Systemic Chemotherapeutic Agents as Adjunctive Periodontal Therapy: A Narrative Review and Suggested Clinical Recommendations

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Abstract

Periodontitis is an inflammatory condition of the periodontium that leads to destruction of the supporting structures of the tooth, including loss of attachment and alveolar bone. A clinician's first line of treatment for periodontitis is traditionally mechanical periodontal therapy, including oral hygiene instructions together with scaling and root planing. However, it has been shown that mechanical therapy may not always be effective in halting disease. Adjunctive chemotherapeutics, such as systemic antibiotics or host-modulating agents, may improve the treatment outcome of periodontitis. Using relevant terms such as "adjunctive antibiotics" and "systemic chemotherapeutics" in a manual search of the PubMed database, the authors have prepared a narrative review of the chemotherapeutics currently used in the field. Results of the search and review show that adjunctive antibiotics may be useful in cases of aggressive periodontitis, refractory periodontitis, and in some patients who are immunocompromised, such as heavy smokers or poorly controlled diabetics. Host-modulating agents are generally recommended only as the last resort and are limited to the use of submicrobial dose doxycycline. Microbial testing may be indicated, particularly in aggressive periodontitis cases or refractory cases. Using these results, a decision tree is provided for clinicians to determine when adjunctive chemotherapeutics may be indicated.

Key words: Antibiotics, anti-bacterial agents, host-modulation, periodontitis, chemotherapeutic

Introduction

Periodontitis is an inflammatory condition of the periodontium that leads to destruction of the supporting structures of the tooth, including loss of attachment and alveolar bone (American Academy of Periodontology, 2001). This can result in periodontal pocket formation, gingival recession, bone loss, tooth mobility, and, eventually, tooth loss. An estimated 47% of Americans suffer from periodontitis (Eke *et al*., 2012), which has both chronic and aggressive presentations. Chronic periodontitis, the more common form, is often associated with local factors, such as plaque (the microbial biofilm) and calculus. Aggressive periodontitis, however, is characterized by rapid loss of attachment that is not matched by severe local factors (Armitage, 1999). The etiology of periodontitis is bacterial plaque and its byproducts in a susceptible host. While Theilade (1986) proposed that total microbial load, rather than specific species were responsible for periodontal disease (also known as the "non-specific plaque hypothesis"), Loesche disagreed. Loesche (1976) described the "specific plaque hypothesis," in which he theorized that periodontitis was caused by the presence of select, putative pathogens. Socransky and Haffajee (1998) later classified bacterial species associated with chronic periodontitis, including the red complex bacteria: *Porphyromonas gingivalis* (*Pg*), *Treponema denticola* (*Td*), and *Tannerella forsythia* (*Tf*) (*Loesche and Grossman*, 2001). Additional species have also been implicated in chronic periodontitis, including *Prevotella intermedia* (*Pi*) and *Fusobacterium nucleatum* (*Fn*) (*Loesche* and *Grossman*, 2001). In addition to the red complex species, a multitude of pathogens have been linked to periodontitis.

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For example, *Aggregatibacter actinomycetemcomitans* (*Aa*) has been shown to be associated with periodontitis, particularly aggressive periodontitis (Slots, 1979).

A clinician's first line of treatment for periodontitis is the hygienic phase of the treatment plan. Traditionally, this includes mechanical periodontal therapy, including oral hygiene instructions together with scaling and root planing (SRP). After completion of the hygiene phase of the treatment plan, the clinician moves to the next stage of treatment, the corrective phase. In periodontal treatment, this includes mechanical therapy performed through periodontal flap surgery (FS). However, it has been shown that mechanical therapy may not always be effective in halting disease (Slots and Rosling, 1983; Kornman and Robertson, 1985). SRP and FS have failed to suppress *Aa* in patients with aggressive periodontitis (Slots and Rosling, 1983; Kornman and Robertson, 1985; Mombelli *et al.,* 2000; Doungudomdacha *et al*., 2001). Several possible reasons for this exist: 1) tooth-related and general anatomical factors may limit access for instrumentation (Bower, 1979; Stambaugh *et al*., 1981); 2) compromised host defense mechanisms (Slots, 2004); and 3) the inability to eliminate the pathogens that invade periodontal tissues (Saglie *et al*., 1982). Therefore, in some cases, treatment must also include adjunctive therapies. Adjunctive therapy describes the use of supplemental treatments used in addition to traditional periodontal therapy. Examples include occlusal therapy, restorative care, lasers and chemotherapy. Chemotherapeutics are chemical agents used to prevent, treat or adjunctively manage periodontal disease (American Academy of Periodontology, 2001). Current periodontal treatments are aimed toward more conservative methods in order to preserve surrounding tissues and to minimize tissue trauma and patient discomfort while eliminating associated bacterial pathogens. Adjunctive chemotherapy may fulfill the above goals. The aims of periodontal chemotherapy are to inhibit bacterial growth, kill putative periodontal pathogens, and to inhibit tissue destruction through host modulation. Adjunctive chemotherapeutics target two primary pathways: 1) therapies to inhibit or kill specific bacterial species, and 2) host-modulation therapies to prevent tissue destruction and bone loss (*Figure 1*). Thus, adjunctive, systemic chemotherapeutic options include antibiotics and host-modulating agents. The purposes of this paper are to update the aims of systemic, adjunctive chemotherapy, to discuss currently used chemotherapeutics in the field, and to provide a decision tree for clinicians to determine when adjunctive chemotherapeutics may be indicated.

A literature search was completed using the PubMed database to create a narrative review that updates the aims of systemic, adjunctive chemotherapy, and discusses currently used chemotherapeutics in the field. Additionally, information from the literature was used to provide a decision tree for clinicians to determine when adjunctive chemotherapeutics may be indicated. Two reviewers (R.S. and T.J.O.) searched the PubMed database manually using several search terms and pairs of search terms, including, but not limited to, the words "adjunctive antibiotics," "adjunctive therapy," "systemic antibiotics," "adjunctive chemotherapeutics," "chemotherapeutics," "host-modulation," "periodontitis," and "periodontal disease." In addition, a manual search of the following journals was conducted: *International Journal of Periodontics and Restorative Dentistry, Journal of Periodontology,* and *Journal of Clinical Periodontology.* Relevant articles from January 1970 to the present were considered under the condition that they were published in the English language. The final date of the literature search was completed on September 26, 2015.

Systemic antibiotics

Systemic antibiotics are the most commonly used systemic chemotherapeutic option (*Table 1*). Inhibiting or killing bacterial species prevents the release of virulence factors, such as lipopolysaccharide (LPS), that can damage the periodontal tissues (*Figure 1*). A systematic review by Herrera *et al.* (2002) showed that systemic antibiotic therapy, in combination with SRP, has significant benefits regarding attachment level (CAL) gain and pocket depth (PD) reduction when compared to SRP alone. In a meta-analysis by Haffajee *et al.* (2003), similar results were found regarding mean CAL gain (0.45 mm). In both papers, the largest benefits were shown for deep pockets (≥ 6 mm) in patients with aggressive periodontitis.

Bactericidal antibiotics kill microorganisms by inhibiting key processes for their survival. Examples used in periodontics include metronidazole, which inhibits DNA synthesis, and penicillins, a class of antibiotics that inhibit cell wall synthesis. Metronidazole is particularly effective against species involved in various forms of periodontitis, such as red complex bacteria and *Pi.* Loesche *et al.* (1992) found that SRP in conjunction with metronidazole reduces the need for periodontal surgery. In 2012, Soares *et al.* found that patients with chronic periodontitis given adjunctive metronidazole with SRP had a lower amount of periodontal pathogens after therapy than patients treated with SRP alone. Results from a systematic review by Rabelo *et al.* (2015) show that SRP in conjunction with metronidazole is also more beneficial to aggressive periodontitis patients than SRP alone.

This implies that adjunctive antibiotic therapy may produce improved clinical outcomes; however, it does not imply that adjunctive antibiotics should be used in lieu of traditional periodontal therapy. Contraindications for the use of metronidazole include hepatic disease and the use of alcohol; metronidazole combined with alcohol may cause effects similar to disulfiram, including severe headaches, nausea and vomiting. A commonly prescribed penicillin for orodental infection is amoxicillin. Amoxicillin targets both Gram-positive and Gram-negative bacterial species.

Table 1. Systemic antibiotics commonly used adjunctively in periodontal disease

Antibiotic	Microbes targeted	Common Adult Dosage
Doxycycline	Non-specific	250 milligrams once daily for 21 days
Metronidazole	*Porphyromonas gingivalis, Tannerella forsythia, Treponema spp.*	500 milligrams three times daily for 8 days
Azithromycin	*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans*	500 milligrams once daily for 4-7 days
Clindamycin	Gram-negative anaerobes	300 milligrams three times daily for eight days
Metronidazole + Amoxicillin	*Aggregatibacter actinomycetemcomitans* or *Porphyromonas gingivalis* with high numbers of Gram-positive pathogens	250 milligrams of metronidazole and 375 milligrams of amoxicillin, each three times daily for 8 days
Metronidazole + Ciprofloxacin	*Aggregatibacter actinomycetemcomitans* or presence of susceptible enteric microorganisms	500 milligrams of each taken four times daily for 8 days

Footnote: Table references Slots (2004) and van Winkelhoff and Winkel (2005).

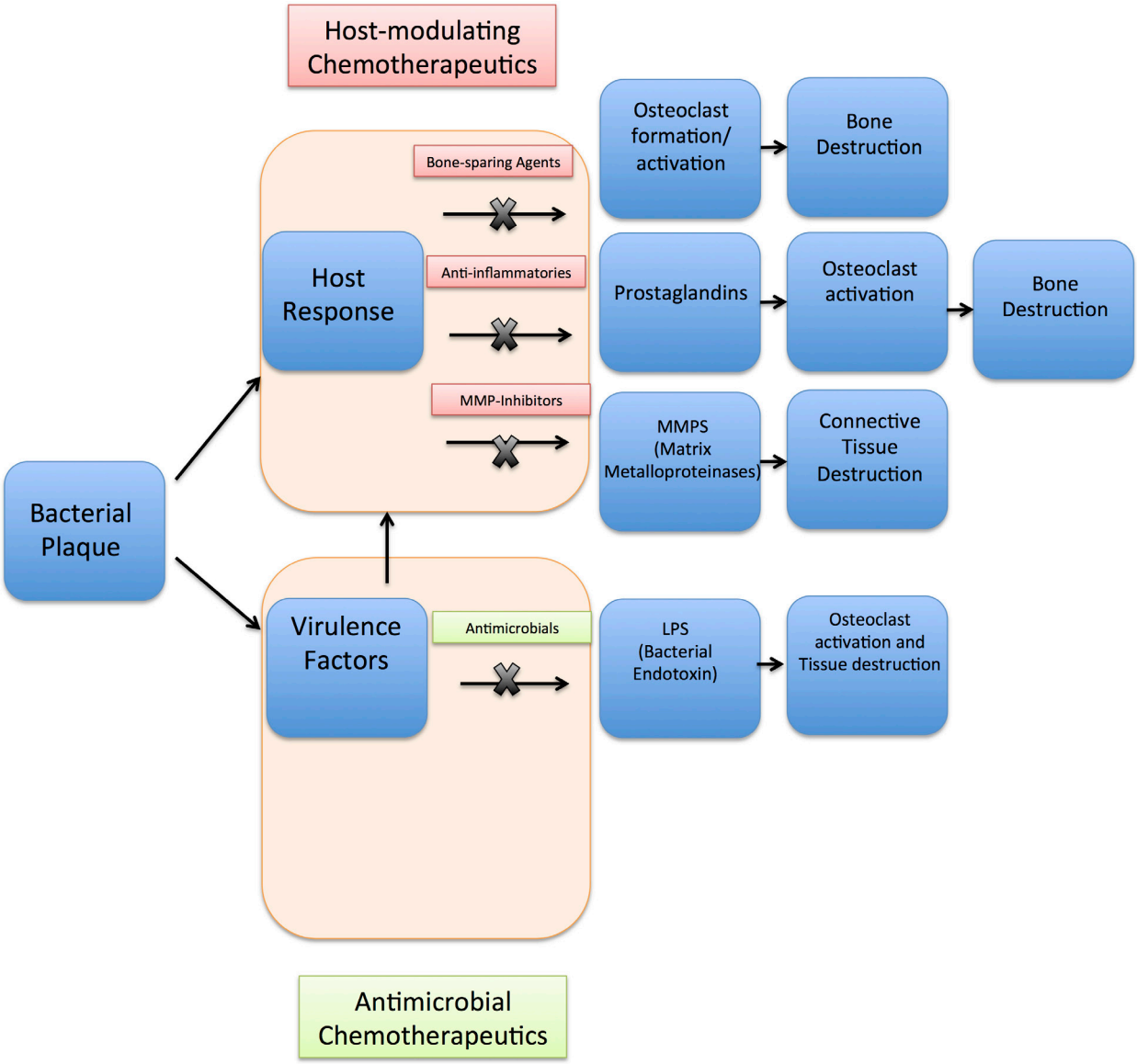

Figure 1. Adjunctive systemic chemotherapeutic therapy targets

Feres *et al.* (2012) showed that amoxicillin, in combination with SRP, reduced red-complex and orange-complex bacterial species. This included a 71% reduction of *Pg* one year after treatment (Feres *et al.*, 2012). However, it has been shown that amoxicillin alone is ineffective in treating chronic and aggressive periodontitis, but is effective when used in combination with metronidazole (Soares *et al.*, 2012; Rabelo *et al.,* 2015). Two considerations for the prescription of amoxicillin include common allergy to penicillin drugs and its inhibition by the beta-lactamase enzyme. Due to this inhibition, the use of augmentin (amoxicillin + clavulanic acid) is often prescribed in lieu of amoxicillin.

Bacteriostatic antibiotics inhibit bacterial growth without killing. In periodontics, the bacteriostatic drugs used are tetracyclines, azithromycin, and clindamycin. They inhibit protein synthesis by binding to the 30s (tetracycline) or 50s (azithromycin and clindamycin) subunits.

Tetracyclines include tetracycline and the semi-synthetics, minocycline and doxycycline. They are used as an adjunctive chemotherapeutic in chronic periodontitis, aggressive and refractory periodontitis cases (Seymour and Heasman, 1995). In one study, more gain in clinical attachment was seen following systemic tetracycline use in combination with non-surgical therapy compared to non-surgical therapy alone (Ramberg *et al.*, 2001). However, these results lasted only short-term (one year.) Several studies show that tetracycline as an adjunct to SRP leads to decreased pocket depths, including moderate and deep pockets (Herrera *et al.,* 2002), and slight increases in clinical attachment (Herrera *et al.*, 2002; Haffajee *et al.*, 2003). In a classic study by Kornman and Robertson (1985) SRP alone was unable to resolve any cases of localized juvenile periodontitis (now referred to as localized aggressive periodontitis, or LAP). However, SRP combined with adjunctive tetracycline administration was effective for some patients. Specifically, the SRP and adjunctive tetracycline was effective for patients who did not test positive for *Bacteroides* species; neither SRP nor SRP with adjunctive tetracycline was effective for patients who did test positive for *Bacteroides* species. These results stress the importance of microbial testing prior to the use of systemic chemotherapy. For example, if microbial testing results show that a patient tests positive for *Bacteroides* species, a clinician would not assume that SRP or SRP with adjunctive tetracycline would be an effective way to treat periodontitis.

Semi-synthetic tetracyclines have increased in popularity due to their less frequent administration rate, longer excretion rate, longer serum half-life, fewer renal effects, and less interaction with dairy products than tetracycline (Goodson, 1994; Slots, 2004). Doxycycline has the highest protein binding capacity and longest half-life of the tetracyclines (Slots, 2004).

Minocycline has the best absorption and tissue penetration, and is more effective than tetracycline in inhibiting Gram-negative, facultative anaerobes (Goodson, 1994; Slots, 2004). There are important interactions of the tetracyclines with the drug warfarin and with food, especially magnesium and calcium. For this reason, they should be taken one hour prior to or two hours after eating. Initially, it was theorized that minocycline could provide beneficial clinical results for deep probing depths because they could decrease levels of salivary proteases (Atilla *et al.*, 1996). To date, minocycline has not shown beneficial clinical results when used as a systemic, adjunctive antibiotic (Herrera *et al.,* 2002).

Azithromycin, a macrolide, is effective against a wide variety of oral bacteria (Blandizzi *et al.*, 1999; Slots, 2004), particularly the red complex species (Mascarenhas *et al.*, 2005). The impact of adjunctive, systematic azithromycin treatment used in conjunction with periodontal therapy has yielded mixed results. Buset *et al.* (2015) wrote a systematic review of randomized control trials (RCTs) utilizing azithromycin as an adjunct to SRP that showed conflicting results for both chronic and aggressive periodontitis patients. Five of seven RCTs with chronic periodontitis patients showed beneficial effects in patients using azithromycin. For example, greater probing depth reductions were shown after 6 months in one study, and smaller mean probing depths at 6 months were observed in another study. The other two RCTs, however, showed no beneficial effects. Regarding aggressive periodontitis, only two RCTs were found; one reporting a positive effect of adjunctive azithromycin on a percentage of teeth with probing depth reductions of 2 mm or more, and one that found no significant difference in probing depth measures between groups utilizing adjunctive azithromycin versus SRP alone.

Although clindamycin works very effectively against Gram-negative anaerobic bacteria (Goodson, 1994), it is infrequently prescribed because of its association with pseudomembranous colitis (a life-threatening condition caused by an overgrowth of *Clostridium dificile).* One study showed that systemic clindamycin used adjunctively with SRP could decrease pocket depths, increase CAL gain, and decrease sulcular bleeding index compared to SRP alone in rapidly progressing periodontitis patients (Sigusch *et al.,* 2001). Despite this finding, systematic reviews show a lack of clinical evidence exists to show that clindamycin is a good selection as an adjunctive, systemic therapy for patients with any form of periodontitis (Herrera *et al.*, 2002; Haffajee *et al.* 2003).

Combination therapy refers to the simultaneous use of antibiotics from different drug classes. Using combination therapy allows for the targeting of a wider range of bacterial species. A synergy between the antibiotic drugs also occurs (Slots, 2004). When using combination therapy it is important that bacteriostatic and bactericidal drugs are not used together. Bactericidal antibiotics require active bacterial growth in order to be effective and are thus ineffective when combined with a bacteriostatic drug that inhibits growth.

Perhaps the most common antibiotic combination therapy used adjunctively with periodontal treatment is metronidazole and amoxicillin. Both drugs are bactericidal. Due to extensive study by van Winkelhoff *et al.* (1989) this combination is coined the "van Winkelhoff cocktail." This combination is particularly effective against *Aa*, eliminating the species in 96.6% (114 of 118) of patients with aggressive, chronic, and refractory periodontitis (van Winkelhoff *et al.*, 1992). Significant reductions were also found in *Pg* and *Pi* (although not as dramatically as the reduction of *Aa*). Patients administered the combination therapy also had lower mean PDs and higher gains in CAL.

Several systematic reviews and meta-analyses have shown promising results for the combination of metronidazole and amoxicillin. Herrera *et al.* (2002) revealed that adjunctive to SRP, the combination leads to the largest change in CAL in deep pockets when compared to other antibiotics. Sgolastra *et al.* (2013) showed that as an adjunct to SRP in chronic periodontitis patients, this combination leads to decreased PD and increased CAL gain compared to SRP alone. However, it failed to show significant differences in bleeding upon probing, suppuration, or the reduction of microbial pathogens. In both chronic and aggressive periodontitis, Zandbergen *et al.* (2013) found the mean reduction in PD was 3.72 mm and mean gain in CAL was 2.66 mm in pockets ≥ 7 mm. In patients with sensitivities to penicillins, a combination therapy of metronidazole and ciprofloxacin, a bactericidal drug that inhibits nucleic acid synthesis, also targets *Aa* (van Winkelhoff and Winkel, 2005). A recent meta-analysis by Keestra *et al.* (2015) showed that, in general, no antibiotic was superior to another as an adjunct to SRP. That said, initial clinical effects on mean probing depths were capable of being sustained for one year only with the combination of metronidazole and amoxicillin, and effects did not last as long with other antibiotics.

The use of systemic antibiotics adjunctive to SRP can provide clinical benefits for patients with both chronic and aggressive forms of periodontitis (Haffajee *et al.* 2003.) The difference in clinical parameters appears remarkable for patients with aggressive periodontitis (Slots and Ting, 2002) and is much more notable than the impact on chronic periodontitis (Haffajee *et al.* 2003).

Host-modulating agents

Destruction of periodontal connective tissue and alveolar bone occurs primarily through the host response to bacterial plaque and its byproducts. The presence of pathogens may lead to the release of pro-inflammatory cytokines, proteases, and other mediators that can cause extracellular matrix destruction and bone resorption (Oringer, 2002). The concept of host-modulation is based upon modulating the host response to the bacterial insult to limit tissue destruction. The three primary treatment modalities for host-modulating chemotherapeutics include 1) enzyme inhibitors (including matrix metalloproteinase (MMP) inhibitors), 2) inhibitors of pro-inflammatory mediators (e.g., prostaglandins (PGE_2), and 3) osteoclast inhibitors (*Table 1, Figure 1*).

It is hypothesized that in response to bacterial invasion, the host produces MMPs of the collagenase family (Caton *et al.*, 2000; Oringer, 2002). MMPs are proteolytic enzymes involved in connective tissue destruction. Therefore, one host-modulating chemotherapeutic modality used in periodontal therapy is MMP inhibitors. The use of host-modulating chemotherapeutics was pioneered in periodontitis by Golub *et al.* (1984), who discovered that tetracyclines possess host-modulating ability by inhibiting tissue collagenase activity in addition to their antimicrobial properties. At low dosage, too low to produce antimicrobial effects, doxycycline is called "sub-antimicrobial dose doxycycline (SDD)." This dosage is often prescribed for long periods of time, ranging from 3-12 months. In a series of studies, Caton *et al.* (2000) found that 1) long-term SDD did not lead to an overgrowth of doxycycline-resistant organisms or changes in the microbial normal flora, 2) SDD had more effectiveness in sites with higher disease severity, and 3) SDD reduced the overall percentage of spirochetes, but did not alter the percentages of other cellular morphotypes. Statistically significant gains were made in CAL and reductions in PD in the treatment groups after 3, 6, and 9 months of treatment. A follow-up study revealed that PD and CAL reductions remained significantly reduced 3 months after discontinuing use of the SDD (Caton *et al.*, 2001). It was hypothesized that SDD may be a beneficial treatment option for patients with periodontitis who smoke; however, smokers with SRP alone had comparable clinical outcomes and biomarker levels to smokers with SRP and adjunctive SDD (Needleman *et al.*, 2007). Anti-inflammatory medications target prostaglandins, inhibiting them from activating osteoclasts. In patients with progressing periodontal disease, prostaglandin (PGE_2) is significantly elevated compared to periodontally stable patients (Oringer, 2002). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) pathway and PGE_2 synthesis. However, effects appear to be minimal (Williams *et al.*, 1989; Oringer, 2002) and concerns of long-term side effects have limited the use of this modality. Bone-sparing agents, such as bisphosphonates, directly target osteoclasts, thereby decreasing bone destruction. Alendronate has been shown to limit progressive bone loss [Oringer, 2002; however, its use as an adjunctive therapy is not recommended because of concerns of drug side effects including medication-related osteonecrosis of the jaw, MRONJ Fernandez Ayora *et al.*, 2015, Mawardi *et al.* 2011, Braun and Iacono, 2006, Hellstein *et al.*, 2011]. While other host-modulating therapies are under investigation, long-term data regarding their safety and side effects is imperative prior to their introduction into clinic (Oringer, 2002). At this time, bisphosphonate use is not recommended for adjunctive periodontal therapy.

Treatment considerations and decision tree

The American Academy of Periodontology recommends the use of adjunctive chemotherapeutics for patients with aggressive, refractory, or recurrent periodontitis, patients with immunosuppression, or patients who do not respond to mechanical therapy (Slots, 2004). Their primary purpose is to be used as a supplement, not replacement for, mechanical debridement. Their use will not provide additional benefits for patients with gingival inflammation or gingivitis (Slots and Rams, 1990), as these conditions are reversible with the use of mechanical therapy alone. There is a great heterogeneity and variability in the studies of antibiotic therapy, including the antibiotic selected, timing of administration, dosage, and duration of use. While no specific recommendation exists regarding timing of administration, Herrera *et al.* (2008) suggest beginning adjunctive antibiotic use at the conclusion of mechanical debridement.

Figure 2 represents the authors' suggestions regarding the adjunctive use of chemotherapeutics in practice based on the literature described in this paper. If a patient presents with chronic periodontitis but is systemically healthy, adjunctive antibiotics are not recommended unless the patient fails to respond to mechanical therapy. Mechanical therapy such as SRP should be completed (Herrera *et al.*, 2008), followed by periodontal surgery in cases that require further treatment. However, if the patient does not respond to surgical therapy, the use of adjunctive antibiotics may be indicated. It is recommended that patients with aggressive periodontitis have adjunctive antibiotic therapy used during their initial, non-surgical treatment. Adjunctive antibiotic use during initial therapy has been shown to result in greater pocket depth reduction than adjunctive antibiotic use in re-treatment (Griffiths *et al.,* 2011.) If a patient presents with a health condition that places them into the immunocompromised category, adjunctive antibiotics may be considered during initial therapy. Conditions in this category include human immunodeficiency virus (HIV), poorly controlled diabetes, heavy use of tobacco products (for example, more than two packs per day), or other conditions affecting the ability to fight infection or host response to inflammatory factors.

Miranda *et al.* studied the impact of adjunctive antibiotics in type 2 diabetics with a randomized control trial in 2014. The control group received SRP alone, while the test group was given adjunctive metronidazole and amoxicillin after SRP. Analysis of the subgingival biofilm showed a decrease in red complex bacterial species (*Tf, Td,* and *Pg*) and *Pi* at 3 months and 12 months in the adjunctive antibiotic group. Additionally, better clinical results were seen, such as a higher mean pocket depth reduction, and higher gains in clinical attachment level. These results were sustained at 12 months. The adjunctive antibiotic group showed a significantly lower amount of residual pocket depths greater than 5 mm compared to controls (4 sites versus 14.9 sites.) This study suggests that adjunctive antibiotics may lead to better results than SRP alone in diabetic patients; however, the clinician should still exercise clinical judgment when deciding if a diabetic patient is considered immunocompromised or if the diabetes is well-controlled.

Compared to non-smokers, smokers have decreased gingival blood flow, decreased gingival crevicular fluid (Morozumi *et al.*, 2004) and a different subgingival microflora (van Winkelhoff, 2001). For example, van Winkelhoff (2001) showed that smokers had higher subgingival levels of *Bacteriodes forsythus* (now referred to as *Tannerella forsythia*), *Peptostreptococcus micros*, *Fusobacterium nucleatum*, and *Campylobacter rectus* when *Aa* and *Pg* are not present. Smokers also have lower neutrophil levels compared to non-smokers, and reduced neutrophil and phagocytosis function (Fredricksson *et al.,* 1999, Pauletto *et al.,* 2000). This cumulative information implies that smokers may have commensal bacteria leading to periodontal infection even when putative pathogens such as *Aa* and *Pg* are not present (van Winkelhoff, 2001), and that smokers have a reduced capacity to fight infection.

Several adjunctive antibiotic regimens have been studied in smokers. In 1999, Palmer *et al.* examined the effect of metronidazole as adjunctive therapy to SRP in smokers and non-smokers and found that it did not have a significant impact on smokers or non-smokers when compared to SRP alone. Smokers had poorer clinical results when compared to non-smokers, though. Winkel *et al.* (2001) combined metronidazole with amoxicillin as an adjunct to SRP and found a better clinical response in smokers compared to those receiving a placebo drug. For example, smokers had decreases in bleeding index, probing pocket depth, and increases in CAL gain when they received the adjunctive antibiotic compared to the placebo. Thus, the authors concluded that smoking may be an important factor in the decision to prescribe adjunctive antibiotics.

Table 2. Host-modulating agents used adjunctively in treating periodontal disease

Host-modulating Agent	Mechanism of Action
Subantimicrobial dose doxycyline (Periostat®)	Matrix metalloproteinase inhibition
Ibuprofen	Non-steroidal anti-inflammatory drug inhibiting prostaglandin synthesis
Flurbiprofen	Non-steroidal anti-inflammatory drug inhibiting prostaglandin synthesis
Bisphosphonate (alendronate; trade name: Fosamax)	Osteoclast inhibition

Figure 2. Adjunctive Systemic Chemotherapy Flow Chart

Additionally, smokers' clinical response was comparable to that of non-smokers. Matarazzo *et al.* (2008) also saw clinical benefits in smokers who had SRP performed with adjunctive antibiotics when compared to SRP alone; this was true for adjunctive therapy with metronidazole alone, but more so for a combination of metronidazole and amoxicillin. Patients with the adjunctive combination therapy had improvements in mean probing depths and clinical attachment levels. Additionally, microbial testing showed that smokers with the adjunctive combination therapy had fewer pathogenic bacteria harbored subgingivally than controls (Matarazzo et al., 2008).

Adjunctive azithromycin use in smokers has been studied by several groups. In smokers with chronic periodontitis, Mascarenhas *et al.* (2005) found that SRP combined with azithromycin compared to SRP alone resulted in a greater PD reduction and CAL gain for moderate-deep pockets (Sgolastra *et al.*, 2013). Dastoor *et al.* (2007) found more rapid healing and decreased gingival inflammation with azithromycin combined with surgery; however, they did not find significant differences in PD or CAL. While some clinicians favor the use of adjunctive azithromycin in smokers, an Angaji *et al.* (2010) systematic review found that no definitive clinical recommendation could be determined. As previously mentioned, the use of SDD adjunctive to SRP did not have significant clinical benefits or changes to biomarkers in smokers when compared to smokers who had SRP alone (Needleman *et al.*, 2007).

It should be kept in mind that smokers might require a prolonged exposure to systemic antibiotics (van Winkelhoff and Winkel, 2005) because smoking decreases gingival blood flow, thus decreasing the amount of antibiotic reaching the periodontal pocket (Morozumi *et al.* 2004).

Prior to prescribing an antibiotic, it is important to consider this decision using sound clinical judgment and evidence. Adverse effects of using antibiotics include possible drug allergy, arbitrary prescription, and the development of antibiotic resistance. The over-prescription of antibiotics and antibiotic resistance are a major, national health concern. Thus, adjunctive antibiotics should only be used as indicated here, in refractory periodontitis cases. While not all patients who are immunocompromised need to immediately be prescribed adjunctive antibiotics with the completion of SRP, it may be a consideration for the clinician. This requires clinical judgment on behalf of the practitioner and possible collaboration with the primary care physician. For example, while the Winkel *et al.* 2001 study discussed previously showed better clinical results for smokers with the use of adjunctive antibiotics, the authors recommended this treatment option be considered in smokers with refractory periodontitis.

According to Slots (2004), the use of microbial testing in conjunction with systemic antibiotic use is highly recommended. Shaddox and Walker, in a 2009 review, stated that microbial testing is useful if it positively affects disease diagnosis, treatment planning, and/or outcome. In this review, they mentioned several studies that showed a positive impact on one or more of these factors after the use of microbial testing. Levy *et al.* (1993) compared the treatment plans of patients with microbial testing involved in the diagnosis versus clinical diagnosis alone and found that patients with microbial testing had less future periodontal surgery performed.

Advantages of using microbial testing include avoiding arbitrary antibiotic prescription, thus, a possible decrease in antibiotic resistance (Suchett-Kaye *et al.*, 2001). In addition, microbial testing can lead to the discovery of bacterial strains resistant to antibiotic therapy (Shaddox and Walker, 2009). Disadvantages include problems with sample collection and/or transport, lack of controlled studies that show real benefit, and the fact that the presence of a species does not indicate its involvement in disease activity (Shaddox and Walker, 2009). Additionally, it is unclear whether or not the sites sampled are representative of the entire mouth (Loomer, 2004; Suchett-Kaye *et al.*, 2001). Samples should be taken from multiple sites of the mouth: when using DNA probes to identify species, the false negative rate was approximately 68% (Haffajee and Socransky, 1992).

Microbial tests should be used to identify specific microorganisms as desired targets for antibiotic therapy; without identifying a target organism, multiple, arbitrary antibiotic prescriptions could be given to the patient (Shaddox and Walker, 2009). Fine (1994) reported cases of refractory periodontitis that were unsuccessfully treated with arbitrary antibiotic therapy that, after microbial testing, were succesfully treated. Performing microbial testing to evaluate pathogens and prescribe an antibiotic according to target pathogens follows the model used in the medical field (Loomer, 2004). The prescription of antibiotics does not necessarily result in better clinical outcomes or the resolution of periodontitis. Mombelli *et al.* (2013) did not see a difference in clinical outcomes when a *Aa*-positive patients had SRP with antibiotics (an amoxicillin and metronidazole combination) versus SRP alone. However, Guerrero *et al.* (2014) found greater improvements in patients who were *Aa*-positive at baseline than those who were not with the use of the same antibiotic combination. Microbial testing may be most valuable in refractory and aggressive cases of periodontitis (Shaddox and Walker, 2009; Loomer, 2004; D'Ercole *et al.,* 2008). While it is arguably most valuable for these patients, microbial testing cannot be used to differentitate between chronic and aggressive forms of periodontitis (Mombelli, 2002).

Microbial testing options include: culture and sensitivity tests, DNA probe (hybridization) (Shaddox and Walker, 2009) or benzoyl-DL-arginine-napthylamide (BANA) testing for red complex bacterial species (Listgarten, 1992). Microbial testing should be completed initially to determine which species are present and the most effective antibiotic for targeting them (Shaddox and Walker, 2009; Fine, 1994). Re-testing is recommended to ensure that the antibiotic is successful; although there is no clinical standard for timing between re-testing, Shaddox and Walker (2009) suggest re-testing at 3 months. Additionally, it may be of benefit to see a negative microbiological finding, which has been associated with periodontal health during maintenance (Loomer, 2004).

If a patient fails to respond to mechanical therapy, surgical therapy, and the use of antibiotics, host-modulating agents may be used in conjunction with a compromised maintenance recall schedule (2 to 3 months recall). At this time, the only host-modulating agent recommended would be the use of submicrobial dose doxycyline.

The *Journal of the American Dental Association* recently published clinical guidelines for the use of adjunctive therapy in periodontics. A task force found that there was favorable evidence to support the use of SDD, because antimicrobial resistance was not of concern and because the benefits of SDD, while small, outweighed potential for harm (Smiley *et al.*, 2015). Weak evidence was found to support adjunctive therapy using systemtic antibiotics, as the moderate benefits were outweighed by potential risks, including allergy, microbial resistance, or other adverse effects. For this reason the authors do not suggest the use of adjunctive antibiotics in every case of periodontitis and reserve the use of adjunctive antibiotics for aggressive periodontitis, immunocompromised patients, or refractory periodontitis cases.

Antibiotic selection should be based on the type of periodontitis, as aggressive and chronic periodontitis are associated with different species of bacteria. Patient factors should be of consideration too, such as allergies to any particular antibiotic class or risk of adverse effects related to that drug class. Regarding chronic periodontitis, Keestra *et al.* (2015) did not find any antibiotic superior to another, statistically. This meta-analysis did not come to a firm conclusion that any antibiotic should be selected over another in treating chronic periodontitis patients. Some microbial testing companies provide recommendations for antibiotic regimens based upon the identified bacterial species present in the patient sample. Additionally, the Shaddox and Walker (2009) report makes recommendations for targeting specific bacterial species. Most bacterial species are susceptible to multiple drugs; however, it is unlikely to be able to target all bacterial species with one antibiotic. Selecting an antibiotic that targets bacterial species capable of invasion (*Aa, Pg, Pi*) may be of value (Shaddox and Walker, 2009). Amoxicillin, azithromycin, ciprofloxacin, and the combination of amoxicillin with metronidazole (Walker and Karpinia, 2002) are good antibiotic selections for targeting *Aa*. Red complex species should not be targeted with amoxicillin alone because beta-lactamases often inhibit this antibiotic. Thus, Shaddox and Walker recommend clindamycin, doxycycline, minocycline, metronidazole, or the combination of amoxicillin with metronidazole.

Regarding aggressive periodontitis, Rabelo *et al.* (2015) showed that metronidazole, metronidazole in combination with amoxicillin, and azithromycin provided clinical benefits in the treatment of aggressive periodontitis when compared to SRP alone. The authors performed two meta-analyses: a standard analysis and a Bayesian network analysis. The standard meta-analysis showed that the use of metronidazole and metronidazole with amoxicillin lead to better PD and CAL results, and azithromycin leads to more CAL gain when compared to SRP alone. The Bayesian network meta-analysis performed additionally showed limited results with doxycycline. Thus, at this time, present evidence suggests that metronidazole or metronidazole with amoxicillin may provide the best results for aggressive periodontitis cases. As previously mentioned, this may be altered by results of microbial testing or patient factors.

Conclusion

In order to responsibly prescribe adjunctive therapy, the clinician must consider the indications for adjunctive chemotherapy use, risk:benefit ratios, as well as statistical and clinical significance of the selected treatment modality. Consideration of these factors on a case-by-case basis can lead to improved outcomes, decreased side effects, and higher overall patient satisfaction. Thus, adjunctive chemotherapeutics can provide an effective way to treat periodontitis when used correctly and responsibly. As always, the principles of evidence-based dentistry should be considered when providing the patient with treatment options.

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