Journal of the International Academy of Periodontology 2015 **17/1 Supplement:** 21–30

Group B
Initiator Paper
Non-surgical periodontal therapy: mechanical debridement, antimicrobial agents and other modalities

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Introduction

The main goals of periodontal therapy are to achieve reductions in probing depth (PD), bleeding on probing and suppuration, to maintain or gain clinical attachment (CA) and to prevent future attachment loss (i.e., maintenance of the long-term stability of the periodontal tissues). These clinical improvements are accompanied by an ecological shift in the subgingival microbial composition, from a microbial profile related to disease to a profile compatible with health (Socransky and Haffajee, 2002; Teles *et al.,* 2006; Feres, 2008). To achieve this microbiological goal, anti-infective treatments should reach not only deep periodontal pockets, but also shallow sites and other oral surfaces, which may harbor periodontal pathogens (Mager *et al.,* 2003; Faveri *et al.,* 2006a). However, to date periodontal treatment remains largely focused on deep pockets (Heitz-Mayfield and Lang, 2013). There is overall consensus that scaling and root planing (SRP), the gold-standard periodontal therapy, should be restricted to intermediate and deep pockets, and that instrumentation of shallow sites should be avoided in order to prevent trauma to both hard and soft tissues and possible consequent attachment loss (Ramfjord *et al.,* 1987; Heitz-Mayfield *et al.,* 2002). This mechanical therapy targets only the tooth surfaces and does not affect other areas of the mouth, such as the tongue and oral mucosae. In addition, SRP might not reach microbial reservoirs at the base of deep pockets, tooth furcations and within epithelial cells and the connective tissue. Consequently, SRP may fall short of inducing the changes in the subgingival microbial composition necessary to achieve and maintain the desired clinical improvements in all subjects, especially in cases of advanced disease where deep periodontal pockets are present (Loesche and Grossman, 2001; Sampaio *et al.,* 2011). Therefore, other forms of therapy, such as different scaling modalities or the adjunctive use of local and systemic antimicrobials, lasers and photodynamic therapies have been proposed in order to potentiate the effects of non-surgical mechanical therapy. In all instances, however, SRP is accepted to be the basis for all periodontal therapy and the additional therapies proposed and scrutinized in this paper are always considered adjunctive and supplemental.

Lasers and photodynamic therapies (PDT)

Laser and photodynamic therapies emerged in the 1990s as promising treatments for periodontitis. The main appeal of the laser therapy was its selective calculus ablation, bactericidal effect and its potential to control bleeding (Ando *et al.,* 1996; Folwaczny *et al.,* 2002; Aoki *et al.,* 2004). Several types of lasers have

Presented at the First IAP Conclave, Bangkok, Thailand, 11-13 April, 2014

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been proposed, either alone or adjunctive to SRP in the treatment of periodontitis, such as the erbium-doped:yttrium-aluminium-garnet (Er:YAG), diode laser (DL) and neodymium-doped:yttrium-aluminum-garnet (Nd:YAG). Three recent systematic reviews have evaluated the overall efficacy of laser therapy in the treatment of chronic periodontitis (Sgolastra *et al.,* 2012c; Sgolastra *et al.,* 2013b; Sgolastra *et al.,* 2014). Sgolastra *et al.* (2012c; 2013b) concluded that there were no statistically significant beneficial effects in the use of Er:YAG-only or DL as adjuncts to SRP, compared to results obtained with SRP only. On the other hand, a subsequent review (Sgolastra *et al.,* 2014) suggested that the adjunctive use of Nd:YAG could potentially provide additional benefits to conventional nonsurgical periodontal therapy, especially in mean PD reduction (0.55 mm, 95 % CI range: 0.34 to 0.76, $p < 0.00001$). However, only three studies, with 6 to 20 months of follow-up, were included in this meta-analysis (Qadri et al., 2010; Eltas and Orbak, 2012a; Eltas and Orgak, 2012b).

Photodynamic therapy (PDT) has been proposed as an adjunct to SRP in the treatment of periodontitis. The antimicrobial property of PDT involves a photoactivated dye (photosensitizer) that is absorbed preferentially by bacterial cells. When the photosensitizer is exposed to the light of a low power laser in the presence of oxygen it generates singlet oxygen and free radicals, which are extremely toxic to some microorganisms (Konopka and Goslinski, 2007; Maisch, 2007). Some of the clinical studies that have investigated the effect of adjunctive PDT associated with SRP in the treatment of chronic periodontitis have shown promising results (Andersen *et al.,* 2007; Braun *et al.,* 2008; Lulic *et al.,* 2009; Giannelli *et al.,* 2012), while other authors failed to show an additional benefit (Christodoulides *et al.,* 2008; Chondros *et al.,* 2009; Polansky *et al.,* 2009; Ruhling *et al.,* 2010; Theodoro *et al.,* 2012). A recent systematic review indicated that SRP in combination with PDT provided better PD reduction (0.19 mm, 95% CI range: 0.07 to 0.31, $p = 0.002$) and CAL gain (0.37 mm, 95% CI range: 0.26 to 0.47, $p < 0.0001$) in comparison with SRP alone at 3 months after treatment. However, this benefit was no longer observed at 6 months (Sgolastra *et al.,* 2013a).

Applying repeated (five times in two weeks) PDT in maintenance patients with residual PD ≥ 5 mm but previously treated for periodontitis, and comparing clinical outcomes to maintenance debridement in combination with a non-activated laser control in a randomized controlled trial (RCT; Lulic *et al.,* 2009), clearly yielded improved clinical outcomes in residual pockets, while regular maintenance debridement failed to demonstrate improvements in both PD and CAL in the residual pockets. Hence, further RCTs are indicated to elucidate positive outcomes of PDT in combination with SRP in maintenance patients.

Four studies to date have assessed the microbiological effects of PDT (Sgolastra *et al.,* 2013a), and only a modest benefit was observed in the composition of the subgingvial microbiota. Two studies showed statistically significantly greater reductions in the prevalence of *Treponema denticola*, *Eikenella corrodens, Capnocytophaga spp.* (Chondros *et al.,* 2009) and *Porphyromonas gingivalis* (Polansky *et al.,* 2009) in subjects treated with SRP plus PDT than in those treated with SRP alone. However, no studies to date have thoroughly examined the effects of the PDT in changing the subgingival microbial profile.

In summary, evidence supporting the added benefits of lasers and PDT in periodontal therapy is still scarce. The most promising results were obtained with the adjunctive use of Nd:YAG to SRP. Therefore, additional RCTs examining the long-term microbiological and clinical effects of Nd:YAG, other laser therapies and PDT are needed before these treatments are incorporated into routine clinical practice.

Full mouth scaling and root planing (FMSRP) and full mouth disinfection (FMD)

In 1995, researchers from the University of Leuven suggested that quadrant-SRP would allow reinfection of already treated sites by a translocation of periodontal pathogens from untreated periodontal sites or other oral niches (e.g., tongue, mucosa and saliva) to recently instrumented pockets. Based on this hypothesis, the authors advocated a treatment protocol that consisted of SRP of all pockets within 24 hours combined with various forms of applications of chlorhexidine (CHX), such as subgingival irrigation, mouthrinsing and tonsil spraying (Quirynen *et al.,* 1995). This protocol was named "full mouth disinfection (FMD)." As a consequence of studies demonstrating that CHX did not necessarily contribute to improved clinical outcomes after FMD (Quirynen *et al.,* 2000), clinicians proposed to treat periodontitis by means of full-mouth SRP in 24 hours, but without the adjunctive use of CHX, a protocol that became known as full-mouth scaling and root planing (FMSRP) (Apatzidou and Kinane, 2004). Three systematic reviews comparing the clinical (Eberhard *et al.,* 2008; Lang *et al.,* 2008; Farman and Joshi, 2008) and microbiological (Lang *et al.,* 2008) effects of FMD and/or FMSRP and conventional quadrant SRP for the treatment of chronic periodontitis were published in 2008. The reviews by Eberhard *et al.* (2008) and Farman and Joshi (2008) failed to show statistically significant differences between the FMSRP and conventional SRP. A discrete benefit for the FMD protocol in reducing PD (0.53 mm, 95% CI range: 0.28 to 0.77, $p = 0.0001$) and gaining CAL (0.33 mm, 95% CI range: 0.04 to 0.63, $p = 0.03$) in sites with PD ≥ 5 mm was reported by Eberhard *et al.* (2008). Lang *et al.* (2008) showed that FMD and FMSRP led to a slightly greater PD reduction in deep sites with PD ≥ 7 mm (0.50 mm, 95% CI range: -0.81 to 0.19, $p = 0.001$ and 0.43 mm, 95% CI range: -0.66 to 0.19, $p < 0.0001$, respectively) than quadrant-wise SRP. No additional reduction in levels and prevalence of specific periodontal pathogens was identified for any of the three treatment modalities (Lang *et al.,* 2008).

Taken together, these systematic reviews have suggested that FMSRP or FMD protocols do not provide clinically relevant advantages over conventional quadrant-wise scaling. Nonetheless, the notion that SRP completed in 24 hours yields clinical improvements similar to those obtained with quadrant-wise SRP is relevant information and represents an important contribution to the periodontal field. Today, it is largely recognized that the FMD and FMSRP protocols are effective alternatives to the quadrant SRP and the choice between treatment modalities is generally based on patient preferences, professional skills, logistic settings and cost-effectiveness (Eberhard *et al.*, 2008; Lang *et al.*, 2008; Farman and Joshi, 2008).

Antiseptics: pocket irrigation and rinsing

Antiseptics have been used as adjuncts to non-surgical periodontal treatment for pocket irrigation (Rosling *et al.,* 1983; Rosling *et al.,* 1986; Rams and Slots, 1996; Guarnelli *et al.,* 2008; Feng *et al.,* 2011), as part of the FMD protocol (Quirynen *et al.,* 1995) or to control supragingival plaque formation during the active phase of periodontal therapy and the healing phase (Faveri *et al.,* 2006b; Feres *et al.,* 2009).

The agents that have been most commonly used for pocket irrigation are Povidine-iodine (PVP-I), essential oils and chlorhexidine digluconate CHX (Rams and Slots, 1996). Overall, studies evaluating the effects of these antimicrobials in periodontal treatment have shown only short-term discrete clinical and microbiological benefits (Rosling *et al.,* 1983; Rosling *et al.,* 1986; Guarnelli *et al.,* 2008; Feng *et al.,* 2011), but these benefits do not seem to be maintained up to 6 months (Leonhardt *et al.,* 2007) or one year post-therapy (Krück *et al.,* 2012). Nonetheless, some studies have also suggested benefits in the use of CHX rinsing as an adjunctive to SRP and during the healing phase of mechanical treatment (Quirynen *et al.,* 2006; Faveri *et al.,* 2006b; Feres *et al.,* 2009). Feres *et al.* (2009) compared the clinical and microbiological effects of SRP alone or combined with professional plaque control or CHX rinsing twice a day for two months in the treatment of patients with chronic periodontitis. The two test treatments were more effective in improving PD and CAL than SRP alone, and the group rinsing with CHX exhibited the greatest reduction in PD in initially intermediate sites 6 months post-therapy. In addition, the most beneficial microbiological changes were observed in CHX-treated subjects, who showed a significant reduction in the proportions of red (*P. gingivalis*, *T. denticola* and *Tannerella forsythia*) and orange (mainly *Fusobaterium spp.*) microbial complexes, as well as an increase in the proportions of the host-compatible bacterial species. The authors concluded that strict plaque control performed during and after SRP, particularly by means of CHX rinsing, improved periodontal treatment outcomes. Subsequently, CHX rinsing was also shown to improve the clinical (Feres *et al.,* 2012) and microbiological benefits of systemic antibiotics, especially in initially shallow sites (Soares *et al.,* 2014).

Local antimicrobial delivery

Local application of antiseptics and antibiotics has been advocated for the treatment of localized periodontitis lesions, either as an adjunct to SRP in the active phase of treatment or to treat re-infected periodontal lesions in patients under maintenance therapy (Bonito *et al.,* 2005). Local release of antimicrobial agents or antibiotics is normally performed by means of fibers, gels, chips or microspheres (Rams and Slots, 1996). Some examples are doxycycline hyclate gel (ATRIDOX®), minocycline hydrochloride microspheres (ARESTIN®), tetracycline hydrochloride fibers (PERIODONTAL PLUS AB, ACTISITE®), metronidazole (MTZ) gel (ELYZOL®) and chlorhexidine gluconate chip (PERIOCHIP®). The greatest advantage of this type of local therapy is in avoiding the side effects of drugs used systemically and reducing the chances of developing bacterial tolerance to medications (Rams and Slots, 1996).

Previous systematic reviews have demonstrated a significant beneficial effect in the adjunctive use of local antimicrobials when compared with SRP alone; however, the clinical magnitude of this effect seems to be rather limited (Hanes and Purvis, 2003; Bonito *et al.,* 2005; Matesanz-Perez *et al.,* 2013). A recent systematic review and meta-analysis (Matesanz-Perez *et al.,* 2013) indicated a statistically significant beneficial effect of the subgingival application of different antimicrobials with a weighted mean difference (WMD) of 0.40 mm in PD reduction and 0.31 mm in CAL gain. The main benefits were observed with the use of tetracycline fibers, sustained released doxycycline and minocycline microspheres. The adjunctive use of tetracycline fibers demonstrated a statistically significant benefit in PD reduction, with a WMD between 0.5 mm and 0.7 mm. Conversely, the benefit in CAL gain was smaller and did not provide a significant advantage over SRP alone. The local application of CHX and MTZ showed a minimal effect when compared to a placebo (WMD between 0.1 mm and 0.4 mm). Although this systematic review described some additional beneficial effect for most of the local antimicrobials evaluated, the clinical relevance of the data reported needs to be interpreted with caution. Most of these studies reported data for deep periodontal pockets, as these are the main targets for locally delivered antiseptics and antibiotics. This may skew the overall benefits of these adjunctive treatments, because these are the sites that respond less favorably to SRP and therefore any adjunctive treatment would lead to additional clinical benefits over those obtained with scaling alone. In addition, only two studies (Eickholz *et al.,* 2002; Sakellari *et al.,* 2010), out of the 52 included in this review showed low risk of bias. Thus, it seems necessary to conduct further clinical studies with strict methodological criteria and longer follow-up periods in order to justify the regular use of locally delivered antimicrobials during periodontal treatment.

Systemic antibiotics

The first clinical studies on the effects of systemic antibiotics on periodontal treatment were conducted at the end of the 1970s and during the 1980s, with the use of tetracycline in the treatment of localized aggressive periodontitis (Slots *et al.,* 1979; Lindhe, 1981; Lindhe and Liljenberg, 1984). The treatment seemed promising, and hence, during the 1980s and 1990s almost all available antibiotics were tested for use in the treatment of chronic or aggressive periodontitis. At the beginning of the 2000s, the two first systematic reviews on the use of systemic antibiotics to treat periodontitis were published (Herrera *et al.,* 2002; Haffajee *et al.,* 2003). Over 10 different antibiotics or combination of drugs were included in these meta-analyses, and both studies suggested that the use of systemically administered adjunctive antibiotics to SRP provided some additional benefit over SRP alone in terms of CAL gain and PD reduction. Herrera *et al.* (2002) reported that the treatments including systemic antibiotics yielded a statistically significantly greater reduction in PD (range 0.2-0.8 mm) and gain in CAL (range 0.2-0.6 mm) in sites with PD ≥ 7 mm in comparison with SRP only. The meta-analysis reported by Haffajee *et al.* (2003) indicated that antibiotics provided statistically significantly better full-mouth CAL gain of 0.3-0.4 mm. Neither study could assign superiority to any antibiotic due to insufficient numbers of studies, different treatment protocols (e.g., drugs, combination of drugs, doses, duration of therapies), small sample sizes and lack of longitudinal data beyond 6 months for the majority of the studies evaluated.

Although several different antibiotics were tested for their use in periodontal treatment up to 2002, certain protocols have been favored, and between 2002 and 2013 the literature converged on the use of three particular drugs: MTZ (Sigusch *et al.,* 2001; Rooney *et al.,* 2002; Carvalho *et al.,* 2004; Xajigeorgiou *et al.,* 2006; Matarazzo *et al.,* 2008; Silva *et al.,* 2011; Feres *et al.,* 2012; Preus *et al.,* 2013), MTZ + amoxicillin (AMX) (Cionca *et al.,* 2009; Silva *et al.,* 2011; Feres *et al.,* 2012; Goodson *et al.,* 2012) and azithromycin (AZT; Smith *et al.,* 2002; Mascarenhas *et al.,* 2005; Dastoor *et al.,* 2007; Haffajee *et al.,* 2007; Haas *et al.,* 2008; Oteo *et al.,* 2010; Sampaio *et al.,* 2011; Emingil *et al.,* 2012; Han *et al.,* 2012).

MTZ arose in the 1980's as a particularly effective drug for the treatment of chronic periodontitis patients mainly due to its efficacy against obligate anaerobes, including some important periodontal pathogens, such as the members of the red complex, *P. gingivalis, T. forsythia* and *T. denticola* (Proctor and Baker, 1971; Loesche *et al.,* 1982; Feres *et al.,* 2001). At that time, important clinical benefits with the adjunctive use of MTZ in periodontal treatment were demonstrated (Loesche *et al.,* 1987; Loesche *et al.,* 1992). These findings were corroborated by several additional studies (Sigusch *et al.,* 2001; Rooney *et al.,* 2002; Loesche *et al.,* 2002; Carvalho *et al.,* 2004; Xajigeorgiou *et al.,* 2006; Feres *et al.,* 2012; Preus *et al.,* 2013).

AZT is a relatively new macrolide that emerged in medicine in the late 1980s (Girard *et al.,* 1987) as a promising drug due to excellent pharmacological properties, which allow its administration only once a day (500 mg) for short periods of time (from 3 to 5 days; Henry *et al.,* 2003). This simple dosage protocol and low incidence of side-effects associated with the use of AZT facilitated patient compliance, which represented a major advantage over other commonly used antibiotics in periodontics, including MTZ and AMX. Unfortunately, the results of the clinical studies evaluating the effects of AZT in association with SRP to treat subjects with advanced periodontitis demonstrated minimal or no additional effects of this antibiotic beyond that attained with mechanical debridement alone (Sampaio *et al.,* 2011; Emingil *et al.,* 2012; Han *et al.,* 2012). In addition, the only clinical trial that directly compared the effect of AZT with another systemic antibiotic, MTZ, detected a statistically significant clinical advantage for MTZ+SRP in comparison with SRP-only, but not for AZT+SRP (Haffajee *et al.,* The association of MTZ + AMX was suggested by van Winkelhoff and co-workers (1989) to treat *Aggregatibacter actinomycetemcomitans*-associated periodontitis, and in 2005, the first placebo-controlled RCT demonstrating the additional benefit of this combination of antibiotics in treating subjects with aggressive periodontitis, which were maintained up to 6 months post-treatment, was published (Guerrero *et al.,* 2005). A few years later, the same benefits were suggested in subjects with chronic periodontitis (Cionca *et al.,* 2009; Cionca *et al.,* 2010). Thus, although various antibiotics have been used as adjuncts to periodontal therapy from the 1970s to 1990s, current literature appears to converge on the use of the combination of MTZ+AMX. This trend may clearly be observed in the literature. From 2002 to 2013, 70% of the published RCTs on the effect of systemic antibiotics in the treatment of periodontal diseases used MTZ+AMX. Moreover, three systematic reviews examining this antibiotic regimen were published (Sgolastra *et al.,* 2012a; Sgolastra *et al.,* 2012b; Zandbergen *et al.,* 2012). Sgolastra *et al.,* (2012a, 2012b) reported a significant reduction in mean PD (0.43 mm, 95% CI range: 0.24 to 0.63, $p < 0.05$ and 0.58 mm, 95% CI range: 0.39 to 0.77, $p < 0.05$) and mean CAL gain (0.21 mm, 95% CI range: 0.02 to 0.4, $p < 0.05$ and 0.42 mm, 95% CI range: 0.23 to 0.61, $p < 0.05$) in favor of SRP in association with MTZ+AMX in subjects with chronic and aggressive periodontitis, respectively. Although the data in these systematic reviews indicated an important benefit of the use of this antibiotic protocol, long-term data beyond 6 months of follow-up were sparse (Pavicic *et al.,* 1994).

Three recently published RCTs presented the long-term effects (1 and 2 years of follow-up) of MTZ+AMX in the treatment of patients with chronic (Feres *et al.,* 2012; Goodson *et al.,* 2012) and aggressive (Mestnik *et al.,*

2012) periodontitis and suggested a sustained benefit of this therapy. Feres *et al.* (2012) evaluated the effects of the adjunctive use of MTZ or MTZ+AMX in the treatment of generalized chronic periodontitis. The mean number of deep sites with PD ≥ 5 mm did not differ among the three groups at baseline (≈38), but there were clear differences at 1 year post-treatment. Subjects receiving only SRP still had a mean of 16.1 residual pockets, compared to 6.3 and 4.7 in the MTZ and MTZ+AMX groups, respectively. SRP was able to bring only 22% of the subjects to a "low risk" profile (≤ 4 sites with PD ≥ 5 mm) for further disease progression (Lang and Tonetti, 2003; Matuliene *et al.,* 2008; Matuliene *et al.,* 2010) at 1 year, as opposed to 61% and 66% reached by SRP+MTZ and SRP+MTZ+AMX, respectively. These findings have clinical implications because they suggest a reduced need for periodontal surgery in subjects receiving one of these antibiotic protocols. Although no statistically significant differences were detected between the two antibiotic groups for this parameter and for the other parameters evaluated by the authors, there was a constant trend towards better clinical outcomes when MTZ and AMX were combined, in agreement with two other studies (Matarazzo *et al.,* 2008; Silva *et al.,* 2011). These sustained long-term clinical benefits obtained with the combination of SRP and MTZ+AMX were corroborated by two other RCTs that evaluated the treatment of chronic (Goodson *et al.,* 2012; Socransky *et al.,* 2013) and aggressive periodontitis (Mestnik *et al.,* 2012).

One question that could be raised is whether the combination of antibiotics and surgeries would provide any additional benefit. An answer to this question was given by the study of Goodson *et al.* (2012), which assessed eight different periodontal therapies and demonstrated that SRP+MTZ+AMX was the best of all treatments in terms of improving attachment levels. When the antibiotic and surgical groups were directly compared, a statistically significant higher mean CAL gain was observed in subjects receiving SRP+MTZ+AMX (1.53 ± 0.16 mm) compared to subjects treated by means of SRP and modified Widman flap (0.96 ± 0.21 mm). Interestingly, when all the eight treatments were compared, it was revealed that the inclusion of periodontal surgery did not significantly improve the clinical response in subjects with advanced chronic periodontitis (Goodson *et al.,* 2012).

Economic evaluation of adjunctive antimicrobials in the treatment of periodontitis

When comparing alternative treatments for a given clinical condition, it is not only important to evaluate their effectiveness, but also their economic costs. If an alternative treatment is more effective and less costly, or less effective and more costly compared to the standard of care, it is quite obvious which treatment may be considered superior. However, for an alternative treatment that is more effective and more costly than the standard of care, it is less clear which treatment may be preferred. What treatment is considered superior will depend on the marginal costs in relation to the additional benefits and on how much payers are willing to pay for the incremental benefits (Higgins *et al.,* 2012).

The costs that may be considered in analysis of cost-effectiveness include out-of-pocket payments by patients, reimbursements by third-party payers, travel costs, opportunity costs, and treatment costs averted (Vernazza *et al.,* 2012). The societal perspective, which combines all relevant costs irrespective of who pays for them, provides the most comprehensive view on costs (Russel *et al.,* 1996). As costs for dental services may vary considerably among countries (Pennington *et al.*, 2011), and even among providers within the same country (Flemmig and Beikler, 2013), they need to be assessed for each healthcare delivery system separately and outcomes cannot be generalized.

Using the perspective of a third-party payer in the United States, average per patient costs for the treatment of moderate to severe periodontitis have been evaluated over a 12-month period. Costs for SPR plus adjunctive local delivery of CHX using a disk device were US$1,568 and for SRP alone, US$1,393. The additional costs for the application of CHX disks were partly offset by a significant reduction in the frequency of periodontal surgery (9.2%) when compared to SRP alone (15.5%; Henke *et al.,* 2001). If a third-party payer were willing to pay the additional cost of US$175 per patient in order to reduce the frequency of periodontal surgery by almost half, adjunctive local delivery of CHX with a disk device was cost-effective.

From the perspective of a self-paying patient, local delivery of MTZ gel as an adjunct to SRP was found to be less effective in providing average attachment gain at affected sites compared to adjunctive local delivery of CHX using a disk device. Adjunctive local delivery of CHX was extensively dominated by the adjunctive local delivery of minocycline gel. Adjunctive minocycline gel was cost-effective if patients were willing to pay £1,761 (in pound sterling) for an average of 1 mm attachment gain compared to no treatment. SRP alone was cost effective if the patients were willing to pay between £1,467 and £1,761 for an average of 1 mm attachment gain (Heasman *et al.,* 2011). Comparing the use of systemic versus local antibiotics, Heasman *et al.* (2011) reported that the costs for an average of 1 mm attachment gain for SRP with adjunctive systemic administration of MTZ and AMX was only £837, suggesting that adjunctive systemic administration of antibiotics was more cost-effective compared to local delivery of antibiotics. Systemic antibiotics might also offer economic benefits if one considers treatment costs averted. Recent publications have indicated that the adjunctive use of systemic MTZ and AMX results in fewer residual deep pockets and, consequently, the need for surgical procedures (Cionca et al., 2009; Mestnik *et al.,* 2012; Feres *et al.,* 2012).

In conclusion, as patients' willingness to pay depends on a number of factors including perceived health state, income, gender, and insurance coverage, cost-effectiveness of alternative treatments may vary considerably among patients (Grytten, 2002; van Steenberghe et al., 2004; Tianviwat et al., 2008; Leung *et al.,* 2010).

Concluding remarks

This review aimed to provide readers with an overview of the current literature on the effectiveness of adjunctive periodontal therapies. The data suggested that the use of adjunctive treatments to SRP might lead to additional clinical benefits to patients with chronic and aggressive periodontitis. Nonetheless, the practical question to be answered is: "Which of these therapies would lead to clinically relevant and long-lasting benefits that would justify its use in the daily clinic?" Apparently, the only adjunctive therapy with compelling data supported by RCTs with long-term evaluation and systematic reviews is the use of systemic MTZ alone or in combination with AMX. There is also some evidence of a clinical benefit for up to 6 months for the use of laser Nd:YAG, and a microbiological benefit up to 1 year for the use of CHX as a mouthwash in combination with SRP+MTZ+AMX during the active phase of therapy.

The data supporting the adjunctive use of MTZ+AMX for the treatment of generalized chronic and aggressive periodontitis are based on the results of numerous RCTs, including two trials with 1 or 2 years of follow-up (Feres *et al.,* 2012; Goodson *et al.,* 2012) and three systematic reviews (Sgolastra *et al.,* 2012a, Sgolastra *et al.,* 2012b, Zandbergen *et al.,* 2012). It is important to mention that this treatment should be considered safe, as there seem to be no major side-effects associated with the intake of MTZ+AMX (Guerrero *et al.,* 2005; Cionca *et al.,* 2009; Mestnik *et al.,* 2010; Silva *et al.,* 2011; Feres *et al.,* 2012). The reduced need for additional treatment associated with the use of adjunctive systemic MTZ+AMX seems to be one of the greatest advantages for patients.

References

Andersen R, Loebel N, Hammond D and Wilson M. Treatment of periodontal disease by photodisinfection compared to scaling and root planing. *Journal of Clinical Dentistry* 2007; **18:**34-38.

Ando Y, Aoki A, Watanabe H and Ishikawa I. Bactericidal effect of erbium YAG laser on periodontopathic bacteria. *Lasers in Surgery and Medicine* 1996; **19:**190-200.

Aoki A, Sasaki KM, Watanabe H and Ishikawa I. Lasers in nonsurgical periodontal therapy. *Periodontology 2000* 2004; **36:**59-97.

Apatzidou DA and Kinane DF. Quadrant root planing versus same-day full-mouth root planing. I. Clinical findings. *Journal of Clinical Periodontology* 2004; **31:**132-140.

Bonito AJ, Lux L and Lohr KN. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. *Journal of Periodontology* 2005; **76:**1227-1236.

Braun A, Dehn C, Krause F and Jepsen S. Short-term clinical effects of adjunctive antimicrobial photodynamic therapy in periodontal treatment: a randomized clinical trial. *Journal of Clinical Periodontology* 2008; **35:**877-884.

Carvalho LH, D'Avila GB, Leão A, Haffajee AD, Socransky SS and Feres M. Scaling and root planing, systemic metronidazole and professional plaque removal in the treatment of chronic periodontitis in a Brazilian population. I. Clinical results. *Journal of Clinical Periodontology* 2004; **31:**1070-1076.

Chondros P, Nikolidakis D, Christodoulides N, Rössler R, Gutknecht N and Sculean A. Photodynamic therapy as adjunct to non-surgical periodontal treatment in patients on periodontal maintenance: a randomized controlled clinical trial. *Lasers in Medical Science* 2009; **24:**681-688.

Christodoulides N, Nikolidakis D, Chondros P, *et al.* Photodynamic therapy as an adjunct to non-surgical periodontal treatment: a randomized, controlled clinical trial. *Journal of Periodontology* 2008; **79:**1638-1644.

Cionca N, Giannopoulou C, Ugolotti G and Mombelli A. Amoxicillin and metronidazole as an adjunct to full-mouth scaling and root planing of chronic periodontitis. *Journal of Periodontology* 2009; **80:**364-371.

Cionca N, Giannopoulou C, Ugolotti G and Mombelli A. Microbiologic testing and outcomes of full-mouth scaling and root planing with or without amoxicillin/metronidazole in chronic periodontitis. *Journal of Periodontology* 2010; **8:**15-23.

Dastoor SF, Travan S, Neiva RF, Rayburn LA, Giannobile WV and Wang HL. Effect of adjunctive systemic azithromycin with periodontal surgery in the treatment of chronic periodontitis in smokers: a pilot study. *Journal of Periodontology* 2007; **78:**1887-1896.

Eberhard J, Jervøe-Storm PM, Needleman I, Worthington H and Jepsen S. Full-mouth treatment concepts for chronic periodontitis: a systematic review. *Journal of Clinical Periodontology* 2008; **35:**591-604.

Eickholz P, Kim TS, Bürklin T, *et al.* Non-surgical periodontal therapy with adjunctive topical doxycycline: a double-blind randomized controlled multicenter study. *Journal of Clinical Periodontology* 2002; **29:**108-117.

Eltas A and Orbak R. Clinical effects of Nd:YAG laser applications during non-surgical periodontal treatment in smoking and nonsmoking patients with chronic periodontitis. *Photomedicine Laser Surgery* 2012a; **30:**360-366.

Eltas A and Orbak R. Effect of 1,064-nm Nd:YAG laser therapy on GCF IL-1β and MMP-8 levels in patients with chronic periodontitis. *Lasers in Medical Science* 2012b; **27:**543-550.

Emingil G, Han B, Ozdemir G, *et al.* Effect of azithromycin, as an adjunct to nonsurgical periodontal treatment, on microbiological parameters and gingival crevicular fluid biomarkers in generalized aggressive periodontitis. *Journal of Periodontal Research* 2012; **47:**729-739.

Farman M and Joshi RI. Full-mouth treatment versus quadrant root surface debridement in the treatment of chronic periodontitis: a systematic review. *British Dental Journal* 2008; **205:**496-497.

Faveri M, Feres M, Shibli JA, Hayacibara RF, Hayacibara MM and de Figueiredo LC. Microbiota of the dorsum of the tongue after plaque accumulation: an experimental study in humans. *Journal of Periodontology* 2006a; **77:**1539-1546.

Faveri M, Gursky LC, Feres M, Shibli JA, Salvador SL and de Figueiredo LC. Scaling and root planing and chlorhexidine mouthrinses in the treatment of chronic periodontitis: a randomized, placebo-controlled clinical trial. *Journal of Clinical Periodontology* 2006b; **33:**819-828.

Feng HS, Bernardo CC, Sonoda LL, *et al.* Subgingival ultrasonic instrumentation of residual pockets irrigated with essential oils: a randomized controlled trial. *Journal of Clinical Periodontology* 2011; **38:**637-643.

Feres M, Gursky LC, Faveri M, Tsuzuki CO and Figueiredo LC. Clinical and microbiological benefits of strict supragingival plaque control as part of the active phase of periodontal therapy. *Journal of Clinical Periodontology* 2009; **36:**857-867.

Feres M, Haffajee AD, Allard K, Som S and Socransky SS. Change in subgingival microbial profiles in adult periodontitis subjects receiving either systemically administered amoxicillin or metronidazole. *Journal of Clinical Periodontology* 2001; **28:**597-609.

Feres M, Soares GMS, Mendes JAV, *et al.* Metronidazole alone or with amoxicillin as adjuncts to nonsurgical treatment of chronic periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. *Journal of Clinical Periodontology* 2012; **39:**1149-1158.

Feres M. Antibiotics in the treatment of periodontal diseases: microbiological basis and clinical applications. *Annals of the Royal Australasian College of Dental Surgeons* 2008; **19:**37-44.

Flemmig TF and Beikler T. Economics of periodontal care: market trends, competitive forces and incentives. *Periodontology 2000* 2013; **62:**287-304.

Folwaczny M, George G, Thiele L, Mehl A and Hickel R. Root surface roughness following Er:YAG laser irradiation at different radiation energies and working tip angulations. *Journal of Clinical Periodontology* 2002; **29:**598-603.

Giannelli M, Formigli L, Lorenzini L and Bani D. Combined photoablative and photodynamic diode laser therapy as an adjunct to non-surgical periodontal treatment: a randomized split-mouth clinical trial. *Journal of Clinical Periodontology* 2012; **39:**962-970.

Girard AE, Girard D, English AR, *et al.* Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. *Antimicrobial Agents and Chemotherapy* 1987; **31:**1948-1954.

Goodson JM, Haffajee AD, Socransky SS, *et al.* Control of periodontal infections: a randomized controlled trial I. The primary outcome attachment gain and pocket depth reduction at treated sites. *Journal of Clinical Periodontology* 2012; **39:**526-536.

Grytten J and Holst D. Do young adults demand more dental services as their income increases? *Community Dentistry and Oral Epidemiology* 2002; **30:**463-469.

Guarnelli ME, Franceschetti G, Manfrini R and Trombelli L. Adjunctive effect of chlorhexidine in ultrasonic instrumentation of aggressive periodontitis patients: a pilot study. *Journal of Clinical Periodontology* 2008; **35:**333-341.

Guerrero A, Griffiths GS, Nibali L, *et al.* Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized placebo controlled clinical trial. *Journal of Clinical Periodontology* 2005; **32:**1096-1107.

Haas AN, de Castro GD, Moreno T, *et al.* Azithromycin as an adjunctive treatment of aggressive periodontitis: 12-month randomized clinical trial. *Journal of Clinical Periodontology* 2008; **35:**696-704.

Haffajee AD, Socransky SS and Gunsolley JC. Systemic anti-infective periodontal therapy. A systematic review. *Annals of Periodontology* 2003; **8:**115-181.

Haffajee AD, Torresyap G and Socransky SS. Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results. *Journal of Clinical Periodontology* 2007; **34:**243-253.

Han B, Emingil G, Ozdemir G, *et al.* Azithromycin as an adjunctive treatment of generalized severe chronic periodontitis: clinical, microbiological and biochemical parameters. *Journal of Periodontology* 2012; **83:**1480-1491.

Hanes PJ and Purvis JP. Local anti-infective therapy: pharmacological agents. A systematic review. *Annals of Periodontology* 2003; **8:**79-98.

Heasman PA, Vernazza CR, Gaunt FL and Pennington MW. Cost-effectiveness of adjunctive antimicrobials in the treatment of periodontitis. *Periodontology 2000* 2011; **55:**217-230.

Heitz-Mayfield LJ and Lang NP. Surgical and nonsurgical periodontal therapy. Learned and unlearned concepts. *Periodontology 2000* 2013; **62:**218-231.

Heitz-Mayfield LJ, Trombelli L, Heitz F, Needleman I and Moles D. A systematic review of the effect of surgical debridement vs non-surgical debridement for the treatment of chronic periodontitis. *Journal of Clinical Periodontology* 2002; **29(Suppl 3):**92-102.

Henke CJ, Villa KF, Aichelmann-Reidy ME, *et al.* An economic evaluation of a chlorhexidine chip for treating chronic periodontitis: the CHIP (chlorhexidine in periodontitis) study. *Journal of the American Dental Association* 2001; **132:**1557-1569.

Henry DC, Riffer E, Sokol WN, Chaudry NI and Swanson RN. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. *Antimicrobial Agents and Chemotherapy* 2003; **47:**2770-2774.

Herrera D, Sanz M, Jepsen S, Needleman I and Roldan S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. *Journal of Clinical Periodontology* 2002; **29(Suppl 3):**136-159.

Higgins AM and Harris AH. Health economic methods: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. *Critical Care Clinics* 2012; **28:**11-24, v.

Konopka K and Goslinski T. Photodynamic therapy in dentistry. *Journal of Dental Research* 2007; **86:**694-707.

Krück C, Eick S, Knöfler GU, Purschwitz RE and Jentsch HF. Clinical and microbiologic results 12 months after scaling and root planing with different irrigation solutions in patients with moderate chronic periodontitis: a pilot randomized trial. *Journal of Periodontology* 2012; **83:**312-320.

Lang NP, Tan WC, Krähenmann MA and Zwahlen M. A systematic review of the effects of full-mouth debridement with and without antiseptics in patients with chronic periodontitis. *Journal of Clinical Periodontology* 2008 Sep; **35(8 Suppl):**8-21.

Lang NP and Tonetti MS. Periodontal risk assessment (PRA) for patients in supportive periodontal therapy (SPT). *Oral Health & Preventive Dentistry* 2003; **1:**7-16.

Leonhardt A, Bergström C, Krok L and Cardaropoli G. Microbiological effect of the use of an ultrasonic device and iodine irrigation in patients with severe chronic periodontal disease: a randomized controlled clinical study. *Acta Odontologica Scandinavica* 2007; **65:**52-59.

Leung KC and McGrath CP. Willingness to pay for implant therapy: a study of patient preference. *Clinical Oral Implants Research* 2010; **21:**789-793.

Lindhe J. Treatment of localized periodontitis. In Genco RJ, Mergenhagen SE (Eds): *Host Parasite Interactions in Periodontal Diseases.* American Society of Microbiology Press. 1981; 381-394.

Lindhe J and Liljenberg B. Treatment of localized juvenile periodontitis. Results after 5 years. *Journal of Clinical Periodontology* 1984; **11:**399-410.

Loesche WJ, Giordano JR, Hujoel P, Schwarcz J and Smith BA. Metronidazole in periodontitis: reduced need for surgery. *Journal of Clinical Periodontology* 1992; **19:**103-112.

Loesche WJ, Giordano JR, Soehren S and Kaciroti N. The nonsurgical treatment of patients with periodontal disease: results after five years. *Journal of the American Dental Association* 2002; **133:**311-320.

Loesche WJ and Grossman NS. Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment. *Clinical Microbiology Reviews* 2001; **14:**727-752.

Loesche WJ, Schmidt E, Smith BA, Caffessee R and Stoll J. Metronidazole therapy for periodontitis. *Journal of Periodontal Research* 1987; **22:**224-226.

Loesche WJ, Syed SA, Laughon BE and Stoll J. The bacteriology of acute necrotizing ulcerative gingivitis. *Journal of Periodontology* 1982; **53:**223-230.

Lulic M, Leiggener Görög I, Salvi GE, Ramseier CA, Mattheos N and Lang NP. One-year outcomes of repeated adjunctive photodynamic therapy during periodontal maintenance: a proof-of-principle randomized controlled clinical trial. *Journal of Clinical Periodontology* 2009; **36:**661-666.

Mager DL, Ximenez-Fyvie LA, Haffajee AD and Socransky SS. Distribution of selected bacterial species on intraoral surfaces. *Journal of Clinical Periodontology* 2003; **30:**644-654.

Maisch T. Anti-microbial photodynamic therapy: useful in the future? *Lasers in Medical Science* 2007; **22:**83-91.

Mascarenhas P, Gapski R, Al-Shammari K, *et al.* Clinical response of azithromycin as an adjunct to non-surgical periodontal therapy in smokers. *Journal of Periodontology* 2005; **76:**426–436.

Matarazzo F, Figueiredo LC, Cruz SE, Faveri M and Feres M. Clinical and microbiological benefits of systemic metronidazole and amoxicillin in the treatment of smokers with chronic periodontitis: a randomized placebo-controlled study. *Journal of Clinical Periodontology* 2008; **35:**885-896.

Matesanz-Pérez P, García-Gargallo M, Figuero E, Bascones-Martínez A, Sanz M and Herrera D. A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis. *Journal of Clinical Periodontology* 2013; **40:**227-241.

Matuliene G, Pjetursson BE, Salvi GE, *et al.* Influence of residual pockets on progression of periodontitis and tooth loss: results after 11 years of maintenance. *Journal of Clinical Periodontology* 2008; **35:**685-695.

Matuliene G, Studer R, Lang NP, *et al.* Significance of periodontal risk assessment in the recurrence of periodontitis and tooth loss. *Journal of Clinical Periodontology* 2010; **37:**191-199.

Mestnik MJ, Feres M, Figueiredo LC, Duarte PM, Lira EA and Faveri M. Short-term benefits of the adjunctive use of metronidazole plus amoxicillin in the microbial profile and in the clinical parameters of subjects with generalized aggressive periodontitis. *Journal of Clinical Periodontology* 2010; **37:**353-365.

Mestnik MJ, Feres M, Figueiredo LC, *et al.* The effects of adjunctive metronidazole plus amoxicillin in the treatment of generalized aggressive periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. *Journal of Clinical Periodontology* 2012; **39:**955-961.

Oteo A, Herrera D, Figuero E, O'Connor A, González I and Sanz M. Azithromycin as an adjunct to scaling and root planing in the treatment of *Porphyromonas gingivalis*-associated periodontitis: a pilot study. *Journal of Clinical Periodontology* 2010; **37:**1005-1015.

Pavicić MJ, van Winkelhoff AJ, Douqué NH, Steures RW and de Graaff J. Microbiological and clinical effects of metronidazole and amoxicillin in *Actinobacillus actinomycetemcomitans*-associated periodontitis. A 2-year evaluation. *Journal of Clinical Periodontology* 1994; **21:**107-112.

Pennington M, Heasman P, Gaunt F, *et al.* The cost-effectiveness of supportive periodontal care: a global perspective. *Journal of Clinical Periodontology* 2011; **38:**553-561.

Polansky R, Haas M, Heschl A and Wimmer G. Clinical effectiveness of photodynamic therapy in the treatment of periodontitis. *Journal of Clinical Periodontology* 2009; **36:**575-580.

Preus HR, Gunleiksrud TM, Sandvik L, Gjermo P and Baelum V. A randomized, double-masked clinical trial comparing four periodontitis treatment strategies: 1-year clinical results. *Journal of Periodontology* 2013; **84:**1075-1086.

Proctor DB and Baker CG. Treatment of acute necrotizing ulcerative gingivitis with metronidazole. *Journal of the Canadian Dental Association* 1971; **37:**376-380.

Qadri T, Poddani P, Javed F, Tunér J and Gustafsson A. A short-term evaluation of Nd:YAG laser as an adjunct to scaling and root planing in the treatment of periodontal inflammation. *Journal of Periodontology* 2010; **81:**1161-1166.

Quirynen M, Bollen CM, Vandekerckhove BN, Dekeyser C, Papaioannou W and Eyssen H. Full- vs. partial-mouth disinfection in the treatment of periodontal infections: short-term clinical and microbiological observations. *Journal of Dental Research* 1995; **74:**1459-1467.

Quirynen M, Mongardini C, de Soete M, *et al.* The role of chlorhexidine in the one-stage full-mouth disinfection treatment of patients with advanced adult periodontitis. Long-term clinical and microbiological observations. *Journal of Clinical Periodontology* 2000; **27:**578-589.

Quirynen M, Teughels W and van Steenberghe D. Impact of antiseptics on one-stage, full-mouth disinfection. *Journal of Clinical Periodontology* 2006; **33:**49-52.

Ramfjord SP, Caffesse RG, Morrison EC, *et al.* 4 modalities of periodontal treatment compared over 5 years. *Journal of Clinical Periodontology* 1987; **14:**445-452.

Rams TE and Slots J. Local delivery of antimicrobial agents in the periodontal pocket. *Periodontology 2000* 1996; **10:**139-159.

Rooney J, Wade WG, Sprague SV, Newcombe RG and Addy M. Adjunctive effects to non-surgical periodontal therapy of systemic metronidazole and amoxycillin alone and combined. A placebo controlled study. *Journal of Clinical Periodontology* 2002; **29:**342-350.

Rosling BG, Slots J, Christersson LA, Gröndahl HG and Genco RJ. Topical antimicrobial therapy and diagnosis of subgingival bacteria in the management of inflammatory periodontal disease. *Journal of Clinical Periodontology* 1986; **13:**975-981.

Rosling BG, Slots J, Webber RL, Christersson LA and Genco RJ. Microbiological and clinical effects of topical subgingival antimicrobial treatment on human periodontal disease. *Journal of Clinical Periodontology* 1983; **10:**487-514.

Rühling A, Fanghänel J, Houshmand M, *et al.* Photodynamic therapy of persistent pockets in maintenance patients – a clinical study. *Clinical Oral Investigations* 2010; **14:**637-644.

Russell LB, Gold MR, Siegel JE, Daniels N and Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *Journal of the American Medical Association* 1996; **276:**1172-1177.

Sakellari D, Ioannidis I, Antoniadou M, Slini T and Konstantinidis A. Clinical and microbiological effects of adjunctive, locally delivered chlorhexidine on patients with chronic periodontitis. *Journal of the International Academy of Periodontology* 2010; **12:**20-26.

Sampaio E, Rocha M, Figueiredo LC, *et al.* Clinical and microbiological effects of azithromycin in the treatment of generalized chronic periodontitis: a randomized placebo-controlled clinical trial. *Journal of Clinical Periodontology* 2011; **38:**838-846.

Sgolastra F, Gatto R, Petrucci A and Monaco A. Effectiveness of systemic amoxicillin/metronidazole as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis: a systematic review and meta-analysis. *Journal of Periodontology* 2012a; **83:**1257-1269.

Sgolastra F, Petrucci A, Gatto R and Monaco A. Effectiveness of systemic amoxicillin/metronidazole as an adjunctive therapy to full-mouth scaling and root planing in the treatment of aggressive periodontitis: a systematic review and meta-analysis. *Journal of Periodontology* 2012b; **83:**731-743.

Sgolastra F, Petrucci A, Gatto R and Monaco A. Efficacy of Er:YAG laser in the treatment of chronic periodontitis: systematic review and meta-analysis. *Lasers in Medical Science* 2012c; **27:**661-673.

Sgolastra F, Petrucci A, Severino M, Graziani F, Gatto R and Monaco A. Adjunctive photodynamic therapy to non-surgical treatment of chronic periodontitis: a systematic review and meta-analysis. *Journal of Clinical Periodontology* 2013a; **40:**514-526.

Sgolastra F, Severino M, Gatto R and Monaco A. Effectiveness of diode laser as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis: a meta-analysis. *Lasers in Medical Science* 2013b; **28:**1393-1402.

Sgolastra F, Severino M, Petrucci A, Gatto R and Monaco A. Nd:YAG laser as an adjunctive treatment to nonsurgical periodontal therapy: A meta-analysis. *Lasers in Medical Science* 2014; **29**:887-895.

Sigusch B, Beier M, Klinger G, Pfister W and Glockmann E. A 2-step non-surgical procedure and systemic antibiotics in the treatment of rapidly progressive periodontitis. *Journal of Periodontology* 2001; **72:**275-283.

Silva MP, Feres M, Sirotto TA, *et al.* Clinical and microbiological benefits of metronidazole alone or with amoxicillin as adjuncts in the treatment of chronic periodontitis: a randomized placebo-controlled clinical trial. *Journal of Clinical Periodontology* 2011; **38:**828-837.

Slots J, Mashimo P, Levine MJ and Genco RJ. Periodontal therapy in humans. I. Microbiological and clinical effects of a single course of periodontal scaling and root planing, and of adjunctive tetracycline therapy. *Journal of Periodontology* 1979; **50:**495-509.

Smith SR, Foyle DM, Daniels J, *et al.* A double-blind placebo-controlled trial of azithromycin as an adjunct to non-surgical treatment of periodontitis in adults: clinical results. *Journal of Clinical Periodontology* 2002; **29:**54-61.

Soares GM, Mendes JAV, Silva MP, *et al.* Metronidazole alone or with amoxicillin as adjuncts to nonsurgical treatment of chronic periodontitis: a secondary analysis of microbiological results from a randomized clinical trial. *Journal of Clinical Periodontology* 2014; **41:**366-376.

Socransky SS and Haffajee AD. Dental biofilms: difficult therapeutic targets. *Periodontology 2000* 2002; **28:**12-55.

Socransky SS, Haffajee AD, Teles R, *et al.* Effect of periodontal therapy on the subgingival microbiota over a 2-year monitoring period. I. Overall effect and kinetics of change. *Journal of Clinical Periodontology* 2013; **40:**771-780.

Teles RP, Haffajee AD and Socransky SS. Microbiological goals of periodontal therapy. *Periodontology 2000* 2006; **42:**180-218.

Theodoro LH, Silva SP, Pires JR, *et al.* Clinical and microbiological effects of photodynamic therapy associated with nonsurgical periodontal treatment. A 6-month follow-up. *Lasers in Medical Science* 2012; **27:**687-693

Tianviwat S, Chongsuvivatwong V and Birch S. Different dental care setting: does income matter? *Health Economics* 2008; **17:**109-118.

van Steenberghe D, Bercy P, De Boever J, *et al.* Patient evaluation of a novel non-injectable anesthetic gel: a multicenter crossover study comparing the gel to infiltration anesthesia during scaling and root planing. *Journal of Periodontology* 2004; **75:**1471-1478.

van Winkelhoff AJ, Rodenburg JP, Goené RJ, Abbas F, Winkel EG and de Graaff J. Metronidazole plus amoxycillin in the treatment of *Actinobacillus actinomycetemcomitans*-associated periodontitis. *Journal of Clinical Periodontology* 1989; **16:**128-131.

Vernazza C, Heasman P, Gaunt F and Pennington M. How to measure the cost-effectiveness of periodontal treatments. *Periodontology 2000* 2012; **60:**138-146.

Xajigeorgiou C, Sakellari D, Slini T, Baka A and Konstantinidis A. Clinical and microbiological effects of different antimicrobials on generalized aggressive periodontitis. *Journal of Periodontology* 2006; **33:**254-264.

Zandbergen D, Slot DE, Cobb CM and Van der Weijden FA. The clinical effect of scaling and root planing and the concomitant administration of systemic amoxicillin and metronidazole: A systematic review. *Journal of Periodontology* 2012; **84:**332-351.