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Emerging Concepts in Periodontal Therapy

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Abstract

Conventional periodontal therapy consists of mechanical scaling and root planing, and surgical treatment. This is still the mainstay of periodontal treatment. Adjunctive antimicrobial treatments, both systemic and local delivery, are becoming more sophisticated and useful in the treatment of recurrent periodontitis. Also very promising are adjunctive treatments that modulate the host response and decrease levels of destructive pro-inflammatory cytokines or matrix metalloproteinases. Smoking is a major risk factor for periodontitis and has a profound impact on the progression of periodontal bone and attachment loss. In the interest of improved periodontal health patients should be encouraged to stop smoking. Finally bacterial endotoxins that stimulate the release of pro-inflammatory cytokines can have systemic effects and may lead to pre-term, low birthweight babies, and cardiovascular diseases such as atherosclerosis, myocardial infarction and stroke. Health professionals need to be cognisant of the effect dental health can have on systemic diseases and refer for treatment when appropriate to ensure that optimum oral and systemic health is achieved for their patients.

1. Periodontal Disease and Periodontal Therapy

Plaque induced gingivitis is an inflammatory response to bacterial accumulation on the teeth and in the subgingival space known as the gingival sulcus. It is characterised by gingival redness, swelling and bleeding when brushing or on subgingival examination with a periodontal probe. Removal of the bacteria, and its calcified counterpart known as dental calculus, reverses the inflammatory response and restores gingival health.[1]

Periodontitis is an inflammatory response to bacterial accumulation, primarily subgingival bacteria, that includes gingivitis but also spreads to deeper periodontal structures such as the gingival connective tissue, periodontal ligament and supporting alveolar bone. The inflammatory lesion destroys these tissues and their attachment to the tooth resulting in a deepening of the sulcus which is known as pocket formation (figure 1). The warm, moist pocket environment fosters the growth of Gram-negative, anaerobic bacteria that proliferate in the subgingival space. Some of these bacteria attach to an adherent biofilm on the tooth root. This subgingival microbial ecosystem becomes increasingly complex and pathogenic with the passage of time, and is inaccessible to personal oral hygiene. Some regard periodontitis as a low-grade infection since, with tissue manipulation or invasion, the subgingival bacteria or their by-products may enter the bloodstream. Bacterial invasion is not a predominant feature of periodontitis but does occur in certain situations.

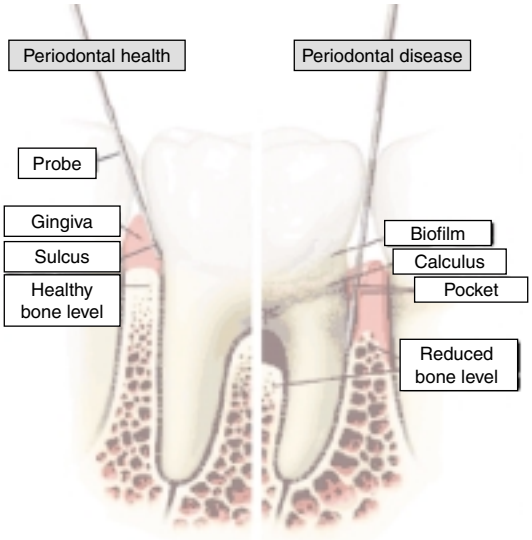

Fig. 1. Diagram of a longitudinal section of the periodontium.

Conventional periodontal therapy is directed at arresting the progression of tissue destruction and alveolar bone loss. Mechanical therapy, termed scaling and root planing, which amounts to scraping away the bacteria, calculus and biofilm, may be effective in shallow pockets.[1] In deeper pockets access and visibility are often problematic and limit the effectiveness of scaling and root planing. In these situations surgical reflection of a flap permits 'open' scaling and root planing for more efficient removal of bacteria and calculus, and allows excision of some inflamed tissue.[2] In most patients these treatments will resolve disease progression. At this point patients are placed on a 3-month recall for professional removal of supra- and subgingival plaque, calculus and biofilm.[3] This well tested time interval interferes with the re-establishment of a complex, pathogenic, bacterial ecosystem and prevents additional periodontal destruction. With continuing periodic treatment, periodontitis will usually remain arrested. The disease is not cured, however, and failure to comply with the 3-month recall therapy will result in recurrence and further tissue destruction.[3]

Currently, the practice of periodontics includes:

- placement of dental implants,
- sinus lift, ridge preservation, ridge augmentation and distraction osteogenesis procedures to prepare for implants or improve aesthetics,
- periodontal plastic surgery to cover exposed roots,
- tooth exposure for purposes of forced orthodontic eruption,
- regenerative procedures to regrow lost bone or soft tissue and rebuild lost periodontium,
- local and systemic antimicrobial therapy,
- and use of drugs to modulate the host inflammatory response thereby preventing further periodontal destruction.

This paper focuses on the impact of drug therapies as adjunctive treatments for periodontitis.

2. Antimicrobial Therapy

2.1 Antibacterial Agents for Gingivitis

Antibacterial therapies for gingivitis primarily include mouth rinses and toothpastes (table I). The most effective is chlorhexidine which is used as a mouthrinse.[4] It is a cationic surface active agent with substantivity or the property of binding to oral hard and soft tissues and being slowly released over time. Toothpastes, which are anionic, cannot be used within 30–60 minutes of chlorhexidine rinsing or they will render it ineffective.[4] The pri-

Table I. Selected antimicrobial agents for adjunctive therapy for gingivitis or prevention of recurrent gingivitis

Generic name	Brand name[a]	Delivery	Regimen
Chlorhexidine	PerioGard	Mouthrinse	Swish for 30s bid
Phenolic essential oils	Listerine	Mouthrinse	Swish for 30s bid
Triclosan	Total	Toothpaste	Brush bid

a US brand name (use of tradenames is for product identification only and does not imply endorsement).

bid = twice daily.

mary disadvantages of chlorhexidine are brown staining of the teeth, which is difficult to remove, altered taste perception and its objectionable taste.[5]

Phenolic agents are also used as a mouthrinse and are American Dental Association (ADA) approved as antigingivitis agents. These agents disrupt the bacterial cell wall, may reduce the endotoxin content on the root surface and can inhibit cyclo-oxygenase activity, thereby reducing inflammation.[5-7] Phenolics lack the property of substantivity and some people find the taste unpleasant. Recently triclosan has been added to toothpaste and has been shown to reduce the clinical signs of gingivitis.[8] Neither triclosan nor the phenolics are as effective an antimicrobial, antigingivitis agent as chlorhexidine.

In some patients antigingivitis agents are recommended immediately following professional tooth cleaning. Failure of scaling to independently resolve gingival inflammation indicates the need for additional mechanical therapy. This should be performed prior to administration of antigingivitis agents, which only mask the unresolved inflammation and prevent the therapist from identifying areas that need further treatment (figure 2).[9] This is inappropriate treatment and may allow sites of unresolved disease to progress to periodontitis.[9]

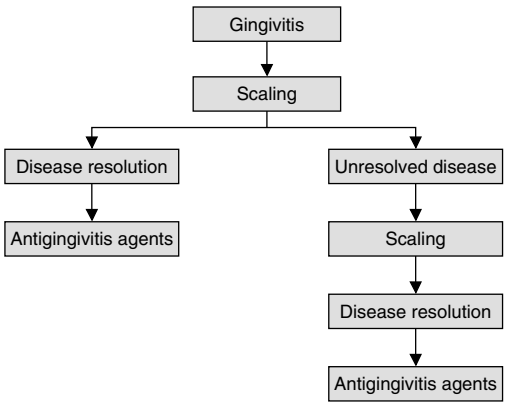

Fig. 2. Flow chart of options for the treatment of gingivitis.

Long-term systemic antibacterial agents are not recommended for the treatment of gingivitis.

2.2 Antimicrobial Agents for Periodontitis

Antimicrobial therapy for periodontitis has substantially expanded over the years using both systemic and local methods of delivery (table II). Periodontitis is a particularly appropriate disease for local delivery since disease activity can be highly site specific. The typical examination of a patient with a full complement of 28 teeth involves probing of six sites per tooth or a total of 168 sites. At any given time only 6% or fewer of these sites exhibit active tissue destruction. Products available for local delivery include tetracycline fibres, doxycycline polymer, minocycline microspheres and chlorhexidine chips.[10,11]

Most patients respond to conventional therapy and need no additional treatment; however, sites with recurrent disease detected at recall visits may benefit from subgingivally delivered antibacterials. Often sites with recurrent disease contain residual calculus missed during therapy. Calculus has a rough surface that promotes plaque attachment and growth. Mechanical removal of the missed calculus will resolve the problem. In patients who have deep pockets remain after scaling and root planing, surgical treatment can reduce the depth, thereby creating an environment less conducive to subgingival plaque growth. Once these options have been exhausted the application of local delivery agents is appropriate, if still necessary (figure 3).[9]

In general, local delivery agents reduce the bacterial load at the sites where they are applied.[10] Usually the bacteria are not eradicated. This may be due to the presence of the biofilm, undetected residual calculus or bacteria not sensitive to the agent used. Reducing the bacterial load may be sufficient to allow host defence to control the inflammatory response, and halt or slow attachment loss at the affected site. These agents have a place in periodontal therapy and, when used appropriately, provide a good means of treating disease recurrence at a small number of localised sites. If the

Table II. Selected approved antimicrobial agents as adjunctive therapy for recurrent, chronic or aggressive periodontitis

Generic name	Brand name[a]	Delivery	Regimen[b]
Tetracycline fibre	Actisite	Local	Place in pocket
Doxycycline polymer	Atridox	Local	Place in pocket
Minocycline microspheres	Arestin	Local	Place in pocket
Chlorhexidine chips	PerioChip	Local	Place in pocket
Tetracycline	Achromycin	Oral	250mg q6h × 14d
Doxycycline	Doryx	Oral	100mg q12h × 14d
Minocycline	Minocin	Oral	100mg q12h × 14d
Amoxicillin	Amoxil	Oral	250–500mg tid × 10d
Amoxicillin/clavulanic acid	Augmentin	Oral	250–500mg tid × 10d
Metronidazole	Flagyl	Oral	250mg tid × 10d
Ciprofloxacin	Cipro	Oral	250mg tid × 10d
Clindamycin	Cleocin HCl	Oral	150mg qid × 10d
Metronidazole + amoxicillin	Flagyl, Amoxil	Oral combination	Each 250mg tid × 10d
Metronidazole + amoxicillin/clavulanic acid	Flagyl, Augmentin	Oral combination	Each 250mg tid × 10d
Metronidazole + ciprofloxacin	Flagyl, Cipro	Oral combination	Each 250mg tid × 10d
Amoxicillin/clavulanate potassium + doxycycline	Augmentin, Doryx	Oral sequential	Augmentin: 500mg tid × 5d Followed by Doryx: 200mg the first day, and 100mg 1 day × 4d
Doxycycline subantibacterial	Periostat	Oral	20mg bid × 6-9mo

a US brand names (use of tradenames is for product identification only and does not imply endorsement).

b Other regimens may be used; higher dosages may be indicated depending on the severity of the infection.

bid = twice daily; **qid** = four times daily; **qXh** = every X hours; **tid** = three times daily.

recurrence is more generalised then systemic antibacterials may be more appropriate.

2.3 Systemic Antibacterials for Periodontitis

Periodontitis is a mixed infection and the primary pathogens are Gram-negative, anaerobic bacteria. In addition, there are several forms of periodontitis, some more aggressive than others, which may have different bacterial aetiologies. Since the infection lacks specificity, the antibacterial of choice can vary from patient to patient. As mentioned previously all conventional therapeutic options should be exhausted before using systemic antibacterials.

The bacteria most often associated with lesions of progressing periodontitis are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola*, *Bacteroides forsythus* and *Actinobacillus actinomycetemcomitans*.[12] The antibacterials most often used to control these infections are tetracycline, doxycycline, minocycline, metronidazole, amoxicillin, amoxicillin/clavulanic acid, ciprofloxacin and clindamycin.[12] Antibacterial combinations that are most useful include amoxicillin plus metronidazole, ciprofloxacin plus metronidazole, or amoxicillin/clavulanic acid followed by doxycycline.[13] Sensitivity testing may be indicated, but is not routinely done, to determine which antibacterial is most appropriate.

Infections caused by *A. actinomycetemcomitans*, seen with early onset forms of periodontitis, can respond to tetracyclines or to amoxicillin plus metronidazole. Recurrent disease may respond to tetracyclines and the long acting forms of the drugs, doxycycline or minocycline, can improve compliance since only twice daily administration is needed. Metronidazole is an appropriate choice for refractory or recurrent disease. Clindamycin is effective in patients with refractory disease, although caution must be exercised because of the possibility of *Clostridium difficile* overgrowth resulting in pseudomembranous colitis.[12] Sys-

temic antibacterials should be used judiciously since mechanical therapy will most often resolve periodontal infections and unnecessary use can lead to antibacterial resistance.

3. Host Modulation Therapy

While antimicrobial treatment, either mechanical or chemical, is one approach to arrest destructive disease activity another possibility is to modulate the host inflammatory response. Currently inhibition of matrix metalloproteinases, arachidonic acid metabolites, such as prostaglandins, and osteoclast activity are the three primary methods under investigation.[14-17]

Tetracyclines inhibit matrix metalloproteinases and prevent the destruction of collagen in periodontal tissues.[18] Systemic subantibacterial dose doxycycline is available for treatment of periodontitis as 20mg twice daily. This may be used in patients with recurrent or refractory disease and has been shown to slow disease progression. As with other drug treatments all mechanical means of therapy should be exhausted before using this agent.

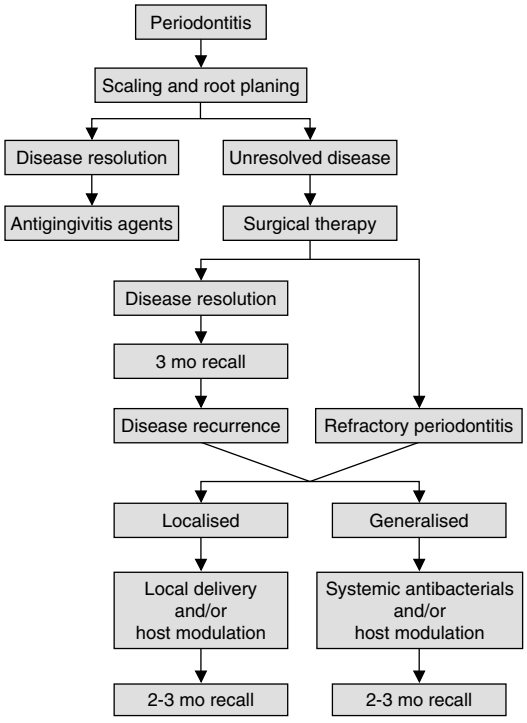

Fig. 3. Flow chart of options for the treatment of periodontitis.

Non-steroidal anti-inflammatory drugs (NSAIDs) block the enzyme cyclooxygenase and thus the final products of the arachidonic acid pathway, most notably the prostaglandins, and more specifically prostaglandin (PG)E_2, which has been associated with the progression of periodontitis.[19] Systemic administration of cyclooxygenase 1 (COX-1) inhibitors has been shown to significantly slow alveolar bone loss.[20] The gastrointestinal complications associated with NSAIDs must be considered if these agents are to be administered on a long-term basis. COX-2 inhibitors are an attractive alternative, however, they also produce similar, but fewer, gastrointestinal adverse effects.[19] The best approach may be local application of these agents.[21] Flurbiprofen and ketoprofen have been tested as a topically applied gel and dentifrice.[22,23] They were effective in reducing the rate of alveolar bone loss in animals. Although further research is needed, topical NSAIDs are a promising adjunct to conventional mechanical and surgical therapy.

Bisphosphonates inhibit osteoclast activity and possibly matrix metalloproteinase activity.[16,24] They are administered to prevent loss of bone density in patients with osteoporosis or osteopenia. Alendronate has been shown to slow periodontal bone loss in humans.[25] Another study has tested topical application of bisphosphonates as a means of slowing alveolar bone loss with promising results.[26] While this area needs more research it shows potential as another adjunctive treatment to prevent or slow disease progression.

Triclosan, mentioned in section 2.1 for its antimicrobial activity, also inhibits COX and lipoxygenase, thus preventing the production of arachidonic acid metabolites.[27] This dual activity has been shown to be effective in reducing the number of sites exhibiting attachment loss.[28] This product is already available and may be useful for patients with periodontitis.

4. The Role of Risk Factors

Smoking is a major risk factor for periodontitis and has been shown to have a profound effect on tooth loss and the progression of periodontitis.[29] In fact, 90% of patients who fail conventional periodontal therapy are smokers.[30] It has a significant impact on the success of dental implants and root coverage surgery.[29] While heart disease and cancer are well known adverse effects of smoking, periodontitis must be added to the list and considered another reason to stop smoking. Dentists need to establish smoking cessation programmes for their patients, or refer them for treatment, to prevent the particularly pernicious effect of smoking on tooth and bone loss.

5. Effect of Periodontitis on Systemic Diseases

Periodontitis has been shown to have systemic effects that may play a role in premature birth and cardiovascular disease.[31] Periodontitis is most often a subclinical infection with increased production of lipopolysaccharide, PGE_2 and tumour necrosis factor (TNF)-α. This can have an adverse effect on pregnancy and lead to a pre-term low birth weight infant.[32] An odds ratio of 7.9 for all cases of pre-term low birth weight babies suggests a strong association with periodontitis. Pregnant patients or those anticipating a pregnancy should have a periodontal examination so that all periodontal and dental infection can be eliminated, preferably prior to the pregnancy.

Cardiovascular diseases, atherosclerosis, myocardial infarction and stroke may also be influenced by periodontitis.[33] The systemic effect can be produced by lipopolysaccharides that promote the release of proinflammatory cytokines such as PGE_2, interleukin-1β and TNF-α.[34] These cytokines promote intimal injury, vasculitis and atheroma formation. Another possible mechanism is elevated serum fibrinogen and white blood cells found in patients with periodontitis, which can induce thrombogenic events.[35] Similarly certain strains of *Streptococcus sanguis* can adhere to platelets and induce aggregation.[36,37] These thrombogenic mechanisms can predispose to myocardial infarction and stroke. The odds ratio for these events ranges up to 2.8, so the association is not as strong as with pre-term low birth weight but nonetheless may be of clinical significance.[34]

6. Conclusions

Antimicrobial therapy in the form of mouth rinses and toothpastes are valuable adjuncts to conventional periodontal therapy. Their continued development will lead to better oral health for dental patients. Host modulation therapy holds great promise as a means of preventing disease recurrence by inhibiting matrix metalloproteinases, arachidonic acid metabolites or osteoclast activity. Patients will significantly benefit as these adjuncts to periodontal therapy are further developed. Smoking is a potent risk factor that can lead to disease progression despite the best therapy available. Patients should be encouraged to stop smoking to improve their oral health. Periodontitis should be treated and controlled not only to preserve the dentition but also to prevent adverse systemic effects that may contribute to pre-term low birth weight babies and cardiovascular diseases.

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