(MET *versus* placebo) followed by SURG followed by SPT	Modified Widman flap	MET 400, 3 ×, 7 d
Haffajee et al. (1988)	SURG+TET	Modified Widman flap	TET 250, 4 ×, 21 d
Müller et al. (1993b)	OHI+supra followed by SRP+CHX+MIN followed by SURG+MIN+CHX then SPT	Modified Widman flap	MIN 200, 1 ×, 3 w
Müller et al. (1993a)	OHI+supra followed by SRP+CHX+MIN followed by SURG+MIN+CHX then SPT	Modified Widman flap	MIN 200, 1 ×, 3 w

PEN, phenoxymethyl penicillin; TET, tetracycline; AUG, amoxicillin/clavulanate; OFLO, ofloxacin; AZI, azithromycin; DOX, doxycycline; MET, metronidazole; MIN, minocycline; ORNI, ornidazole; CIP, ciprofloxacin; EOP, early onset periodontitis; JP, juvenile periodontitis; P, periodontitis; L., localized; G., generalized; mod, moderate; adv, advanced; Ch., chronic; PD, periodontal disease; *Aa*, *A. actinomyctemcomitans*; OHI, oral hygiene instruction; SRP, scaling and root planing; SURG, surgery; supra, supragingival prophylaxis; SPT, supportive periodontal therapy; w, weeks; d, days; m, months; y, years.

- To prevent post-surgical complications, including infection.
- In periodontal surgery aiming for periodontal regeneration.
- Specific disease profiles

Because of the concept of specific infection and the key role that *A. actinomycetemcomitans* may play, particularly in localized aggressive periodontitis (described in the papers as localized juvenile periodontitis), the adjunctive use of systemic antimicrobials with periodontal treatment has received considerable attention, both clinically and scientifically. The reported results, however, do not demonstrate consistent findings. Although systemic antimicrobials combined with non-surgical mechanical debridement were able to improve treatment outcomes in many studies, this therapy often failed to eliminate *A. actinomycetemcomitans* from subgingival areas. One hypothesis to explain

this failure was the possibility that *A. actinomycetemcomitans* may invade the periodontal tissues, and, therefore, different studies were designed to evaluate whether periodontal surgery together with systemic antimicrobials could overcome this problem and significantly improve the results.

Early studies assessing this hypothesis suggested that a more predictable result was achieved with the combination of SRP, surgery and systemically administered tetracycline (Lindhe & Liljenberg 1984, Kornman & Robertson 1985) or doxycycline (Mandell et al. 1984). These favourable results were attributed to the suppression of subgingival *A. actinomycetemcomitans*, or, at least, its eradication in a large percentage of sites (Lindhe & Liljenberg 1984, Kornman & Robertson 1985). In some studies, microbiological assessments were also performed, but plaque samples were usually taken from a limited number of sites. These studies, in general, should be interpreted with caution, because some of them demonstrated an added beneficial effect provided by the antibiotics, but this effect was not necessarily consistent from one study to another. In addition, some of these studies included small samples: from four patients (Jaffin et al. 1984, Mandell et al. 1984) to eight patients (Kornman & Robertson 1985). Moreover, study designs also showed important limitations such as: split-mouth designs (Mandell et al. 1984), clinical protocols of sequential stages of treatment (Kornman & Robertson 1985), case reports (Jaffin et al. 1984) or lack of a proper control group (Jaffin et al. 1984, Lindhe & Liljenberg 1984). More recently, despite clinical improvements (mean CAL gain of at least 2 mm and mean residual PPD <4 mm), *A. actinomycetemcomitans* was not eliminated from pooled subgingival samples in any of the patients treated with adjunctive minocycline to modified Widman flap. Therefore, the authors concluded that the evaluated protocol would be appropriate in localized forms of periodontitis in *A. actinomycetemcomitans*-positive patients, but inappropriate in more severe and generalized forms (Müller et al. 1993a, b).

Additional studies have evaluated the adjunctive effect of selected antimicrobial agents, such as metronidazole (Mahmood & Dolby 1987, Söder et al. 1999) or tetracycline (Haffajee et al. 1988), combined with periodontal surgery in the treatment of other periodontal conditions. In the treatment of moderate to severe periodontitis, adjunctive metronidazole to surgery (Mahmood & Dolby 1987) did not significantly improve the effects of surgery and placebo, although a positive benefit in the group using metronidazole could be observed. In subjects showing current disease progression, adjunctive tetracycline (Haffajee et al. 1988) improved the results in CAL gain and decreased the levels of some suspected periodontal pathogens while increasing the levels of certain ''beneficial'' species. In smokers, who tend to have a less favourable response to periodontal therapy, the use of antimicrobials, such as metronidazole in combination with surgery, had a limited additional effect (Söder et al. 1999).

- To prevent post-surgical complications, including infection (Table 3).

Periodontal surgery, as any other surgery in the oral cavity, may be associated with the risk of developing post-operative complications, such as infection (suppuration, pain, swelling,

Table 3. Study design, patients and treatment description of selected papers assessing post-surgical infection

Author and year	AB	Country	Design	Patients	Surgeries, *n*	Treatment plan	Periodontal surgery
Pack & Haber (1983)	PEN,ERY	USA	Retrospective	218	927	SURG+(PEN or ERY)	Different periodontal, osseous and mucogingival SURG
Powell et al. (2005)	Not defined	USA	Retrospective	395	1.053	SURG+AB	Different periodontal, osseous and mucogingival SURG
Checchi et al. (1992)	TET	Italy	Retrospective	231	498	OHI+SRP then SURG+TET(53/498)+CHX	360 osseous contouring, 138 mucogingival SURG
Appleman et al. (1982)	CEP, placebo	USA	CCT	31		SURG+(CEP *versus* placebo)	Apically positioned flap
Kidd & Wade (1974)	PEN, placebo	UK	RCT	17		SURG+(PEN *versus* placebo)	Curettage+osseous re-contouring

Author and year	AB dosage	AB-moment	Rate of infection	With AB	Without AB
Pack & Haber (1983)	PEN 250, 4 ×, 7 d or ERY 250, 4 ×, 7 d	Day of surgery	9/927 (1%)	1/43 (2%)	8/884 (<1%)
Powell et al. (2005)	Not defined	Pre- and/or post-surgery	22/1053 (2.09%)	Pre- and post-surgery 8/281 (2.85%), pre-surgery 1/29 (3.45%)	14/772 (1.81%)
Checchi et al. (1992)	TET 250, 4 ×, 7 d	Immediately after surgery	21/498 (4.20%)	2/53 (3.80%)	19/445 (4.40%)
Appleman et al. (1982)	CEP 500, 4 ×, 3 d	1 h before		Other variables Bacteremia, pain, swelling, antibiotic susceptibility	
Kidd & Wade (1974)	PEN 250, 4 ×, 5 d	Immediately before surgery		Pain, swelling, healing, number of aspirins	

AB, antibiotics; PEN, penicillin; ERY, erythromycin; TET, tetracycline hydrochloride; CEP, cephalexin; SURG, surgery; CHX, chlorhexidine; RCT or CCT, randomized or controlled clinical trial; d, days.

redness, bacteraemia). However, whether the administration of systemic antimicrobials diminishes this risk is still a matter of controversy and this adjunctive use of systemic antibiotics with different surgical procedures is based more on empiricism than on scientific data.

The main argument for the controversy is the low incidence of infections reported after periodontal surgery, ranging from 1% for all procedures (Pack & Haber 1983), 2.09% (Powell et al. 2005) or 4.2% (Checchi et al. 1992). It should be pointed out that most of these studies are retrospective, with a limited sample size, ranging from 218 patients and 927 surgical procedures (Pack & Haber 1983), to 231 patients and 498 surgical procedures (Checchi et al. 1992). Only one large-scale, retrospective study (Powell et al. 2005), of multiple surgical modalities in different periodontal practices, included 395 patients and 1053 surgical procedures. Perhaps it is necessary to design and conduct comprehensive and accurate surveys to further explore the prevalence of clinical infections post-surgically, and thus being able to assess what risk factors are relevant in their development and which treatment protocols are able to significantly reduce its occurrence.

Although some studies have reported that adjunctive use of antibiotics can reduce pain and swelling, and can improve wound healing and treatment outcomes, when compared with a placebo, no statistically significant differences were found. Some reports (Kidd & Wade 1974) support the concept that healing is more rapid and the discomfort is smaller under antibiotic (penicillin) coverage during periodontal surgery. However, other studies (Pack & Haber 1983, Checchi et al. 1992, Powell et al. 2005) do not support the routine use of prophylactic antibiotics, such as tetracyclines (Checchi et al. 1992), penicillin or erythromycin (Pack & Haber 1983) and cephalexin (Appleman et al. 1982), because these regimens were ineffective in preventing post-operative infection. They concluded that unless there is a medical indication, there is no justification for using prophylactic antibiotic in periodontal surgery. Even in some reports, an indiscriminate and prolonged use of antibiotics may result in a higher rate of infection. In addition, the risks involved with the use of systemic antibiotics (adverse events, etc.) must always be considered against the limited benefits.

- In conjunction with periodontal surgery aiming for periodontal regeneration (Table 4).

Studies evaluating regenerative procedures with barrier membranes show a wide variability and lack of predictable results. Negative outcomes after these surgical procedures have been associated with membrane exposure and subsequent membrane infection and contamination of the healing wound

Table 4. Study design, patients and treatment features of selected papers assessing systemic antimicrobials as adjuncts to regenerative surgery

Author and year	AB	Country	Design	Groups	Length	Patients	Age	Indication
Nowzari et al. (1996)	AMO+CLAV	USA	Cohorts	2	6 m	42	29–69	2–3 wall defects
Mombelli et al. (1996)	ORNI, placebo	Switzerland	RCT (split mouth)	2 × 2	50 w	10	35–65	Class II furcation
Demolon et al. (1994)	AMO+CLAV	USA	CCT	2	1 y	15	36–70	Class II furcation
Demolon et al. (1993)	AMO+CLAV	USA	CCT	2	4 w	15	36–70	Class II furcation
Nowzari et al. (1995)	AMO+CLAV	USA	RCT	2	24 w	18	37–71	2–3 wall defects
Loos et al. (2002)	AMO+MET	The Netherlands	RCT (split mouth)	2 × 2	12 m	25		2 proximal defects ⩾6 mm
Sculean et al. (2001)	AMO+MET	Germany	RCT	2	1 y	34		1 intra-bony defect
Vest et al. (1999)	MET+CIP+DOX	USA	RCT	2	9 m	24		Class II furcation

Author and year	Treatment sequence	Regenerative technology	Dosage (mg)	Sequence AB-surgery
Nowzari et al. (1996)	(SRP *versus* SURG) followed by GTR+IBU+CHX+AUG followed by SPT	ePTFE	AMOX+CLAV 500+125, 3 ×, 8 d	1 h prior membrane
Mombelli et al. (1996)	OHI+SRP+(GTR *versus* non GTR & ORNI *versus* placebo) followed by SPT	ePTFE	ORNI 1000, 1 ×, 10 d	2 w after first surgery
Demolon et al. (1994)	SRP+GTR+CHX+(AUG *versus* nothing)	ePTFE	AMOX+CLAV 250+125, 3 ×, 10 d	1 h before surgery
Demolon et al. (1993)	SRP+GTR+CHX+(AUG *versus* nothing) followed by SPT	ePTFE	AMOX+CLAV 250+125, 3 ×, 10 d	1 h before surgery
Nowzari et al. (1995)	OHI+SRP followed by GTR+IBU+CHX+(AUG *versus* nothing) followed by SPT	ePTFE	AMOX+CLAV 500+125, 3 ×, 8 d	1 h prior membrane
Loos et al. (2002)	OHI+supra+SRP+SURG+CHX followed by CHX+(AMOX+MET *versus* nothing & GTR *versus* non)	Polylactic acid	AMOX+MET 375+250, 3 ×, 7 d	4 d before SURG
Sculean et al. (2001)	OHI+supra+SRP followed by EMD+CHX+(AMOX+MET *versus* nothing) followed by SPT	Enamel matrix proteins	AMOX+MET 375+250, 3 ×, 7 d	First day of surgery
Vest et al. (1999)	GTR+CHX+(MET+CIP+DOX *versus* nothing)	Polylactic acid+DFDBA	MET (250, 3 ×), CIP (250, 2 ×); DOXY (50, 1 ×); 7 d	First day of surgery

PEN, phenoxymethyl penicillin; AMO, amoxicillin; CLAV, clavulanate; CIP, ciprofloxacin; DOX, doxycycline; MET, metronidazole; MIN, minocycline; ORNI, ornidazole; IBU, ibuprofen; OHI, oral hygiene instruction; SRP, scaling and root planing; SURG, surgery; supra, supragingival prophylaxis; SPT, supportive periodontal therapy; DFDBA, demineralized freeze-dried bone allograft; GTR, guided tissue regeneration; ePTFE, expanded polytetrafluoroethylene; RCT or CCT, randomized or controlled clinical trial; w, weeks; d, days; m, months; y, years.

(Murphy 1995, Nowzari et al. 1996), which result in reduced regeneration. Because of this, most researches investigating regenerative procedures have used adjunctive systemic antibiotics as part of the surgical protocol (Cortellini & Bowers 1995, Machtei & Schallhorn 1995, Cortellini & Tonetti 2000, Kornman & Robertson 2000, Sanz & Giovannoli 2000). However, the study of Powell et al. (2005), which evaluated the prevalence of post-surgical infections after various periodontal surgical procedures, concluded that the use of regenerative membranes did not significantly increase infection rates (3.00%) compared with the non-use of membranes (1.88%).

The rationale for using antibiotics in these procedures is to try to increase the predictability of the results by controlling the subgingival microflora in the early healing phase, in order to reduce the risk of post-operative infection and thus reduce the chance of bacterial contamination of the exposed membranes. However, the clinical utility and the long-term efficacy of the use of systemic antibiotics during regenerative surgical procedures can be questioned.

The most relevant study design to assess the value of systemic antimicrobials in regenerative procedures is the one including a group with surgery plus antibiotic and another group with surgery plus placebo or nothing. Some of these studies have shown an additional benefit in the regenerative outcomes in the test group, either with amoxicillin plus clavulanate (Nowzari et al. 1995) or ornidazole (Mombelli et al. 1996). Other reports, however, indicate that the group with adjunctive antibiotics showed significant improvements in the evaluated clinical parameters, but did not have any significant effect on osseous healing in class II furcation defects (Vest et al. 1999). Demolon et al. (1993, 1994) found large differences among individuals and lack of sufficient bone formation to fill any of the furcation defects, indicating a low predictability of the procedure. In addition, they observed, at the 1-year reentry surgery, that bone filling was limited and not consistent with the observed clinical improvements. They concluded that the use of antibiotic may have helped to control initial inflammation (Demolon et al. 1993), but it had no direct effects of clinical significance on bone regeneration or soft tissue attachment at 12 months (Demolon et al. 1994). Other authors question this added clinical benefit of applying barrier membranes and systemic antibiotics, because none of them were relevant factors, and only smoking has a strong impact on the therapeutical outcomes in intra-osseous defects (Loos et al. 2002).

Studies of guided tissue regeneration with and without antibiotics have used different regimens (Table 4). Currently, there are no studies that have compared the effects of different antibiotic regimens, or the best time to prescribe them, but it is important to consider that the microbial colonization of the membranes begins within 3 min. after their insertion into the mouth (Nowzari et al. 1996). The wide variation in the regimens used demonstrates that there is no general agreement among clinicians on which is the most appropriate antibiotic, its dose, duration of therapy or the time to begin its administration.

In most of the published studies evaluating the efficacy of the application of enamel matrix derivatives (EMD) in regenerative periodontal surgery, a post-operative antibiotic regimen was used. Very few studies have compared this surgical approach with and without the systemic administration of antibiotics. Sculean and colleagues have performed one such study and they observed no differences between treatments, indicating that the positive healing can be in great part be attributed to the use of EMD. This study shows that careful patient selection, a meticulous surgical technique and close post-operative plaque control are more important factors for the outcome of the therapy than the routine administration of antibiotics. It should be emphasized that the application of EMD in periodontal regenerative surgery leads to fewer post-surgical complications than for other regenerative approaches, such as the use of barrier membranes or graft materials and, consequently, the possibility of a post-operative infection is lower (Sculean et al. 2001).

Is the Efficacy of the Adjunctive Systemic Antimicrobial Therapy Dependent on the Quality of the Debridement of the Subgingival Biofilm and the Sequence Debridement–Antibiotic Usage?

Because subgingival bacteria are organized in biofilms, in principle, they are less susceptible to antimicrobials, unless there is a previous disruption by mechanical debridement and in this manner the antimicrobial results should be improved.

Following this rationale, three hypotheses can be proposed:

- The better the quality of the debridement, the better the results.
- Debridement should precede antibiotic intake.
- The time elapsed between the debridement and the antibiotic intake should be reduced to a minimum, in order to avoid biofilm re-organization.

Methods

Search and selection of relevant papers

In order to evaluate these hypotheses, the previous systematic search carried out 5 years ago was extended (Herrera et al. 2002). Briefly, studies were selected if they were designed as RCT or controlled clinical trials (CCT) in which systemically healthy patients with either aggressive periodontitis (Ag.P.) or chronic periodontitis (Ch.P.) were treated with SRP plus systemic antimicrobials in comparison with SRP alone or with placebo, and followed for a minimum of 6 months. The main outcome measures that were considered in these trials were changes in CAL and PPD.

The extended search was performed in PubMed, with the following strategy:

(periodontitis OR periodontal diseases) AND (antibiotic OR antimicrobial OR metronidazole OR ciprofloxacin).

The search was restricted to RCT, CCT, systematic reviews and guidelines, from 2001 to October 2007, and papers published in English.

A total of 202 references were retrieved. After screening of the titles and abstracts by two independent reviewers (D. H. and S. R.), 22 papers were considered as suitable and full-length papers were obtained.

The full-length paper revealed that two papers did not fulfil the inclusion–exclusion criteria (Purucker et al. 2001, Loesche et al. 2005), with regard to reported study design and outcome variables, and to the use of local antibiotic therapy, respectively, and two more were already present in the papers

selected for the previous systematic review (Golub et al. 2001, Sigusch et al. 2001).

Finally, 18 papers were selected, and their data were analysed and extracted. During data extraction, an additional paper (Giannopoulou et al. 2006) was excluded, because the sample was the same as in another included paper (Mombelli et al. 2005) and the outcome variables were just related to gingival crevicular fluid.

After data extraction, the appropriateness of including papers evaluating the efficacy of low-dose doxycycline (LDD) was considered. This drug was included in the previous systematic review (Herrera et al. 2002), due to the antimicrobial nature of the molecule, although it was not used for its antimicrobial activity. In this review, because this drug is used on a long-term basis, and its mode of action will not provide any information with respect to the proposed questions, we decided not to include the data from the selected papers, or from the LDD papers selected in 2002 (Caton et al. 2000, Golub et al. 2001).

From the 17 newly selected papers, eight dealt with LDD (Caton et al. 2001, Novak et al. 2002, Emingil et al. 2004a, b, Lee et al. 2004, Preshaw et al. 2004, Mohammad et al. 2005, Needleman et al. 2007) and were not considered for the data analysis. Therefore, nine additional papers (Rooney et al. 2002, Smith et al. 2002, Ehmke et al. 2005, Guerrero et al. 2005, Mascarenhas et al. 2005, Mombelli et al. 2005, Xajigeorgiou et al. 2006, Gomi et al. 2007, Haffajee et al. 2007) were identified together with the 23 studies selected in 2002, after excluding the other referred studies assessing LDD (Caton et al. 2000, Golub et al. 2001).

Data from 32 papers were analysed, including 45 test groups comparing 10 different systemic antimicrobials (amoxicillin, metronidazole, spiramycin, azithromycin, tetracycline, doxycycline, clindamycin) or combinations (amoxicillin plus metronidazole, spiramycin plus metronidazole, amoxillin plus clavulanate), in populations from 10 different countries (Japan; the United States and Canada; Finland, Sweden, the Netherlands, the United Kingdom, Germany, Greece and Switzerland) in three continents.

Five pairs of papers reported results from the same sample material: Listgarten et al. (1978) reported site-based results from the same sample from which Hellden et al. (1979) described full-mouth results; Joyston-Bechal et al. (1984) described 22-week results from the same population that Joyston-Bechal et al. (1986) reported 3-year results; similarly, Ehmke et al. (2005) described 24-month results from the same study as the 12-month report of Flemmig et al. (1998); Palmer et al. (1998) first presented the results for the whole population and later compared the results of smokers and non-smokers (Palmer et al. 1999); and finally, McCulloch et al. (1990) and Kulkarni et al. (1991) also described results from the same patient sample.

The study design, characteristics of the patient sample and description of periodontitis of the 32 papers are summarized in Table 1.

Data extraction and evaluation

A number of factors were considered to evaluate the quality of debridement:

- Operator (dentist, hygienist or dental student).
- Use of local anaesthesia (yes or no).
- Total time spent in debridement (in hours).
- Number of days of active (debridement) treatment.
- Chronology of debridement (debridement only once as initial therapy, or subsequent debridement sessions at later stages).

The drug dosage was evaluated by calculating the total dosage, also taking into account the duration of the prescription and the number of cycles.

The relation between the debridement and the antibiotic usage was evaluated as follows:

- With debridement (coincidence of both antibiotic and debridement, both starting the same day and lasting equally).
- With debridement plus additional time of drug intake (similar to the previous, but the antibiotic lasted longer than debridement).
- Immediately after debridement (antibiotic intake starts after the last session of debridement).
- With new debridement (antibiotic was given when a subsequent debridement was performed, not after initial debridement).
- Mostly before debridement (most of the antibiotic was taken before the debridement was completed).
- Delayed.

In addition, data on adverse events were also extracted and evaluated.

To assess the clinical efficacy of the adjunctive therapy, three outcome variables were compared between the test and placebo groups: changes in PPD, in CAL and in BOP. If multiple variables for the same measurement were available, the one with significant results was selected.

Results

Amoxicillin plus metronidazole (Tables 5a and 5b)

Seven comparisons were available, two of them belonging to the same patient sample at two different time periods: 12 (Flemmig et al. 1998) and 24 months (Ehmke et al. 2005). All comparisons showed an advantage in clinical outcomes for the test groups, most of them statistically significant. One study in advanced periodontitis (Rooney et al. 2002) and another in generalized Ag.P. (Guerrero et al. 2005) demonstrated statistically significant improvements over SRP alone in the three selected outcome variables (PPD, CAL and BOP). In these two studies, the debridement was performed by periodontists, anaesthesia was used (if needed) and 3–4 h were spent. Most of the antibiotic was taken after debridement. In contrast, in the studies reporting less beneficial results, debridement was performed by less experienced clinicians, and in the study that did not find significant differences (Flemmig et al. 1998), debridement was performed by dental students.

Metronidazole (Tables 5a and 5b)

Data from 14 comparisons were available. Two sets of three comparisons reported results from the same patient sample: one study reported results after 22 weeks for all patients (Joyston-Bechal et al. 1984), or 22 weeks and 3 years for the patients who finished the study (Joyston-Bechal et al. 1986); another study reported first results for the whole sample (Palmer et al. 1998) and then stratified by smoking status (Palmer et al. 1999).

Three of the studies described very positive results for the adjunctive treatment, and five positive results. Conversely,

Table 5a. Factors affecting debridement and antibiotic intake in studies evaluating amoxicillin plus metronidazole or metronidazole

Author and year	Operator/s	Anaesthesia	Sessions	Time spent (h)	Period of DB	AB use	Previous or delayed DB	Days	mg per dose	Intakes/ day	Total dosage
Amoxicillin+metronidazole											
Berglundh et al. 1998)	Not stated	Yes	3–5	NA	Not described	With DB (all?)	No	14	375+250	3	15,750+10,500
Flemmig et al. (1998)	Dental student	Yes	4	8	Not described	Immediately after DB	No	8	375+250	3	9000+6000
Rooney et al. (2002)	Periodontist	Yes	NA	3	7–12 d	Immediately after DB	No	7	250+200	3	5250+4200
Guerrero et al. (2005)	Periodontist	As needed	1	4	1 d	With DB+6d	No	7	500+500	3	10,500+10,500
Mombelli et al. (2005)	One clinician	Not explained	2–4	NA	1 w	With new DB (local)	Previous DB	7	375+250	3	7875+5250
Ehmke et al. (2005)	Dental student	Yes	4	8	Not described	Immediately after DB	No	8	375+250	3	9000+6000
Xajigeorgiou et al. (2006)	One clinician	Yes	4 and 1	NA	2 w and NA	With new DB	Previous DB 6w before	7	500+500	3	10,500+10,500
Metronidazole											
Lindhe et al. (1983b)	Not stated	Not explained	4	NA	2 w	With DB	New AB cycles (two)	14*	200	4	33,600
Joyston-Bechal et al. (1984)	Hygienist	Not explained	2	NA	1 w	Immediately after DB	New AB(1)+DB(2) cycles	5†	200	3	6000
Loesche et al. (1984)	Not stated	Not explained	NA	NA	Not described	With DB (all?)	No	7	250	3	5250
Joyston-Bechal et al. (1986)	Hygienist	Not explained	2	NA	1 w	Immediately after DB	New AB(1)+DB(2) cycles	5†	200	3	6000
Joyston-Bechal et al. (1986)	Hygienist	Not explained	2	NA	1 w	Immediately after DB	New AB(1)+DB(2) cycles	5†	200	3	6000
Soder et al. (1990)	Hygienist	Not explained	NA	2–5	Not described	1 m after	No	7	400	3	8400
Saxen & Asikainen (1993)	Dental student	Not explained	NA	NA	Not described	Unclear	New DB every 3months	10	200	3	6000
Palmer et al. (1998)	Hygienist	Yes	2	3	1 w	Immediately after DB	No	7	200	3	4200
Palmer et al. (1999)	Hygienist	Yes	2	3	1 w	Immediately after DB	No	7	200	3	4200
Palmer et al. (1999)	Hygienist	Yes	2	4	1 w	Immediately after DB	No	7	200	3	4200
Sigusch et al. (2001)	Hygienist and not stated	Not explained and yes	4–5 and 1–2	NA and 2–4	NA and 2 d	Immediately after DB	Previous DB	8	500	2	8000
Rooney et al. (2002)	Periodontist	Yes	NA	4	7–12 d	Immediately after DB	No	7	200	3	4200
Xajigeorgiou et al. (2006)	One clinician	Yes	4 and 1	NA	2 w and NA	With new DB	Previous DB 6w before	7	500	3	10,500
Haffajee et al. (2007)	Dentists	Yes	4	NA	3 w	With 1st and 2nd q DB	No	14	250	3	10,500

†Two cycles of drug.

DB, debridement; AB, antibiotic; NA, not available; w, weeks; m, months.

Table 5b. Clinical outcomes of studies evaluating amoxicillin plus metronidazole or metronidazole

Author and year	Variable PPD	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable CAL	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable BOP	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats
Amoxicillin+metronidazole												
Berglundh et al. (1998)	%>5(0–12 mm)	23%	36%	NS	⩾6	1.5	2.1	**<0.05**	4s/t (0–24 months)	49%	58%	NS
Flemmig et al. (1998)					⩾7 mm	1.032	1.405	NS	6s/t (base 4–6 mm)	26.8%	33.03%	NS
Rooney et al. (2002)	%>5 mm	6.90%	14.60%	**<0.001**	4s/t (%sites CAL>5 mm)	6.10	10.60	**<0.05**	4s/t; %BOP	20.70%	39.80%	**<0.001**
Guerrero et al. (2005)	%>6 mm	5.30%	10.80%	**<0.05**	⩾7	1.3	2.3	**<0.001**	6s/t	21%	32%	**0.02**
Mombelli et al. (2005)	2s/p (>4 mm)	1.6	2.6	***SS (at 6 m)***	2s/p (>4 mm)	0.4	2.3	**0.02**	2s/p (>4 mm)	20.0%	30.0%	NS
Ehmke et al. (2005)					⩾7 mm	0.3	1.7	**<0.05**				
Xajigeorgiou et al. (2006)	*n* sites>6 mm	58%	80%	**<0.05**	6s/t, all sites	0.48	0.92	NS	6s/t, all sites	63.0%	72.0%	NS
Metronidazole												
Lindhe et al. (1983b)	4s/p (⩾6 mm) %>6 mm	72%	66%	No Stat	4s/p⩾6 mm	1.6	1.8	No Stat	BOP is Gi = 2+3	89%	84%	No Stat
Joyston-Bechal et al. (1984)	All teeth, 4s/t	0.93	1.18	***<0.05 (at 22 w)***								
Loesche et al. (1984)	All teeth (baseline⩾6 mm)	1.55	3.19	**0.03**	⩾6	0.23	1.42	**0.05**				
Joyston-Bechal et al. (1986)	All teeth, 4s/t	0.62	1.03	NS								
Joyston-Bechal et al. (1986)	All teeth, 4s/t	0.9	1.28	NS								
Soder et al. (1990)	4s/t (deeper of mesial and distal)	0.41	0.46	NS								NS
Saxen & Asikainen (1993)	4s/t; only>3 (%>3)	7.30%	16.00%	No Stat					4s/t; only>3 mm	12.4%	21.5%	No Stat
Palmer et al. (1998)	6s/t only>4.5 mm	1.7	1.5	NS	6s/t only>4.5 mm	0.51	0.67	NS	6s/t Only>4.5 mm	7.2%	11.9%	NS
Palmer et al. (1999)	6s/t only>4.5 mm	1.98	1.83	NS	6s/t only>4.5 mm	0.53	0.79	NS	6s/t Only>4.5 mm	28.2%	44.0%	NS
Palmer et al. (1999)	6s/t only>4.5 mm	1.12	1.2	NS	6s/t only>4.5 mm	0.47	0.43	NS	6s/t Only>4.5 mm	47.4%	46.6%	NS
Sigusch et al. (2001)	6s/t, baseline 3 w; ⩾6	1.1	4.3	**SS**	6s/t, baseline 3 w (⩾6)	−0.1	2.8	SS				
Rooney et al. (2002)	4s/t, %>5 mm	6.90%	10.80%	**<0.05–0.001**	4s/t (%sites CAL>5 mm)	6.1%	9.4%	NS	4s/t; %BOP	20.70%	29.30%	NS
Xajigeorgiou et al. (2006)	6s/t, %>6	58%	87.80%	**<0.05**	6s/t, all sites	0.48	1.24	NS	6s/t, all sites	63.0%	59.0%	NS
Haffajee et al. (2007)	6s/t, >6	1.66	2.96	**<0.01**	6s/t, >6 mm	1.26	2.45	***p*<0.05**				

In bold, inter-group statistically significant differences in changes baseline–final evaluation; in bold plus italics, inter-group statistically significant differences at a follow-up visit.
SRP, scaling and root planing; AB, antibiotic; NA, not available; Stats, statistical analyses; inter, inter-group; intra, intra-group; s, site; p, patient; t, tooth; NS, not statistically significant; SS, statistically significant; PPD, probing pocket depth; CAL, clinical attachment level; BOP, bleeding on probing; w, weeks; d, days; m, months.

six studies were not able to detect statistically significant differences.

From these studies, no clear trend was found, although it seems that dosage was more relevant in the results than factors related to debridement. More recent studies, prescribing higher dosages and including patients with more aggressive forms of periodontitis, tended to report better results.

Doxycycline (Tables 6a and 6b)

Five comparisons were selected, two of them from the same patient sample (McCulloch et al. 1990, Kulkarni et al. 1991). One of the studies showed very good results, with statistically significant inter-group differences. Two additional studies found significant differences, but only intra-group (Kulkarni et al. 1991) or at a specific visit (Ng & Bissada 1998). The other two studies did not report significant benefits in aggressive periodontitis patients, and the results for doxycycline were poor in comparison with those using other antimicrobial agents evaluated (Sigusch et al. 2001, Xajigeorgion et al. 2006).

No clear trend could be observed regarding quality of debridement, because the beneficial effects were observed only in one report in active sites in refractory cases.

Tetracycline (Tables 6a and 6b)

Data were available from five comparisons, although two of them belonged to the same patient sample (Listgarten et al. 1978, Hellden et al. 1979).

None of them demonstrated additional benefits. The drug prescription was made in coincidence with the debridement period, as most classical studies did. The most recent study assessing tetracycline was published in 1993.

Amoxicillin and amoxicillin plus clavulanate (Tables 6a and 6b)

Only one study assessed amoxicillin alone, and showed additional benefits in terms of PPD reductions. In this study, debridement was performed by a periodontist within 7–12 days, and the drug was prescribed after the last session of SRP. In contrast, no statistically significant advantage was observed by the three studies evaluating amoxicillin plus clavulanate. Although information on the quality of debridement was not clear, the drug was given 6 weeks after SRP in one study (Winkel et al. 1999), another did not provide statistical data (Walker et al. 1993) and two studies only reported results from selected active sites in refractory patients (Walker et al. 1993, Magnusson et al. 1994).

Azithromycin (Tables 6a and 6b)

Four studies were available, all of them published since 2002. Two of them demonstrated statistically significant benefits in PPD, and in either CAL (Mascarenhas et al. 2005) or BOP (Gomi et al. 2007). In both studies, Ch.P. patients were included. In the other studies (Smith et al. 2002, Haffajee et al. 2007), no additional significant improvements were found. In these two studies the patient sample included patients with either Ag.P. or Ch.P., although the age range of both four studies coincided.

The most relevant difference when comparing these studies that obtained positive results and the ones that did not was the period of active debridement treatment, being 1 day (Gomi et al. 2007) or a maximum of 1 week (Mascarenhas et al. 2005) for the positive studies and 2 (Smith et al. 2002) or 3 weeks (Haffajee et al. 2007) for the negative.

In two studies, antibiotic intake started immediately after finishing debridement, but in one case, without positive results, this debridement was performed within 2 weeks (Smith et al. 2002), while in the other, with positive results, within a maximum of 1 week (Mascarenhas et al. 2005).

In the other two studies, the prescription regime was different: in one, it started after the first session of SRP, which lasted 3 weeks (one session per week) and no positive results were reported (Haffajee et al. 2007); in the other, antibiotic intake started 3 days before SRP, which was performed in 1 day (Gomi et al. 2007). It should be pointed out that azithromycin maintains relevant serum and tissue levels for up to 6 days (Malizia et al. 1997).

Clindamycin (Tables 6a and 6b)

Three studies were available: two in refractory patients (Walker et al. 1993, Magnusson et al. 1994) and another in Ag.P. (Sigusch et al. 2001). One of the studies did not include a statistical evaluation (Walker et al. 1993), while the other two reported statistically significant benefits for the adjunctive therapy, in both cases with debridement under local anaesthesia.

Spiramycin and spiramycin plus metronidazole (Tables 6a and 6b)

Two studies for spiramycin alone (Al Joburi et al. 1989, Bain et al. 1994) and one for the combination with metronidazole (Chin et al. 1988) were evaluated. Statistically significant benefits were only seen when the comparison were performed at intermediate visits (Chin et al. 1988, Bain et al. 1994). The studies used the antibiotic together with debridement, with additional days for the drug if necessary, as is common in classical studies (the more recent of these series of studies was published in 1994).

Adverse effects (Table 7)

Adverse events were more frequent in test than in control groups. This was especially evident when two antibiotics were combined, mainly for the combination of amoxicillin and metronidazole. However, most adverse effects were related to gastrointestinal problems and were considered minor by the patients. Few adverse effects led to dropout from the studies. No proper evaluation of adverse microbiological effects was reported.

Discussion

Can systemic antimicrobials be efficacious if the biofilm is not disrupted?

The evaluated studies (both on biofilm properties and the clinical studies), the classical review published in 1993 (Greenstein 1993), the Position Papers by the American Academy of Periodontology (AAP 1996, Slots 2004) and a systematic review and a consensus report (Haffajee et al. 2003) clearly suggest that the use of systemic antimicrobials as monotherapy in the treatment of periodontitis is not recommended. However, the publication of the study performed by Lopez et al. (2006) raised controversy on the use of antimicrobials for the treatment of periodontitis, and in particular, used as monotherapy (Feres-Filho et al. 2006, Mombelli 2006, Walter & Weiger 2006), which was already initiated after

Table 6a. Factors affecting debridement and antibiotic intake in studies evaluating tetracyclines, macrolides, penicillins and clindamycin

Author and year	DB-related factors					AB and DB		AB dosage			
	operator/s	anaesthesia	sessions	time spent (h)	period of DB	antibiotic use	previous or delayed DB	days	mg per dose	intakes/ day	total dosage
Doxycycline											
McCulloch et al. (1990)	Not stated	Not explained	2–4	2–4	Not described	With new DB+20 d	New DB at 1, 3, 7 m	21	200(1 d) then 100	1	2200
Kulkarni et al. (1991)	Not stated	Not explained	2–4	2–4	Not described	With new DB+20 d	New DB at 1, 3, 7 m	21	200(1 d) then 100	1	2200
Ng & Bissada (1998)	Not stated	Yes	1	NA	1 day	With DB+41 d	No	42	200(1 d) then 100	1	4300
Sigusch et al. (2001)	Hygienist and not stated	Not explained and yes	4–5 and 1–2	NA and 2–4	NA and 2 days	Immediately after DB	Previous DB	8	200	1	1600
Xajigeorgiou et al. (2006)	One clinician	Yes	4 and 1	NA	2 w and NA	With new DB	Previous DB 6 w before	14	200(1st day) and 100	1	1500
Tetracycline											
Listgarten et al. (1978)	Not stated	Not explained	2–4	NA	2 w	With DB	New AB cycle after 4 w	14*	250	4	28,000
Hellden et al. (1979)	Not stated	Not explained	2–4	NA	2 w	With DB	New AB cycle after 4 w	14*	250	4	28,000
Lindhe et al. (1983a)	Not stated	Yes	2–4	NA	1 w	With DB	Lower dose for 1 y	350	250	4 (2w), then 1	87,500
Al Joburi et al. (1989)	Not stated	Not explained	2	6	1 w	With DB+7 d	No	14	250	4	14,000
Saxen & Asikainen (1993)	Dental student	Not explained	NA	NA	Not described	Unclear	New DB every 3 m	12	250	4	12,000
Amoxicillin											
Rooney et al. (2002)	Periodontist	Yes	NA	5	7–12 days	Immediately after DB	No	7	250	3	5250
Augmentin											
Walker et al. (1993)	Not stated	Not explained	1	NA	1 day	With DB+13 d	No	14	250+125	3	10,500+5250
Magnusson et al. (1994)	Not stated	Yes	NA	NA	Not described	Unclear	New DB every 3 m	14	250+125	3	10,500+5250
Winkel et al. (1999)	Not stated	Yes	3–6 and NA	NA	Not described	With new DB+9 d	Previous DB 6 w before	10	500+125	3	15,000+3750
Azithromycin											
Smith et al. (2002)	Hygienist	Not explained	3	NA	2 w	Immediately after DB	No	3	500	1	1500
Mascarenhas et al. (2005)	Not stated	Not explained	2	NA	1 w (maximum)	Immediately after DB	No	5	500 (1 d), 250 (4 d)	1	1500
Haffajee et al. (2007)	Dentists	Yes	4	NA	3 w	With 1st q DB	No	3	500	1	1500
Gomi et al. (2007)	Not stated	Yes	1 (test) and 4–6	1.5 (test) and NA	1d (test) and 5w	Before sub DB	Previous supra DB	3	500	1	1500

Clindamycin											
Walker et al. (1993)	Not stated	Not explained	1	NA	1 day	With DB+9 d	No	10	150	4	6000
Magnusson et al. (1994)	Not stated	Yes	NA	NA	Not described	Unclear	New DB every 3 m	10	NA	4	NA
Sigusch et al. (2001)	Hygienist and not stated	Not explained and yes	4–5 and 1–2	NA and 2–4	NA and 2 days	Immediately after DB	Previous DB	8	150	4	4800
Spiramycin+metro											
Chin et al. (1988)	Not stated	Not explained	2	6	1 w	With DB+7 d	No	14	2.25 UI+375	2	63 UI+10,500
Spiramycin											
Al Joburi et al. (1989)	Not stated	Not explained	2	6	1 w	With DB+7 d	No	14	1.5 UI	2	42 UI
Bain et al. (1994)	Not stated	Not explained	NA	3–5	2 w	With DB	No	14	1.5 UI	2	42 UI

DB, debridement; AB, antibiotic; NA, not available; w, weeks; d, days; m, months; y, years.

Table 6b. Clinical outcomes of studies evaluating tetracyclines, macrolides, penicillins and clindamycin

Author and year	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats
	PPD				CAL				BOP			
Doxycycline												
McCulloch et al. (1990)	1s/p active	− 1.3	0.8	NS	Additional loss(>2 mm)	79%	45%	**<0.05**				
Kulkarni et al. (1991)	NA				1s/p active	− 0.78	4.10	Only intra				
Ng & Bissada (1998)	6s/t, all sites	− 0.3	0.3	NS	6s/t all sites	− 0.9	0.4	***SS(at 24 w)***				
Sigusch et al. (2001)	6s/t, ⩾6	1.1	1.2	NS	6s/t, ⩾6	− 0.1	0.9	NS				
Xajigeorgiou et al. (2006)	6s/t, all sites	0.69	0.89	NA	6s/t all sites	0.48	0.81	NS	6s/t, all sites	63.0%	67,0%	NS
Tetracycline												
Listgarten et al. (1978)	1s/p	2.2	2.4	NS	1s/p	0	0	NS				
Hellden et al. (1979)	all sites>3 mm; 6s/t	1.8	2.2	NS	Sites>3 mm; 3s/t (buccal)	0.30	0.49	NS	BOP is Gi>0	59.0%	65.2%	NS
Lindhe et al. (1983a)	4s/p (incisor+pre-molar)	2.3	3.1	NS	4s/p (incisor+pre-molar)	1.4	1.7	NS	4s/p	85%	100%	NS
Al Joburi et al. (1989)	2s/p, 4loc/s; initial⩾7	2.85	3.04	NS	2s/p, 4loc/s; initial⩾7	1.54	1.79	NS				
Saxen & Asikainen (1993)	4s/t, %>3 mm (base-6 m)	7.30%	11.40%	No Stats					4s/t; only>3 mm	12.4%	28.0%	No Stats
Amoxicillin												
Rooney et al. (2002)	4s/t; %>5 mm	− 6.9	− 10.8	**<0.05–0.001**	4s/t (%sites CAL>5 mm)	6.10	8.70	NS	4s/t; %yes/no	20.7	27.9	NS
Augmentin												
Walker et al. (1993)	1s/p active; NA				1s/p active; 9 m	0.85	2.18					
Magnusson et al. (1994)	1s/p active	0.73	1.55	NS	1s/p active	0.84	1	NS	1 s/p active	25%	8%	NS
Winkel et al. (1999)	6s/t; ⩾6	2.7	2.4	NS	6s/t; ⩾6	1.7	1.1	NS	4s/t; yes/no	30.0%	40.0%	NS

Table 6b. (Contd.)

Author and year	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats	Variable	SRP change	SRP+AB change	SRP *versus* SRP+AB inter Stats
Azithromycin												
Smith et al. (2002)	4s/t, >5 mm	2.22	3.09	NA	NA	NA	NA	NA	4s/t; %yes/no	16.6	23.4	NS
Mascarenhas et al. (2005)	6s/t, >6 mm	1.98	3.52	$<$**0.05**	6s/t; $\geqslant 6$	1.32	3.52	$<$**0.05**	6s/t %BOP	17.7%	18.6%	NS
Haffajee et al. ((2007)	6s/t, >6 mm	1.66	2.35	NS	6s/t, >6	1.26	1.7	NS				
Gomi et al. (2007)	Mean	0.75	1.62	$<$**0.001**	Mean	1.47	2.62	NS	Mean %BOP	18.5	26.0	$<$**0.01**
Clindamycin												
Walker et al. (1993)	1s/p active; NA				1s/p active; 9 m	0.85	2	No Stats				
Magnusson et al. (1994)	1s/p active	0.73	0.93	NS	1s/p active	0.84	-0.15	**0.005***	1 s/p active	25%	25%	NS
Sigusch et al. (2001)	6s/t, $\geqslant 6$	1.1	4.4	**SS**	6s/t; baseline 3 w; $\geqslant 6$	-0.1	2.4	**SS**				
Spiramycin+metro												
Chin et al. (1988)	2site/p, 4 loc/site				2s/p; 4 loc/s	0.60	0.60	***p*$<$*0.05(at 6 m)***				
Spiramycin												
Al Joburi et al. (1989)	2s/p, 4loc/s; initial$\geqslant 7$	2,85	2,57	NS	2s/p; 4loc/s; initial$\geqslant 7$	1.54	1.46	NS				
Bain et al. (1994)	2s/p; proximal; $\geqslant 6$	2,4	2,87	***0.007(at 24 w)***	2s/p; >6 mm (prox)	1.58	1.87	NS				

In bold, inter-group statistically significant differences in changes baseline-final evaluation, and in bold plus italics, at a follow-up visit.
SRP, scaling and root planing; AB, antibiotic; NA, not available; Stats, statistical analyses; inter, inter-group; intra, intra-group; s, site; p, patient; loc, location; t, tooth; NS, not statistically significant; SS, statistically significant; PPD, probing pocket depth; CAL, clinical attachment level; BOP, bleeding on probing; w, weeks; m, months; y, years.

the publication of the excellent results of the paper by Guerrero et al. (2005), and the evaluation of antimicrobial susceptibilities by van Winkelhoff et al. (2005), with different letters to the editor or editorials (Mombelli 2005, van Winkelhoff 2005, Haffajee 2006, Needleman & Wisson 2006). All comments stated that the risk of using antimicrobials (systemic side effects, increase in antimicrobial resistance) should lead to restriction in their use in periodontitis in certain patients and certain conditions. In addition, their use should be combined with debridement, based on the knowledge of the biofilm characteristics and the evidence available from clinical studies. The results provided by Lopez et al. (2006) have not been substantiated by other authors and in fact, although in the title the antimicrobial systemic therapy was considered as ''the only therapy'', supragingival professional debridement was provided (by a periodontist and totalling 90 min. of treatment) and, secondly, although the periodontitis was defined as moderate to severe, the proportions of moderate and deep PPD and mean CAL were more close to initial disease (Armitage 1999) (percentage of 4–6 mm sites at baseline 6.31 ± 6.17 and 15.27 ± 9.73, for control and test groups, respectively; percentage of >6 mm sites at baseline 0.88 ± 1.88 and 3.11 ± 5.00, respectively; and mean CAL at baseline 3.73 ± 0.82 and 3.84 ± 0.56), being possible that for this severity, that supragingival debridement may have a powerful subgingival impact. All these factors make it reasonable to interpret their results with caution, and thus maintain the previous conclusions, already published by Greenstein (1993) and agreed upon by the position papers of the American Academy of Periodontology (AAP 1996, Slots 2004).

Can the type of debridement (non-surgical *versus* surgical) of the subgingival biofilm impact upon the clinical outcomes of the adjunctive antimicrobial therapy?

Although the scientific literature includes numerous studies that have described the effects of the administration of systemic antimicrobials in combination with different periodontal treatments, there is limited evidence to support its use as an adjunct to periodontal surgery (Ciancio 2002, Haffajee et al. 2003).

Table 7. Percentage of patients affected of adverse effects associated with the use of systemic antimicrobials

	% patients SRP	% patients SRP+AB	Adverse effects description
Amoxicillin+metronidazole			
Berglundh et al. (1998)	NA	NA	NA
Flemmig et al. (1998)	0%	30%	Diarrhoea and 2 excluded
Rooney et al. (2002)	0%	0%	No
Guerrero et al. (2005)	19%	55%	Diarrhoea, taste, stomach, unwellness
Mombelli et al. (2005)	NA	NA	NA
Ehmke et al. (2005)	0%	30%	Diarrhoea and 2 excluded
Xajigeorgiou et al. (2006)	0%	20.0%	Gastrointestinal
Metronidazole			
Lindhe et al. (1983b)	NA	NA	NA
Joyston-Bechal et al. (1984)	NA	NA	NA
Loesche et al. (1984)	NA	NA	Metalic taste
Joyston-Bechal et al. (1986)	NA	NA	NA
Joyston-Bechal et al. (1986)	NA	NA	NA
Soder et al. (1990)	19%	30%	Diarrhoea, taste
Saxen & Asikainen (1993)	NA	NA	NA
Palmer et al. (1998)	NA	NA	NA
Palmer et al. (1999)	NA	NA	NA
Palmer et al. (1999)	NA	NA	NA
(Sigusch et al. (2001)	NA	NA	NA
(Rooney et al. (2002)	0%	0%	No
(Xajigeorgiou et al. (2006)	0%	8.3%	Metallic taste
Haffajee et al. (2007)	0%	8.3%	Dizziness, diarrhoea
Doxycycline			
McCulloch et al. (1990)	0.0%	10.3%	Gastrointestinal-mild
Kulkarni et al. (1991)	0.0%	0.0%	No effects
Ng & Bissada (1998)	0.0%	0.0%	No effects
Sigusch et al. (2001)	NA	NA	NA
Xajigeorgiou et al. (2006)	0.0%	0.0%	
Tetracycline			
Listgarten et al. (1978)	NA	NA	NA
Hellden et al. (1979)	NA	NA	NA
Lindhe et al. (1983a)	NA	NA	NA
Al Joburi et al. (1989)	0.0%	3.7%	Diarrhoea
Saxen & Asikainen (1993)	NA	NA	NA
Amoxicillin			
Rooney et al. (2002)	0.0%	0.0%	No
Amoxicillin and clavulanate			
Walker et al. (1993)	NA	NA	NA
Magnusson et al. (1994)	NA	NA	NA
Winkel et al. (1999)	20.0%	20.0%	Mild diarrhoea
Azithromycin			
Smith et al. (2002)	0.0%	0.0%	No
Mascarenhas et al. (2005)	0.0%	0.0%	No
Haffajee et al. (2007)	0.0%	8.0%	Allergic reaction, difficulty swallowing the tablets
Gomi et al. (2007)	0.0%	65.0%	1 diarrhoea, 10 need analgesics
Clindamycin			
Walker et al. (1993)	NA	NA	NA
Magnusson et al. (1994)	NA	NA	NA
Sigusch et al. (2001)	NA	NA	NA
Spiramycin and metronidazole			
Chin et al. (1988)	0.0%	15.4%	Mild diarrhoea
Spiramycin			
Al Joburi et al. (1989)	0.0%	0.0%	No effects
Bain et al. (1994)	0.0%	2.1%	Abdominal (2 excluded)

SRP, scaling and root planning; AB, antibiotic; NA, not available.

An initial overview of the selected papers revealed that the use of antibiotics as part of a surgical protocol may have two distinct objectives: to prevent possible complications, including infection, and as an adjunct in the treatment of periodontitis, trying to enhance the clinical or microbiological outcomes. The use of systemic antimicrobials in regenerative periodontal surgeries has usually combined both aims: on the one hand, to prevent post-operative complications when a foreign body is placed inside the periodontium; on the other, to improve the regenerative outcomes by reducing bacterial contamination.

The prevention of post-surgical infections through the routine use of perioperative antibiotics appears for the most part to be based on empiricism, and this antibiotic prophylaxis has not been shown to offer an advantage in preventing infections (Pack & Haber 1983, Checchi et al. 1992, Powell et al. 2005). Additional indications of the prophylactic use of antibiotics, including the prevention of bacterial endocarditis (Wilson et al. 2007), or in medically compromised patients (Pallasch & Slots 1996, Powell et al. 2005), should be considered following updated guidelines.

There have been relatively few controlled trials assessing the additional effect on periodontal outcomes of adjunctive antimicrobials used in conjunction with periodontal surgeries (Kunihira et al. 1985, Haffajee et al. 1995, Palmer et al. 1996, Kleinfelder et al. 2000, Dastoor et al. 2007). Some studies suggest that there might be a beneficial effect with antimicrobial use, although often these benefits were not clearly better than those of the control groups, either because the differences did not reach the level of statistical significance or the magnitudes were of little clinical relevance (Kunihira et al. 1985, Mahmood & Dolby 1987, Palmer et al. 1996, Dastoor et al. 2007).

Different reviews investigating regenerative procedures in periodontal treatment have recommended the use of systemic antibiotic therapy, as part of the treatment protocol (Cortellini & Bowers 1995, Machtei & Schallhorn 1995, Cortellini & Tonetti 2000, Kornman & Robertson 2000, Sanz & Giovannoli 2000), with the aim of controlling the subgingival microflora in the early healing phase and to reduce complications, such as the infection from exposed membranes, and in this manner trying to increase the predictability of results. However, the clinical need and the long-term efficacy of the adjunctive use of systemic antibiotics in periodontal regenerative surgical procedures can be questioned, because there are few controlled trials assessing this use (Demolon et al. 1993, 1994,

Mombelli et al. 1996, Nowzari et al. 1996, Vest et al. 1999, Sculean et al. 2001, Loos et al. 2002), and the results are controversial (Demolon et al. 1993, 1994, Loos et al. 2002).

Is the efficacy of the adjunctive systemic antimicrobial therapy dependent on the quality of the debridement of the subgingival biofilm and the sequence debridement–antibiotic usage?

The results of this section should be interpreted with caution, due to a lack of direct evidence. From the previously analysed studies, it can be concluded that the quality of the debridement, and the time of the prescription of the drug, in relation to the debridement, may influence the clinical outcome. Especially, the results from the studies assessing amoxicillin plus metronidazole and azithromycin may suggest that if the operator has higher skills, the drug is provided immediately after debridement, the debridement is accomplished within the shortest period of time and anaesthesia is involved, clinical results significantly improve in the groups using adjunctive antimicrobials. To further support these statements, two of the studies with the best results in favour of the adjunctive therapy carried out the full-mouth debridement within the same day (Guerrero et al. 2005, Gomi et al. 2007).

In the 1990s, Loesche & Giordano (1994) re-analysed data from two previous placebo-controlled studies: one with metronidazole (or placebo) prescribed after the first session of debridement (Loesche et al. 1991) and the other after the last session of debridement (Loesche et al. 1992). Thirty-nine out of 50 and 33 out of 46 patients, respectively, were evaluated at the end of the study. A statistically significant protocol effect (favouring the protocol of 1992, debridement first, then medication) was observed for changes in PPD and in CAL (in initial pockets $\geqslant 7$ mm, $p \leqslant 0.01$), and for changes in the subgingival microflora (evaluated by darkfield microscopy and by culturing). Although the conclusions were evident, many studies evaluating the adjunctive value of antimicrobials to SRP, and designed after the publication of this paper, have still selected a different protocol.

Based on the conclusions by Loesche & Giordano (1994), on the evaluation of RCTs provided in the present review, and on the understanding of the biofilm characteristics, it should be suggested that the antimicrobial will be more effective when the biofilm has been disrupted and still not re-organized. In other words, carry out a good-quality debridement during a short period of time, and immediately prescribe the antimicrobial drug. If the debridement is accomplished within 24 h, the drug intake could even be started before the debridement (Guerrero et al. 2005, Gomi et al. 2007).

In addition to the above, the risk of adverse effects should be considered, especially when more than one antibiotic is prescribed. The evaluation of the risk/benefit ratio should include this factor, and although reported adverse effects tend to be minor, serious problems cannot be discounted.

Summary and Conclusions

In the present review, different aspects of the use of systemic antimicrobials in the treatment of periodontitis have been addressed, especially focusing on the fact that the target pathogens are organized in biofilms.

Limitations of the present analyses are evident. The selected papers are quite heterogeneous and many additional factors could have influenced the outcomes, as has been discussed previously (Herrera et al. 2002, Haffajee et al. 2003). As examples, drug dosage and plaque control are important factors that should be taken into consideration: Loesche & Giordano (1994) reported that the use of low dosages of metronidazole (total dose < 4 g) demonstrated significantly inferior results than with the use of higher dosages ($\geqslant 5.25$ g); plaque control was evaluated by Kornman et al. (1994), who concluded that supragingival plaque control is an essential factor in attaining certain clinical and microbial outcomes following systemic antibiotic therapy in periodontitis.

The heterogeneity of the experimental designs used precludes any attempt at a more systematic approach in reviewing the literature, including meta-analysis. This variability includes:

- The type, severity and extension of the periodontal disease.
- The number of subjects.
- The number of sites evaluated per subject and the conditions of the selected sites, because some studies reported on evaluation of all teeth, while others reported on measurements only from selected sites.
- The quality and nature of the clinical measurements performed in the studies and the duration of the follow-up.
- The prescribed antibiotics and their dosage and duration of administration.
- The selected mechanical procedures used, and the concomitant mechanical debridement also differed among the studies.
- The study design.

It is clear that systemic antimicrobials may have a role in the treatment of periodontitis. However, due to the problems related to their indiscriminate use (especially systemic side effects, microbiological adverse effects and increase in bacterial resistances), the use of systemic antimicrobials in periodontitis should be restricted to certain patients and certain periodontal conditions (Herrera et al. 2002, Lindhe & Palmer 2002).

Moreover, when a decision has been made to prescribe the drug, it should be used under the most optimal conditions in order to achieve the best possible results. Some of these optimal conditions are related to the properties of the target, especially the biofilm characteristics that increase bacterial resistance against antimicrobials.

Within the limitations of the reviewed literature and the methods of evaluation, we can conclude the following:

- If systemic antimicrobials are indicated as part of periodontal therapy, they should be adjunctive to mechanical debridement.
- Lack of data prevents us from making any conclusion regarding the preferred type of adjunctive debridement (non-surgical *versus* surgical). Furthermore, there is not enough evidence to support the use of adjunctive systemic antimicrobials with periodontal surgery.
- There is no direct evidence to recommend a specific protocol for the use of adjunctive systemic antimicrobials with non-surgical mechanical debridement. However, indirect evidence suggests that antibiotic intake should start on the day of debridement completion; debridement should be completed within a short time (preferably < 1 week)

and with an adequate quality, because these may help to improve the results.

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Clinical Relevance

Scientific rationale for the study: The optimum protocol for the use of systemic antimicrobials in the treatment of periodontitis has not been defined clearly.

Principal findings: Evidence is available to support the adjunctive use of systemic antimicrobials to non-surgical debridement in certain patients. The same evidence is lacking for its adjunctive use to periodontal surgery. No studies comparing both treatment alternatives were identified.

Practical implications: If systemic antimicrobials are going to be used, they should be adjunctive to non-surgical debridement, and debridement should be performed with adequate quality, within 1 week, and antibiotic intake should start on the day of debridement completion.