Nonsurgical Approaches for the Treatment of Periodontal Diseases

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Periodontal diseases are the most common dental conditions. Gingivitis is gingival inflammation associated with plaque and calculus accumulation. Gingivitis may or may not progress to more advanced forms of the disease known as periodontitis, which is associated with alveolar bone loss and diagnosed by increases in probing depths, loss of clinical attachment, and radiographic evidence of bone loss. Periodontitis is chronic and progressive and there is no known cure. Periodontal disease, however, is treatable and may even be prevented. Risk for periodontal disease and lack of treatment of periodontitis have been linked to the systemic health of the patient. Periodontitis is a complex interaction between an infection and a susceptible host.

Periodontal disease is initiated by an infection; however, it appears to behave not like a classic infection but more like an opportunistic infection. As a biofilm-mediated disease, periodontal disease is inherently difficult to treat. One of the greatest challenges in treatment arises from the fact that there is no way to eliminate bacteria from the oral cavity, so bacteria will always be present in the periodontal milieu. In addition, the bacteria within the biofilm are more resistant to antimicrobial agents and various components of the host response. When certain, more virulent species exist in an environment that allows them to be present in greater proportions, there is the opportunity for periodontal destruction to occur. Although it is apparent that plaque is essential for the development of the disease, the

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severity and pattern of the disease are not explained solely by the amount of plaque present.

In the 1980s, research began to focus on the relationship between the bacteria in the oral cavity and the response of the individual challenged by these bacteria or the bacterial host [1]. As a result of multiple studies, it was recognized that although there is evidence that specific bacterial pathogens initiate the pathogenesis of periodontal disease, the host response to these pathogens is equally if not more important in mediating connective tissue breakdown including bone loss. It has become clear that certain host-derived enzymes known as the matrix metalloproteinases (MMPs) and changes in bone resorptive osteoclast cell activity driven by factors known as cytokines and other inflammatory mediators such as prostanoids cause most of the tissue destruction in the periodontium (Fig. 1) [2].

Risk factors

It has been recognized that the severity of periodontal disease, its rate of progression, and its response to therapy vary from patient to patient. Bacteria are essential for the initiation of the disease but insufficient by themselves to cause the disease. The host must be susceptible, and it is the patient's risk factors that determine susceptibility to the disease. Risk factors are patient characteristics associated with the development of a disease.
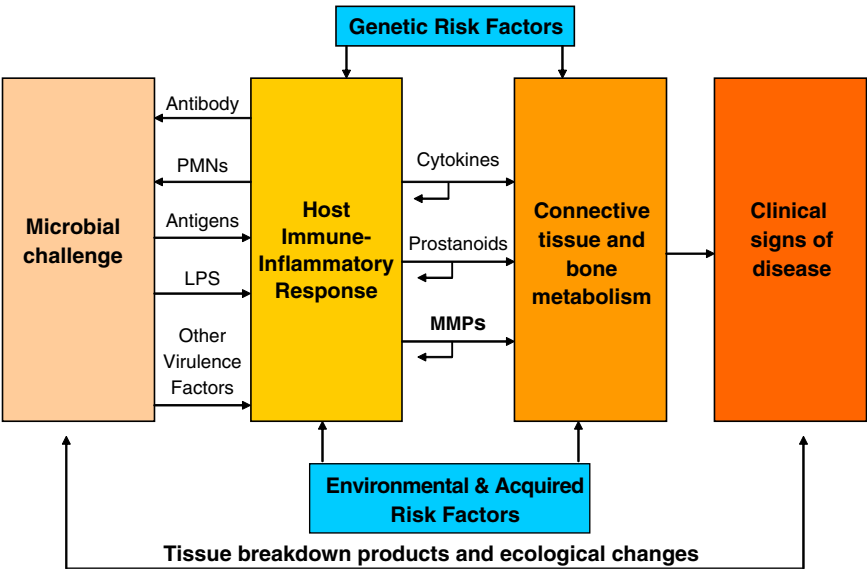
Fig. 1. The pathogenesis of periodontitis. LPS, lipopolysaccharide; PMNs, polymorphonuclear neutrophils. (*Adapted from* Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. Periodontol 2000 1997;14:10; with permission.)

Risk assessment in the patient with periodontitis

There are a number of environmental and acquired risk factors that play a major role in the host response and can increase a patient's susceptibility to periodontitis. Listed in Box 1 [3–5] are the risk factors that should be

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Box 1. Risk assessment for periodontitis

1. Heredity as determined by genetic testing and family history
2. Smoking including frequency, current use, and history
3. Hormonal variations such as those seen in
    a. pregnancy in which there are increased levels of estradiol and progesterone that may change the environment and permit the virulent organisms to become more destructive
    b. menopause in which the reductions in estrogen levels lead to osteopenia and eventually osteoporosis
4. Systemic diseases such as
    a. diabetes (the duration and level of control are important)
    b. osteoporosis
    c. immune system disorders such as HIV
    d. hematologic disorders such as neutropenias
    e. connective tissue disorders such as Marfan's and Ehlers-Danlos syndromes
5. Stress as reported by the patient
6. Nutritional deficiencies that may require a dietary analysis
7. Medications such as
    a. calcium channel blockers
    b. immunomodulatory agents
    c. anticonvulsants
    d. those known to cause dry mouth or xerostomia
8. Faulty dentistry such as overhangs and subgingival margins
9. Excessive occlusal loads
10. Poor oral hygiene resulting in excessive plaque and calculus
11. History of periodontal disease
12. Additional risk factors including hyperlipidemia and possibly arthritis

Data from Refs. [3–5].

assessed because they can affect the onset, rate of progression, and severity of periodontal disease and response to therapy.

It is important to document and determine the patient's risk and to convey to the patient that these risk factors can be more than additive. The value of risk assessment is that it can help the practitioner to establish an accurate diagnosis, provide an optimal treatment plan, and determine appropriate maintenance programs. Risk assessment may help to explain variability in treatment responses. In patients with multiple risk factors, the practitioner may proceed with caution with regard to invasive surgical procedures and may aggressively use pharmacologic adjuncts such as antimicrobials and host modulatory therapy in addition to mechanical therapy. When considering a risk-based approach to therapy, there is less watching and waiting to see what will happen and more frequent active treatment and maintenance therapy. It is also important to note that risk assessment is an ongoing process because a patient's risk changes throughout his or her life.

Risk modification

Some of these risk factors can be modified to reduce a patient's susceptibility to periodontitis. In addition to more frequent dental visits, including active treatment and maintenance visits, risk reduction may include the strategies listed in Box 2. The field of "perioceutics," or the use of pharmacologic agents specifically developed to better manage periodontitis, is emerging to aid in the management of susceptible patients who develop periodontal disease. When patients are unable to effectively reduce risk—such as the risk presented by the patient's genetics, smokers who are unable to kick the habit, patients who are unable to maintain adequate oral hygiene, the inability to reduce stress, diabetics who are poorly controlled despite the physician's best efforts, and the inability or unwillingness of the physician to alter medications—patients may require the use of perioceutics. Perioceutics includes antimicrobial therapies that can be used to address changes in the microflora and host modulatory therapy that can be used to address a host response consisting of excessive levels of enzymes, cytokines, and prostanoids and excessive osteoclast function that may be related to certain risk factors.

The antimicrobial approach

The antimicrobial approach to periodontal therapy has been used for many years, recognizing that the prevalence and severity of these diseases can be reduced by mechanical plaque removal or by the use of a variety of systemic or topically applied antimicrobial agents aimed at inhibiting pathogenic bacteria.

Box 2. Risk reduction strategies

1. More frequent visits for those with a genetic predisposition and the use of perioceutics (use of pharmacotherapeutics for the management of periodontitis)
2. Smoking cessation using one or more of the six approved regimens; these regimens rarely are successful as sole therapies (multiple forms of therapy often are used in combination with counseling to achieve success)
3. Hormonal variations such as those seen in
   a. pregnancy require good oral care before pregnancy to prevent complications during pregnancy; treatment of women during pregnancy may be necessary to prevent adverse pregnancy outcomes
   b. menopause may require hormonal supplements, calcium, and other medications and supplements prescribed by the physician to prevent osteopenia
4. Systemic diseases that require consultation with the physician include
   a. diabetes (for improved glycemic control)
   b. osteoporosis (requiring calcium supplements, bisphosphonates)
   c. immune system and hematologic disorders
   d. connective tissue disorders
5. Stress management; possible referral to a psychologist or psychiatrist
6. Nutritional supplementation; possible referral to a nutritionist
7. Medications can be changed in consultation with the physician
8. Corrective dentistry
9. Occlusal adjustments
10. Improved oral hygiene

Mechanical therapy

Brushing and flossing, as part of an oral hygiene routine, is the first-line approach to microbial reduction. The American Dental Association (ADA) recommends brushing for 2 minutes twice a day and flossing once a day. Many patients also use interproximal brushes, stimudents, and other mechanical aids to reduce plaque levels. Proper oral hygiene can effectively reduce gingivitis and aid in the treatment of periodontitis. Oral hygiene instructions should be given to all patients undergoing periodontal therapy. The unfortunate reality is that despite clinicians' best efforts, many patients

do not spend a sufficient amount of time brushing and most cannot or will not floss on a daily basis [6]. These circumstances result in a population in which more than 50% of adults have gingivitis [7]. Studies have demonstrated that powered toothbrushes, particularly those that work with rotation oscillation action, are safe and often more effective than manual toothbrushes at reducing plaque and gingivitis in the long- and short-term [8]. Powered brushes with timers help patients to comply with the recommended 30 seconds per quadrant of toothbrushing twice a day. Despite attempts to encourage plaque removal solely by mechanical means, adjuncts to existing home care routines have been developed to aid in the removal of plaque.

Tooth scaling by the dental care provider is also a key component in treating and preventing gingivitis. Aggressive subgingival debridement includes scaling and root planing (SRP) by manual instrumentation or with sonic or ultrasonic scalers. SRP has become the "gold standard" nonsurgical treatment of periodontitis, with multiple clinical studies demonstrating that it effectively reduces the microbial load and leads to reductions in bleeding on probing and probing depths and allows for gains in clinical attachment. A review of nonsurgical mechanical pocket therapy by Cobb [9] reveals mean probing depth reductions and clinical attachment level gains of 1.29 mm and 0.55 mm, respectively, for initial probing depths of 4 to 6 mm before treatment and 2.16 mm and 1.19 mm, respectively, for initial probing depths of >6 mm before treatment. Conventional non-surgical periodontal therapy involves performing SRP in single or multiple quadrants or sextants per visit and is usually completed in 2 to 6 weeks. The new concept of full-mouth disinfection for the prevention of reinfection from bacterial reservoirs has recently been introduced and shows promising results but requires further investigation [10]. In addition, the use of lasers within the periodontal pocket is being investigated and may emerge as a new technical modality for nonsurgical therapy in the near future [11].

Mechanical removal of plaque and calculus (nonsurgical and with surgical access) is time-consuming, operator and patient dependent, and difficult to master [12]. Although mechanical and surgical interventions continue to be the most widely used methods of controlling disease progression, instrumentation inevitably leaves behind significant numbers of microorganisms, including putative pathogens. Recolonization of these pathogens can occur within 60 days of SRP, resulting in the need for regular maintenance visits. The need for chemotherapeutic agents as adjuncts to mechanical and surgical debridement is compelling.

Antiseptics

Antiseptics can be used topically or subgingivally. They are agents that kill oral microorganisms that cause gingivitis, periodontitis, and caries. Antiseptics are not antibiotics or disinfectants and do not cause bacterial resistance.

Rinses and irrigation

Antiseptic mouthrinses have been used to aid in controlling plaque build-up. They have been used to complement, not replace mechanical therapy. Two clinically proven ADA-accepted antiseptic mouthrinses are Peridex (Zila, Inc., Phoenix, Arizona; chlorhexidine gluconate) and Listerine Antiseptic Mouthrinse (four essential oils; Pfizer, Inc., Morris Plains, New Jersey), studied in clinical trials of at least 6 months' duration. Both of these rinses have demonstrated an extremely broad spectrum of kill *in vitro* and *in vivo*. In a number of randomized, double-blinded, controlled 6-month clinical studies, these two agents demonstrated comparable efficacy for improving reductions in plaque and gingivitis compared with brushing alone [13,14]. Clinical studies have demonstrated additional benefits with the use of these antiseptic mouthrinses, such as control of oral malodor [15,16], enhancement of the benefits of oral irrigation [17,18], improvement in the gingival health around dental implants [19], reductions in plaque and gingivitis in orthodontic patients [20], reductions in bacteria in saliva and dental aerosols when used preprocedurally [21], and support of early healing after gingival flap surgery [22,23].

Chlorhexidine gluconate. Chlorhexidine gluconate is available at 0.12% in the United States and has strong substantivity [24]. Chlorhexidine is available only by prescription and is partly to fully covered by some prescription plans. Chorhexidine can stain teeth, the tongue, and aesthetic restorations. It can promote supragingival calculus formation and may alter taste perception [25]. When prescribed, it is recommended that patients rinse twice a day for 30 seconds with 15 mL after brushing and flossing and after toothpaste has been completely rinsed out of the mouth.

Listerine. Listerine is available over-the-counter and is composed of a fixed combination of essential oils: thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), and menthol (0.042%). Some patients complain of a transient tingling sensation. Listerine's comparable efficacy in reducing interproximal plaque and gingivitis to the "gold standard" of flossing was demonstrated in a recent study in which 611 subjects rinsed twice daily or flossed once daily as an adjunct to brushing for 6 months [26,27]. In addition, the incremental benefit (with regard to plaque and gingivitis reduction) of Listerine in patients who were already brushing and flossing was demonstrated in a brush, floss, and rinse study [28]. The recommendation for use is rinse twice a day for 30 seconds with 20 mL after brushing and flossing.

Toothpaste

Triclosan. Triclosan is present in a toothpaste (Colgate Total; Colgate Palmolive, Piscataway, New Jersey) currently available in the United States. Triclosan is a substantive antibacterial agent that adheres to the oral mucosa, hard, and soft tissues for up to 12 hours. Colgate Total is approved by the

Food and Drug Administration (FDA) and accepted by the ADA for treatment of gingivitis, plaque, caries, calculus, and oral malodor. Placebo-controlled studies in smokers [29] and in subjects with recurrent periodontitis [30] suggest that an oral hygiene regimen including a triclosan/copolymer dentrifice may sustain the short-term effect of nonsurgical therapy in smokers and improve on healing after nonsurgical treatment of recurrent periodontitis as measured by improvements in gingival inflammation, probing depths, and probing attachment levels. Triclosan *in vitro* has anti-inflammatory effects, inhibiting cytokine-stimulated (interleukin 1β and tumor necrosis factor α) production of prostanoids (prostaglandin E_2) from monocytes, reducing the activity of the enzyme cyclooxygenase 2 responsible for the production of prostanoids in culture, and inhibiting bone resorption in a parathyroid hormone–induced release of calcium from bone cultures [31].

Locally applied antiseptic

Periochip. Periochip (Dexcel Pharmaceuticals, Israel) is an orange-brown, biodegradable, rectangular chip rounded at one end that has an active ingredient of chlorhexidine gluconate (2.5 mg) that is released into the pocket over a period of 7 to 10 days. It has been found to suppress the pocket flora for up to 11 weeks post application [32]. In a 9-month randomized, blinded, and controlled parallel arm study, Periochip, as an adjunct to SRP, significantly reduced probing depths and maintained clinical attachment levels relative to baseline at 9 months compared with controls with repeated application of the Periochip up to three applications per site over 9 months [33]. Periochip effects on alveolar bone were demonstrated in a 9-month randomized, blinded, and placebo-controlled study. After 9 months of adjunctive treatment with Periochip, no sites exhibited bone loss and 25% of the sites experienced bone gain as measured through subtraction radiography [34]. In contrast, 15% of periodontal sites treated with SRP alone experienced bone loss. Periochip has a documented safety profile and does not cause any visible staining. The most frequently observed adverse event in the clinical trials was mild to moderate toothache, which often resolved spontaneously and required no further treatment. This adverse event occurred less frequently with subsequent Periochip placements. Periochip is the only locally applied nonantibiotic antimicrobial approved by the FDA as an adjunct to SRP procedures for the reduction of probing pocket depth or as part of a routine periodontal maintenance program. The recommendation for use adjunctive to SRP involves isolation of the periodontal pocket of 5 mm or more, drying the surrounding area, and grasping the Periochip with a forceps and inserting the chip, curved end first, into the pocket to its maximum depth. The chip can be maneuvered further into position with a plastic instrument. One site can be treated per chip.

Antibiotics

Locally applied antimicrobials

To have a therapeutic effect on the microflora, antimicrobial agents must reach adequate concentrations to kill or inhibit the growth of target organisms. The drug of choice has to reach the site where the organisms exist, stay there long enough to get the job done, and not cause harm. Mouthrinses do not reach the depths of periodontal pockets, whereas irrigation can deliver drugs to the base of the pocket. Because the gingival crevicular fluid (GCF) in the pocket is replaced about every 90 seconds, the duration of exposure during subgingival irrigation is short, and topically applied subgingival agents are rapidly washed out. With regard to the systemic administration of antibiotics to patients with periodontitis, early research suggested that doxycycline administered systemically [35,36] was highly concentrated in the GCF at levels 5 to 10 times greater than found in serum. Furthermore, tetracyclines show substantivity because they bind to the tooth structure and are slowly released as still-active agents. Even this supposed hyperconcentration of the drug in the GCF resulted in a level of antibiotic to which many organisms were not susceptible. More recent work has challenged earlier findings of hyperconcentration of tetracyclines in the GCF. In the 2 hours after the administration of a single dose of tetracycline (250 mg), minocycline (100 mg), or doxycycline (100 mg), the concentration of these tetracyclines was found to be highest in the plasma, intermediate in the GCF (doxycycline achieving the highest levels), and lowest in the saliva [37]. Further experimentation may be required to resolve this issue because there was a great deal of variability in the average GCF concentrations (0–8 μg/mL) in this study, and steady-state levels of the drug were never achieved. To address the issue of reaching adequate concentrations at the base of the pocket with adequate duration, controlled local delivery of antimicrobials was developed (Table 1).

Dental research has provided us with a better understanding of the microbial etiology and the nature of periodontitis. Periodontitis, initiated by bacteria, frequently appears in localized areas in the patient's mouth or is confined to localized areas by treatment. These infected localized areas lend themselves well to treatment with a controlled local delivery system using an antimicrobial [38]. Antimicrobial agents may be applied directly to the pocket, thereby eliminating many of the adverse side effects associated with

Table 1
Periodontal antimicrobial delivery systems

Objective	Mouthrinse or toothpaste	Local irrigation	Systemic delivery	Controlled delivery
Reach the pocket >4 mm	Poor	Good	Good	Excellent
Adequate concentration	Poor	Good	Fair	Excellent
Adequate duration	Poor	Poor	Fair	Good

systemic delivery of antibiotics. Nonresorbable and resorbable intrapocket delivery systems have been used. There is evidence that local delivery of sustained-release antimicrobials may lead to improvements in periodontal health, although a few side effects such as transient discomfort, erythema, recession, transient resistance, and allergy have been reported. Oral candidiasis has been reported in a small number of cases with local tetracycline delivery.

Systems have been developed for the release of all three commercially available tetracyclines at high doses and at a regular rate over a 10- to 14-day period. The first such FDA-approved system, Actisite, was developed by Dr. Max Goodson in 1983 [39]. Actisite consisted of a nonresorbable polymer fiber of ethyl vinyl acetate, 25% saturated with tetracycline hydrochloride. Use of this product resulted in substantially higher doses of tetracycline in the pocket (1590 μg/mL in the GCF and 43 μg/mL in the tissue) than could be achieved by systemic dosing (2–8 μg/mL). A local concentration of 30 μg/mL eliminates most pathogenic bacteria associated with periodontal diseases. When using locally applied antimicrobials, the area being treated is saturated with doses of the therapeutic agent that can be sustained for prolonged periods. Despite the high doses of drug that are achieved locally, serum levels of the drug do not exceed 0.1 μg/mL. The use of a singly applied tetracycline fiber as an adjunct to SRP proved to be more effective than scaling alone at reducing bleeding on probing, pocket depth, and achieving attachment gain as early as 60 days after placement, with additional improvements at 6 months. At 6 months after a single application of Actisite, the respective average results for SRP plus tetracycline fiber therapy versus SRP only were 1.81 mm versus 1.08 mm for pocket depth, 1.56 mm versus 1.08 mm for attachment gain, and 63% versus 50% for bleeding on probing reductions [40]. Subsequent studies concluded that SRP combined with full-mouth Actisite therapy versus SRP alone resulted in increased bone density (+2.43 computer-assisted densitometric image analysis [CADIA] versus −2.13 CADIA) and increased alveolar bone height (+0.24 mm versus −0.29 mm) at 6 months after therapy [41]. Despite its demonstrated efficacy, this product is no longer marketed to the dental community. Actisite was difficult to use, requiring considerable operator skill, and because it was not resorbed, a second visit had to be scheduled to remove it. In attempts to improve on ease of placement of local antimicrobials into the pocket and to obviate the need for a second visit to remove the product, bioabsorbable delivery systems were developed.

Atridox. The second FDA-approved locally delivered tetracycline to be developed was Atridox (Atrix Laboratories, Inc., Fort Collins, Colorado), a 10% formulation of doxycycline in a bioabsorbable, "flowable" poly-DL-lactide and *N*-methyl-2-pyrrolidone mixture delivery system that allows for controlled release over 7 days. This system is supplied in two prefilled syringes to be mixed at chairside and applied subgingivally to the base of the

pocket through a cannula. The flowable polymer gel of Atridox fills and conforms to pocket morphology, then solidifies to a waxlike substance after contact with GCF. Significant reductions (60%) in anaerobic pathogens are sustained for up to 6 months after placement of Atridox [42]. In subjects with chronic adult periodontitis, the application of this doxycycline gel at baseline and 4 months later resulted in reductions in probing depths (1.3 mm) and gains in clinical attachment (0.8 mm) equivalent to SRP alone at 9 months after baseline [43]. An important finding of these studies was that for the Atridox treatment group, smoking status did not seem to affect the outcome of clinical parameters such as probing depth reductions and clinical attachment level gains, whereas smokers and even former smokers did not respond as well to mechanical therapy alone [44]. A recent study supports these findings, indicating that locally applied Atridox improves the healing following nonsurgical therapy in smokers [45]. The side effect profile was equivalent to placebo. Despite the results of the initial phase III studies, it is likely that this agent will be used not as a monotherapy for the management of periodontal disease but as an adjunct to mechanical therapy.

Removal of the offending plaque and calculus deposits by SRP has proved to be effective. Disruption of the biofilm improves on the efficacy of antimicrobial agents. Phase IV studies conducted to support improved outcomes by using Atridox as an adjunct to scaling have demonstrated incremental benefits of use [46]. One arm of a 6-month study involved initiating therapy with ultrasonic scaling combined with Atridox, followed at 3 months by SRP alone in those sites with pocket depths that remained >5 mm. Results showed that this approach was at least as effective in improving probing depths and clinical attachment levels as the second arm of the study that involved SRP alone followed at 3 months by ultrasonic scaling and Atridox in those sites with pocket depths that remained >5 mm. The main difference between the two arms of this study was that the response was far more dramatic at 3 months for the combination therapy than the SRP alone, but the addition of either therapy at the 3-month interval allowed for equivalence to be achieved by 6 months.

Atridox is the only resorbable site-specific locally applied antibiotic proven to promote clinical attachment gains and reduce pocket depths, bleeding on probing, and levels of pathogenic bacteria. Clinical use of the product involves twisting and locking together two syringes—one with a purple stripe containing Atrigel and the second containing 50 mg of doxycycline hyclate—and pushing the contents of one into the other, back and forth, mixing for about 90 seconds (or about 100 times). After completion of mixing, all contents are placed into the syringe with the purple stripe and a blunt metal or plastic cannula is screwed on to the end and bent to resemble a periodontal probe. The cannula tip is placed into the base of the pocket and the Atridox is expressed, withdrawing the syringe as the pocket begins to fill. When the pocket is filled, the product is separated from the cannula by pressing the tip up against the tooth. A wet plastic

instrument may be used to tap the product lightly into the pocket if it is desirable to place additional Atridox into the site. A single syringe of Atridox can be used to treat multiple sites (approximately 8–12), the number of sites depending on the severity of the disease.

Arestin. With regard to minocycline, there is a non–FDA-cleared ointment product of 2% (wt/wt) minocycline hydrochloride known as Dentamycine (Wyeth, United Kingdom) or PerioCline (Sunstar, Japan) and marketed in a number of countries. In a four-center double-blinded randomized trial conducted in Belgium, the minocycline ointment was applied once every 2 weeks for four applications due to insufficient sustained-release properties. Probing depth reductions were significantly greater in the SRP plus minocycline group versus SRP alone, whereas there was only a trend toward improvement in clinical attachment levels and bleeding indices in the SRP plus minocycline treatment group [47]. In a long-term 15-month study, after placement of the gel subgingivally at baseline, at 2 weeks, and at 1, 3, 6, 9, and 12 months, results showed a statistically significant improvement for all clinical and microbiologic parameters for adjunctive minocycline ointment [48].

A minocycline microsphere system (Arestin; Johnson and Johnson, New Brunswick, New Jersey) has been approved by the FDA. The Arestin microspheres are bioadhesive, bioresorbable, allow for sustained release, and are administered as a powder with a proven safety record. Arestin is indicated as an adjunct to SRP procedures for reduction of pocket depth in patients with adult periodontitis. Arestin may be used as part of a periodontal maintenance program, which includes good oral hygiene and SRP. In subjects with chronic adult periodontitis, the application of minocycline microspheres three times over the course of 9 months (at baseline and at 3 and 6 months) resulted in an average of 0.25 mm improvement above average probing depth reductions seen with SRP alone at month 9 [49]. When the data are stratified in accordance with severity of baseline probing depths, there are 20% improvements in mild sites, 40% in moderately diseased sites, and 100% in severely diseased sites compared with SRP alone. SRP plus Arestin resulted in a greater percentage of pockets showing a change of pocket depth ≥ 2 mm and ≥ 3 mm compared with SRP alone at 9 months. The data also show that for pockets of 5 to 7 mm at baseline, greater reductions in pocket depths occurred in pockets that were deeper at baseline. In smokers, the mean reduction in pocket depths at 9 months was less in all treatment groups than in nonsmokers; however, SRP plus Arestin produced significantly greater pocket depth reductions than SRP alone at 6 and 9 months [49].

Arestin is delivered to sites of 5 mm or greater through a cartridge (containing 1 mg of minocycline hydrochloride) attached to a handle. The tip is removed from the cartridge and placed subgingivally, and the handle is depressed to express the Arestin from the cartridge. A single site can be treated with a single cartridge.

Periochip. For information on Periochip, see the section "Locally applied antiseptic."

Systemic antimicrobials

For the most part, systemic antimicrobial therapy has been reserved for advanced cases of periodontitis: (1) for sites that have not responded as expected to debridement with or without locally applied chemotherapeutic agents and/or host modulatory agents, and (2) for patients diagnosed with aggressive forms of periodontitis that demonstrate progressive periodontal destruction. Systemic antibiotics may be recommended as adjuncts to conventional mechanical therapy, but strong evidence for their use as a monotherapy has not been developed. There appears to be a consensus that systemic antimicrobial therapy should be reserved for situations that cannot be managed with mechanical therapy alone (with or without locally applied antimicrobials or antiseptics), such as severe or acute infections, early-onset periodontal diseases, aggressive types of periodontitis, and recurrent or refractory cases [50]. For these special situations, randomized double-blinded clinical trials and longitudinal assessments of patients indicate that systemic antimicrobials may be useful in slowing disease progression [51]. Acute necrotizing ulcerative gingivitis can be cured with metronidazole [52], and aggressive adolescent periodontitis associated with *Actinobacillus actino-mycetemcomitans* can be controlled or eradicated with metronidazole-amoxicillin combination therapy [53].

Systemic antibiotic therapy has the advantage of simple, easy administration of a drug or combination of drugs to multiple periodontal sites and extradental oral sites that may harbor periodontal pathogens. The disadvantages include uncertain patient compliance, the inability of the drugs to achieve adequate concentration at the site of infection, increased risk of adverse drug reactions, the potential for the selection of multiple antibiotic-resistant organisms, and the overgrowth of opportunistic pathogens [50]. Microbial analysis can be used to determine the specific antimicrobial susceptibility pattern of the suspected pathogens, can help to choose the appropriate antibiotics, and may be followed-up with additional testing to verify the elimination or suppression of the putative pathogens. For some clinicians, microbial analysis may be reserved for cases that are refractory to an initial course of antimicrobial therapy. Common antibiotic therapies for the treatment of periodontitis include metronidazole, 500 mg, three times a day for 8 days; clindamycin, 300 mg, three times a day for 8 days; doxycycline or minocycline, 100 to 200 mg, every day for 21 days; ciprofloxacin, 500 mg, twice a day for 8 days; azithromycin, 500 mg, every day for 4 to 7 days; metronidazole and amoxicillin, 250 mg of each drug, three times a day for 8 days; and metronidazole and ciprofloxacin, 500 mg of each drug, twice a day for 8 days [54]. For adult patients with acute periodontal abscesses, an antibiotic regimen as an adjunct to incision and drainage is amoxicillin (1 g loading dose followed by 500 mg, three times a day for

3 days), with patient follow-up re-evaluation. For patients with allergies to β-lactam drugs, antibiotic regimens include azithromycin (1 g loading dose followed by 500 mg, every day for 2 days) or clindamycin (600 mg loading dose followed by 300 mg, four times a day for 3 days).

The host modulatory approach

Host modulation is a new term that has been incorporated into dental jargon and has not been well defined. The definition of *host* from a medical dictionary reads "the organism from which a parasite obtains its nourishment or in the transplantation of tissue, the individual who receives the graft" [55]. The definition for the term *modulation* is "the alteration of function or status of something in response to a stimulus or an altered chemical or physical environment" [55]. In diseases of the periodontium that are initiated by bacteria, it is clear that the host is the individual who harbors these pathogens; however, it was not clear for many years that it was possible to modulate the host response to these pathogens. Host modulation with chemotherapeutics or drugs is an exciting new adjunctive therapeutic option for the management of periodontal diseases. The concept of host modulation is fairly new to the field of dentistry but is universally understood by most physicians who routinely apply the principals of host modulation to the management of a number of chronic progressive disorders including arthritis and osteoporosis.

A number of host modulatory agents have been investigated in clinical trials for their potential use as adjuncts to mechanical nonsurgical periodontal therapy. These agents have included the systemic (flurbiprofen) and topical (ketoprofen) use of nonsteroidal anti-inflammatory drugs, the systemic use of subantimicrobial-dose doxycycline (SDD; Periostat [Colla-Genex Pharmaceuticals, Newtown, Pennsylvania]), and the systemic use of bisphosphonates (Fosamax). The only systemic host modulatory agent approved by the FDA for adjunctive use in conjunction with nonsurgical periodontal procedures is Periostat. The points of intervention of these agents in the host response can be seen in Fig. 2. In addition, a number of local host modulatory agents have been investigated in clinical trials for their potential use as adjuncts to surgical procedures not only to improve on wound healing but also to stimulate regeneration of lost bone, periodontal ligament, and cementum, restoring the complete periodontal attachment apparatus. These agents have included enamel matrix proteins (Emdogain), bone morphogenetic proteins 2 and 7, growth factors (platelet-derived growth factor and insulin-like growth factor), and tetracyclines. The initial local host modulatory agent approved by the FDA for adjunctive use during surgery was Emdogain; platelet-derived growth factor combined with a resorbable synthetic bone matrix (GEM 21S) was approved recently by the FDA. Emdogain has also been studied as an adjunct to nonsurgical therapy. The results of a 3-month double-blinded, split-mouth, controlled
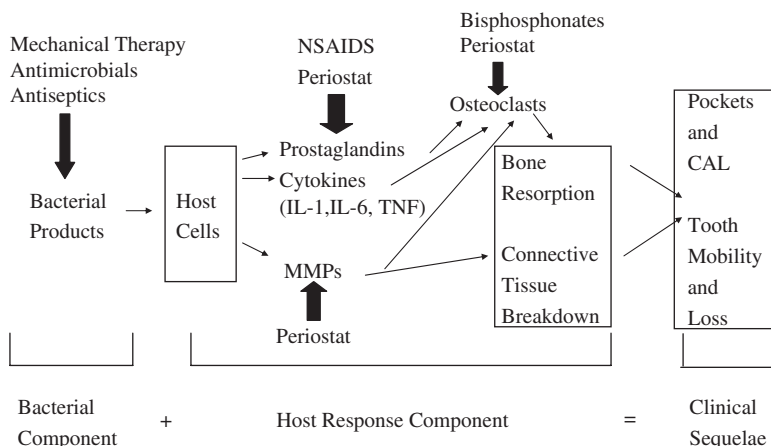
Fig. 2. Points of intervention for nonsurgical therapy. CAL, clinical attachment loss; IL, interleukin; NSAIDS, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

and randomized study do not support the use of Emdogain during routine nonsurgical debridement of periodontal pockets as measured 3 months post SRP [56]. Histologic evaluation of human intrabony defects following nonsurgical periodontal therapy with and without application of Emdogain failed to show periodontal regeneration with subgingival application of Emdogain [57]. The clinical utility of host modulation for nonsurgical procedures in clinical practice is limited in the remainder of this article to the use of SDD (Periostat).

SDD is a 20-mg dose of doxycycline (Periostat) that is FDA approved and ADA accepted. It is indicated as an adjunct to SRP in the treatment of chronic periodontitis. It has been evaluated as taken twice daily for up to 9 months of continuous dosing in clinical trials. The duration of use may vary from patient to patient. A risk factor assessment in addition to clinical evaluation of patients can help guide the practitioner with regard to length of use and need for repeat use. A minimum of 3 months of host modulatory therapy is suggested for reasons described later. Current clinical studies in susceptible patient populations such as osteopenic women are investigating extended continuous use of up to 2 years. The 20-mg twice per day dose exerts its therapeutic effect by enzyme, cytokine, and osteoclast inhibition, rather than by any antibiotic effect. Research studies have found no evidence of any detectable antimicrobial effect on the oral flora or the bacterial flora in other regions of the body and have identified clinical benefit when SDD is used as an adjunct to SRP. At the present time, SDD is the only FDA-approved, ADA-accepted host modulatory therapy specifically indicated for the treatment of chronic periodontitis.

SDD works so well as a host modulatory agent because of its pleiotropic effects on multiple components of the host response (see Fig. 2). The only

enzyme (MMP) inhibitors that have been tested for the treatment of periodontitis are members of the tetracycline family of compounds. In an early study using these different tetracyclines, Golub et al [58] reported that the semisynthetic compounds (ie, doxycycline) were more effective than tetracycline in reducing excessive collagenase activity in the GCF of adult periodontitis patients. Recent clinical trials have focused on doxycycline because it was found to be a more effective inhibitor of collagenase than minocycline or tetracycline [59,60] and because of its safety profile, pharmacokinetic properties, and systemic absorption. In an effort to eliminate the side effects of long-term tetracycline therapy (especially the emergence of tetracycline-resistant organisms), SDD capsules were prepared and tested [61]. Each capsule contained 20 mg of doxycycline compared with the commercially available 50- and 100-mg antimicrobially effective capsules. In multiple clinical studies conducted using SDD, there has not been a difference in the composition or resistance level of the oral flora [62,63], and recent studies demonstrate no appreciable differences in fecal or vaginal microflora samples [63]. In addition, these studies have demonstrated no overgrowth of opportunistic pathogens such as *Candida* in the oral cavity, gastrointestinal, or genitourinary systems.

With regard to MMP inhibition, Golub et al [64] reported that a 2-week regimen of SDD reduced collagenase in GCF and in the adjacent gingival tissues surgically excised for therapeutic purposes. Subsequent studies using SDD therapy adjunctive to routine scaling and prophylaxis indicated that after 1 month of treatment, there were continued reductions in the excessive levels of collagenase in the GCF but after cessation of SDD administration, there was a rapid rebound of collagenase activity to placebo levels, suggesting that a 1-month treatment regimen with this host modulatory agent was insufficient to produce a long-term benefit [65]. In contrast, during the same study, a 3-month regimen produced a prolonged drug effect without a rebound in collagenase levels to baseline during the no-treatment phase of the study. The mean levels of GCF collagenase were significantly reduced (47.3% from baseline levels) in the SDD-treated group versus the placebo group, which received scaling and prophylaxis alone (29.1% from baseline levels). Accompanying these reductions in collagenase levels were gains in the relative attachment levels in the SDD-treated group [65,66]. Continuous drug therapy over a period of several months appears to be necessary for maintaining near normal collagenase levels over prolonged periods. It is reasonable to speculate, however, that these MMPs will eventually reappear in susceptible patients, and those individuals having the most risk factors and the greatest microbial challenge will require more frequent host modulatory therapy than other patients.

A series of double-blinded placebo-controlled studies of 3, 6, and 9 months' duration showed clinical efficacy based on the reduction of pocket depth, gains in clinical attachment levels, biochemical efficacy based on the

inhibition of collagenase activity, and protection of serum alpha$_1$-antitrypsin (a naturally occurring protective mediator) from collagenase attack in the periodontal pocket [59,67,68]. Golub et al [69] showed that a 2-month regimen of SDD significantly decreased the level of bone-type collagen breakdown products (pyridinoline cross-linked carboxyterminal telopeptide of type I collagen) and MMP-8 and MMP-13 enzyme levels (neutrophil and bone-type collagenase) in adult periodontitis subjects, providing biochemical evidence of reduction of bone resorption to support computer-assisted subtraction radiography data [70,71], the latter providing evidence of a reduction in the loss of alveolar bone height after 12 months of therapy with SDD.

A 9-month randomized, double-blinded placebo-controlled trial conducted at five dental centers demonstrated clinical efficacy and safety of SDD versus placebo as an adjunct to SRP, the ''gold standard'' of periodontal therapy. Again, the benefits of host modulatory therapy in addition to mechanical therapy were seen, with statistically significant reductions in probing depths, bleeding on probing, gains in clinical attachment levels, and the prevention of disease progression [72,73]. In a discontinuation study in which SDD administration was discontinued after 9 months of continuous therapy, the incremental improvements demonstrated in the SDD group were maintained for at least 3 months post treatment. There was no rebound effect in pocket depth reductions or clinical attachment level gains; in fact, there appeared to be slight continued improvements in both of these clinical parameters [72,73], presumably due to the enhanced clinical status of the patients who benefited from adjunctive Periostat and the known persistence of doxycycline in the bone and soft tissue of the periodontium. The clinical relevance of such findings confirms the utility of an MMP inhibitor in the management of adult periodontitis.

Recent phase IV clinical studies have been performed that have revealed clinical and biochemical success using SDD in different populations of susceptible individuals, including subjects who are genetically susceptible [74]; subjects who have severe generalized periodontitis [75], diabetes [76,77], or osteoporosis [78]; subjects who are institutionalized geriatric patients [79]; and smokers [80]. The use of SDD in these at-risk patient populations significantly improved clinical response to SRP, and in the case of smokers, the subjects who were treated with SRP plus SDD experienced probing depth reductions and clinical attachment level gains equivalent to, and in some studies superior to, the response seen in nonsmokers who were treated with SRP alone [80]. In addition, it becomes apparent that the use of systemic host modulatory therapy by the dentist may not only improve the patient's periodontal condition but also provide systemic benefits for other inflammatory disorders with related tissue destruction, such as arthritis, cardiovascular disease, dermatologic conditions, diabetes, osteoporosis, and so forth. Dental studies have reported dramatic reductions in hemoglobin A$_{1c}$ levels (a long-term marker of glycemic control) in addition to

improvements in clinical parameters in diabetic subjects treated with SDD plus SRP compared with SRP alone [76,77]. Dental studies in osteoporotic women have reported reductions in the loss of alveolar bone height and bone density (as measured by computer-assisted densitometric image analyses) in addition to clinical attachment level gains and no attachment loss in subjects treated with SDD plus SRP compared with subjects treated with SRP alone who experienced no attachment level gains and loss of attachment in a number of sites over the 12 months of the study [78]. Another assumption that can be made is that patients who are currently being prescribed host modulatory agents by their physicians, such as nonsteroidal anti-inflammatory drugs, bisphosphonates, or tetracyclines, and newer agents targeting specific cytokines for the management of medical conditions may be experiencing periodontal benefits from these systemically administered medications.

In the clinical trials of SDD (20-mg dose), the drug was well tolerated, and the profile of unwanted effects was virtually identical in the SDD and placebo groups [73,75,81,82]. SDD is indicated in the management of chronic periodontitis [68,73,83,84]. SDD should not be used in conditions such as gingivitis or periodontal abscess, or whenever an antibiotic is indicated. SDD can be used in aggressive periodontitis cases that are being treated nonsurgically [75]. Furthermore, emerging studies have supported the efficacy of SDD as an adjunct to periodontal surgery [85]. SDD may also be of benefit in cases that are refractory to treatment or in patients with risk factors such as smoking or diabetes in whom the treatment response might be somewhat limited. SDD is contraindicated in anyone with a history of allergy or hypersensitivity to tetracyclines. It should not be given to pregnant or lactating females or children less than 12 years old (because of the potential for discoloration of the developing dentition). Doxycycline may reduce the efficacy of oral contraceptives, so advice should be given to use alternative forms of birth control, if necessary. There is a risk of increased sensitivity to sunlight (manifested by an exaggerated sunburn) seen with higher doses of doxycycline, but this has not been reported in any of the clinical trials at the subantimicrobial dose. A typical prescription for Periostat (20-mg doxycycline tablets) is for at least 3 months (180 tablets, 1 tablet twice a day until complete), and refills may be provided for longer courses of therapy.

SDD treatment can also be combined with the local delivery of antibiotics to the periodontal pocket by way of sustained delivery systems. The two treatments target different aspects of the pathogenic process: local delivery systems deliver antimicrobial concentrations of an antibacterial agent directly to the site of the pocket, whereas SDD is a systemic host response modulator. Thus, combining these two complementary treatment strategies is another example of how antibacterial therapy (ie, SRP plus locally applied antibiotics) can be combined with host modulatory therapy (SDD) to maximize the clinical benefit for patients. Preliminary results from a 6-month 180-patient clinical trial designed to evaluate the safety and

efficacy of SDD combined with a locally applied antimicrobial (Atridox) plus SRP versus SRP alone demonstrated that patients receiving the combination of treatment experienced more than a 2-mm improvement in mean attachment level gain and pocket depth reduction, which was highly statistically significant ($P < 0.0001$) compared with SRP alone.

Clinical application

The author has implemented a three-pronged approach to periodontal therapy in her clinical practice (Fig. 3). The initial visit by a patient includes a medical and dental history, a risk assessment profile, periodontal charting, and radiographic analysis. The patient must be made aware of the fact that periodontal disease is not curable but that it can be treated and well controlled with constant monitoring by the dentist/hygienist and good patient compliance. The patient must also be informed of the need for periodontal therapy, which should not be considered optional or elective but necessary to promote not only good oral health but also good general health, as recent studies have suggested.

Initial therapy consists of risk reduction strategies (see Box 2). Modification of any risk factors such as smoking, nutrition, stress, contributing
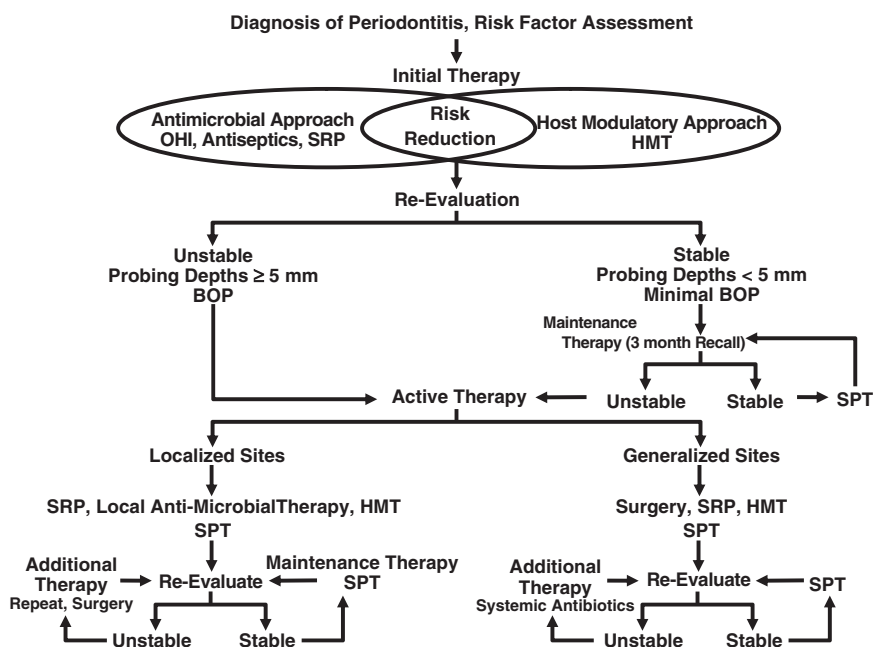
Fig. 3. Periodontal therapy treatment algorithm. BOP, bleeding on probing; HMT, host modulatory therapy; OHI, oral hygiene instruction; SPT, supportive periodontal therapy (reinforce OHI, scaling, antiseptics).

medications, faulty restorations, poor oral hygiene, and poor diabetic control should be addressed at this time. Oral hygiene instructions are extremely important and must be reinforced continuously over the course of therapy; the use of adjunctive antiseptic agents is often employed. SRP is the core of nonsurgical therapy, with anesthesia administered as needed. At-home oral hygiene and in-office SRP approaches are designed to reduce the bacterial load. In addition, an initial course of host modulatory therapy (Periostat) may be prescribed to reduce excessive levels of enzymes, cytokines, and prostanoids, especially in susceptible patients as identified by risk assessment. A patient's refusal or inability to modify contributing risk factors is an important consideration for treatment planning and evaluation of therapeutic responses. In the case of adjunctive chemotherapies, the more risk factors and the poorer the hygiene, the greater the need for antiseptics, antibiotics, and host modulation of longer duration or repeat therapy in the future.

After completion of initial therapy, re-evaluation is the next step (see Fig. 3). At this point, the decision is made to continue with active (additional) therapy or to place the patient in the maintenance phase of therapy. If all probing depths are < 5 mm and there is minimal bleeding on probing and gingival inflammation, then the decision is made to place the patient in the maintenance phase of therapy. The patient is typically maintained on the host modulatory agent through the first maintenance visit. If the treated sites remain stable for this 3-month period, then the patient is removed from the host modulatory agent and placed in the typical maintenance program (3- to 4-month visits) until the need for additional active therapy is required. If there are probing depths ≥ 5 mm at re-evaluation, then the therapeutic approach may differ depending on the number of sites per quadrant and radiographic assessment of the sites.

Typically for isolated sites with probing depths ≥ 5 mm at re-evaluation, a nonsurgical approach may include rescaling the sites and placement of a locally applied antimicrobial agent (ie, Atridox, Arestin, or Peiochip), with the continued adjunctive use of the host modulatory agent. Sites treated with locally applied antimicrobials should be re-evaluated at 3 months and a decision can be made by the clinician as to whether an additional application of the same locally applied antimicrobial may be used or another locally applied antimicrobial may be administered, and so forth. Clinicians must use their clinical judgment. If this treatment is insufficient to achieve adequate pocket depth reduction or if there are multiple sites in a quadrant with probing depths ≥ 5 mm, then a surgical approach may be indicated to reduce the probing depths through resective or regenerative techniques. After all probing depths are < 5 mm, the patient is placed in the maintenance phase of therapy as described earlier.

In certain patients with aggressive periodontitis or in those truly refractory to the therapy described previously, the use of systemic antimicrobials or additional host modulatory agents in a polypharmacologic approach can be considered. Microbial and antibiotic susceptibility testing

may be helpful in these situations. Examples of additional host modulatory approaches have included low doses of nonsteroidal anti-inflammatory drugs (flurbiprofen), which demonstrated incremental benefits in a small clinical study [86] or low doses of bisphosphonates, which have not yet been investigated in combination in human clinical studies but have shown incremental benefits in animal studies of osteoporosis. Patients who are difficult to manage, who are most susceptible with multiple risk factors, or who present with moderate to severe disease requiring comprehensive periodontal treatment planning should be referred to the periodontal specialist for care and close monitoring.

To improve our ability to make appropriate treatment decisions for patients undergoing periodontal therapy, it would be extremely useful to have access to the types of diagnostic tests that are available to our medical colleagues. Therapeutic technologies have surpassed our ability to adequately diagnose active versus inactive lesions, identify subtle changes in the tissues and, thereby, prevent additional loss of attachment and bone. Studies have shown that SRP alone, although effective at improving clinical parameters such as probing depths that are routinely used to assess the outcome of periodontal procedures, may not be sufficient to reduce excessive levels of many of the underlying destructive mediators, particularly in susceptible patients. In the future, dental diagnostics currently being developed to aid in clinical assessment of patients may be performed in a centralized diagnostic laboratory facility rather than at chairside. Oral samples and perhaps even blood samples collected from patients and sent to a centralized diagnostic laboratory will include plaque samples for microbial assessments, buccal cheek swabs for genetic testing, and GCF (single or multiple sites or full-mouth rinse collections) and saliva for analysis of host response mediators such as enzymes, cytokines, and prostanoids. The information gained from improved quantitative diagnostics will be used to create a profile of the patient's risk—not only for oral disease but also potentially for systemic disorders—to determine the patient's level of periodontal disease activity, aid in treatment planning decisions, and better monitor the patient's response to therapy. Until such diagnostic techniques are made available, clinicians have no choice but to rely on clinical judgment to determine the most appropriate course of therapy.

Summary

Periodontal pathogens and destructive host responses are involved in the initiation and progression of periodontitis in the individual at risk for disease. Therefore, the successful long-term management of this disease may require a treatment strategy that integrates therapies that address all of these components. There is now overwhelming evidence for the role of bacterial pathogens and host-derived MMPs, cytokines, and other mediators in the destructive processes of periodontal disease, distinguishing them as viable

targets for chemotherapeutic adjunctive approaches. The introduction of novel adjunctive therapies to enhance the efficacy of existing mechanical procedures has contributed favorably to an integrated approach for the long-term clinical management of periodontitis.

Finally, as the era of periodontal medicine evolves, the additional benefits of adjunctive local and systemic antimicrobials and systemic host modulatory approaches need to be considered. In particular, host modulators used to manage periodontal disease by inhibiting mediators of host tissue destruction such as MMPs, cytokines, and prostanoids may have additional beneficial effects on systemic diseases such as cardiovascular disease, diabetes, and osteoporosis. The surgeon general's report [87] recognizes "the mouth as a mirror of health or disease, as a sentinel or early warning system, as an accessible model for the study of other tissues and organs, and as a potential source of pathology affecting other systems and organs." The findings discussed in this article with regard to the use of therapeutics to better manage chronic periodontal disease may have applications to other associated systemic diseases such as diabetes, cardiovascular disease, stroke, respiratory disease, and adverse pregnancy outcomes. The proper management of periodontitis may prove to have an impact on general health, making a significant contribution to human welfare.

Acknowledgments

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