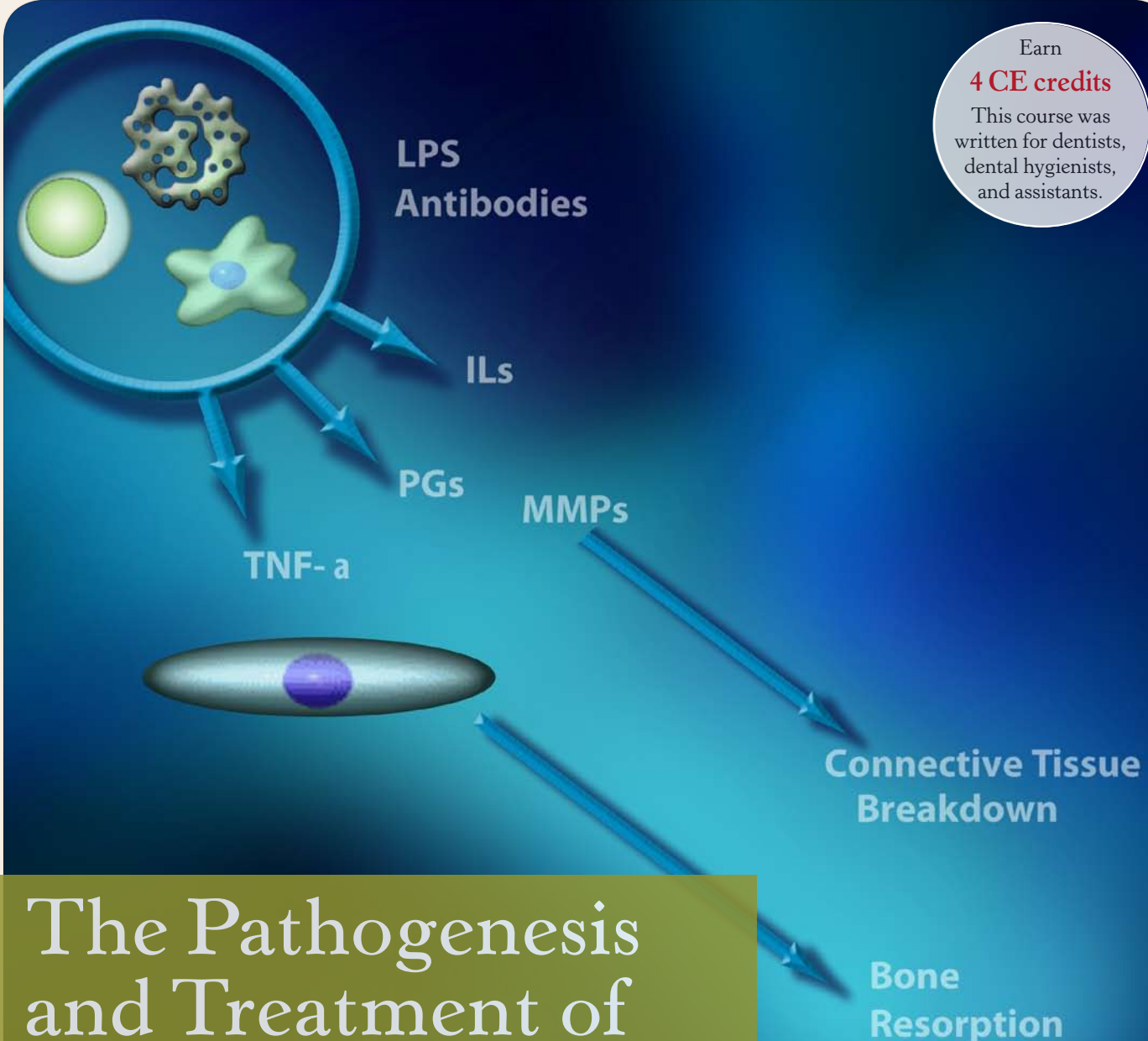


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The Pathogenesis and Treatment of Periodontal Disease

A Peer-Reviewed Publication
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Educational Objectives

The overall goal of this article is to provide the clinician with information related to the pathogenesis, risk and treatment of periodontal disease. Upon completion of this course, the clinician will be able to:

1. Understand the pathogenesis of periodontal disease
2. Know the risk factors for periodontal disease and the factors that may play a role in responsiveness to periodontal therapy
3. Understand the adjunctive therapeutic options available in the treatment of periodontal disease and their utility
4. Know the factors involved in selecting locally applied antimicrobials.

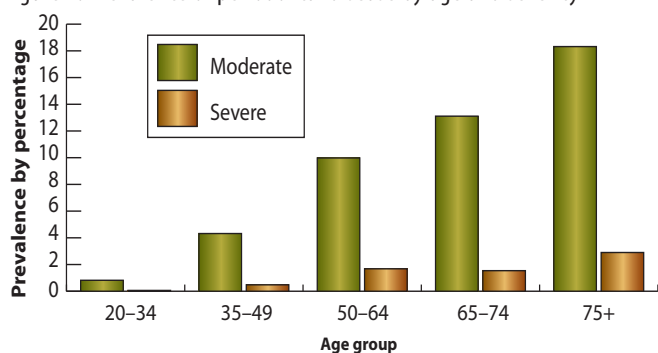
Abstract

Periodontal disease is progressive and episodic in nature, with tissue destruction resulting from the host response to bacterial antigens and irritants. Risk factors encompass systemic influences, external influences, intrinsic factors and local factors. An individual patient's responsiveness to treatment also depends on the host response and the presence of risk factors. Adjunctive systemic and/or local therapy can positively impact periodontal therapy. Considerations in determining which to select include clinical preference and efficacy.

Introduction

Periodontal disease is an inflammatory process involving progressive, episodic loss of the periodontal attachment apparatus, resulting ultimately in tooth loss in susceptible patients. From the 1999-2004 National Health and Nutrition Examination Survey III (NHANES III) data, Eke and Barker estimated that the prevalence of moderate and severe periodontal disease was less than 1% in the under-35 age group, with increasing prevalence in older age groups. In the 75-and-older age group, it is estimated that the prevalence in the United States is approximately 18% for moderate periodontitis and 7% for severe periodontitis (Figure 1).¹

Figure 1. Prevalence of periodontal disease by age and severity¹



Moderate: Greater than 4 mm clinical attachment loss (CAL) or two or more interproximal sites with 5 mm probing pocket depth¹ (PPD); **Severe:** Two or more interproximal sites with 6 mm CAL and one or more interproximal sites with 5 mm PPD¹

Biofilm and periodontal disease

Dental biofilm, also known as plaque, develops and matures over a period of several weeks, initially developing supragingivally with mainly aerobic bacteria. Over time, the flora changes from

predominantly gram-positive to gram-negative, from facultative aerobes to strictly anaerobic species, with more motile forms present. Mature subgingival biofilm takes up to 12 weeks to develop.² As biofilm accumulates, gingivitis develops over a period of several days in the presence of periodontal bacteria.³ Gingivitis may be a nonspecific bacterial infection dependent on the level of plaque present.⁴

It should be noted that no individual is truly biofilm free; there is either a healthy biofilm in place or a pathogenic biofilm contributing to caries and periodontal disease. The supragingival biofilm forms a reservoir for periodontal bacteria and the development of subgingival biofilm. As the biofilm matures, the concentration and virulence of the periodontal bacteria change. Socransky and Haffajee have categorized bacteria by their periodontal pathogenicity, using a color classification to identify the virulence of various oral bacteria, with the orange and red complexes denoting the most pathogenic bacteria.⁵ A recent study on supragingival plaque by Haffajee et al. in 187 subjects found that, over a period of seven days from baseline after professional prophylaxis, plaque regrowth resulted in the development of bacterial complexes similar to subgingival biofilm. The amount of supragingival plaque changed the flora composition. The heaviest plaques were found to harbor a higher proportion of green and orange complexes, and the lighter plaque harbored yellow, orange and purple bacterial complexes. The total number of bacteria was associated with the level of gingival inflammation, recession and pocket depth.^{6,7}

Mature subgingival biofilm is dynamic, well organized and structured as a solid mass with fluid-filled channels within it; protects bacteria in its depth with diffusion barriers; and enables the migration and colonization of periodontal bacteria at adjacent periodontal sites and in periodontal tissues themselves.⁸ This is a key point, as biofilm disruption is a necessary step when using either local or systemic antibiotic therapy. Undisrupted biofilm may decrease the efficacy of antimicrobial therapy. Subgingival bacteria were classified by Socransky and Haffajee and grouped into five major complexes of varying virulence. Across all subjects with periodontal disease, the first complex (the red complex) was consistently associated with periodontal disease, as evidenced by bleeding upon probing and pocket depth measurements. This red complex includes *Tannerella forsythia* (*T. forsythia*, previously known as *Bacteroides forsythus*), *Porphyromonas gingivalis* (*P. gingivalis*) and *Treponema denticola* (*T. denticola*).⁹ Research the same year by Dibart et al. in 51 individuals determined that in clinically healthy subjects the majority of sites were associated with the presence of *Streptococcus oralis* (*S. oralis*), while in diseased sites greater numbers of *T. forsythia* (*B. forsythus*), *Prevotella intermedia* (*P. intermedia*), *Capnocytophaga ochracea* and *Campylobacter rectus* were found.¹⁰

Virulent periodontal bacteria, specifically *P. gingivalis* and *Actinobacillus actinomycetemcomitans* (now *Aggregatibacter actinomycetemcomitans*), are commonly found in patients with periodontal disease and rarely found in patients with a healthy periodontium. Van Winkelhoff et al. found a significantly greater

presence of specific bacteria in patients with periodontal disease: *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia* (*B. forsythus*), *P. intermedia*, *Fusobacterium nucleatum* and *Peptostreptococcus micros*. They concluded that the presence of these bacteria is a marker for destructive periodontal disease.¹¹

Pathogenesis of periodontal diseases and chronic inflammation

The inflammatory response in periodontal disease includes the activation of leucocytes, neutrophils, T-lymphocytes and plasma cells and the release of antibodies, lipopolysaccharides and chemical inflammatory mediators that include cytokines, chemokines and C-reactive protein. The lipopolysaccharides are present in the gram-negative bacterial cell walls and act as powerful stimulants for the complex host response. The initial increased presence of neutrophils at the site is followed by the release of cytokines by neutrophils and macrophages. Chemical mediators released include tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1) and prostaglandins. The inflammatory process includes the stimulation of fibroblasts by IL-1 and the secretion of matrix metalloproteinases (MMPs, of which collagenase is the most prominent) by polymorphonuclear neutrophils. MMPs are responsible for increased collagen breakdown, and TNF- α is primarily responsible for increased osteoclast activity resulting in bone resorption. MMPs can also activate cytokines and chemokines, exacerbating the destructive process. Collagen production is inhibited by the reduced activity of fibroblasts in response to TNF- α .

The lymphocytes release antibodies as protective mechanisms but also activate the osteoclasts, resulting in bone loss. T-lymphocytes secrete receptor activator of nuclear factor kappa- β ligand (RANKL), which is involved in osteoclast activity and therefore bone resorption. These destructive inflammatory mediators are inhibited by the secretion of osteoprotegerin and tissue inhibitors of metalloproteinases (TIMPs).

The level of periodontal destruction depends on the balance between destructive and protective inflammatory mediators. While periodontal bacteria are required for infective periodontal disease, individual response determines disease progression. In vitro, it has

been found that individual response is affected by genetic signaling pathways that influence the expression of inflammatory mediators in response to bacterial lipopolysaccharides.^{12, 13, 14, 15, 16}

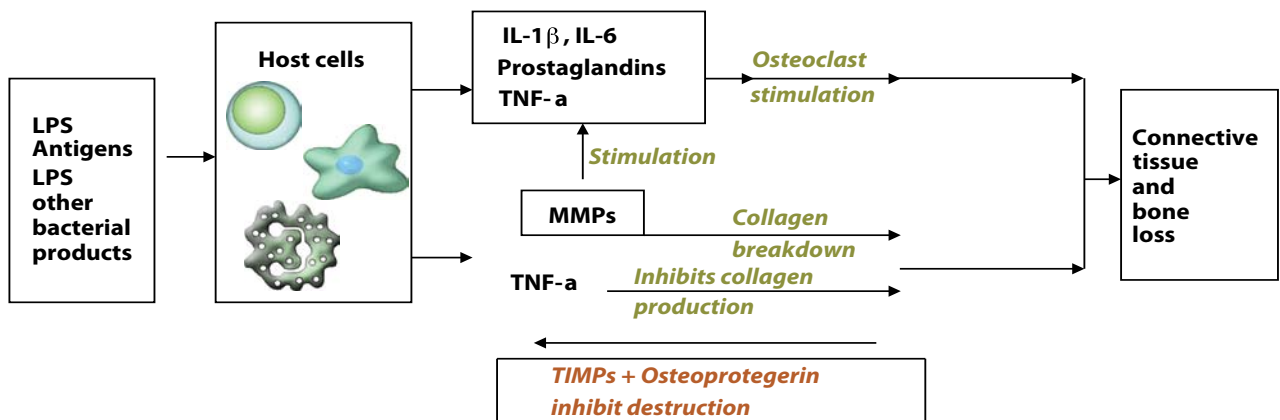
Risk factors for periodontal disease

The initiation and progression of periodontal disease depend on the presence of pathogenic bacteria, host response and risk factors. These risk factors encompass systemic influences (such as poorly controlled or uncontrolled diabetes mellitus), external influences (such as smoking), intrinsic factors and local factors. They include oral hygiene, gender, race, socioeconomic status, age, systemic health status, use of medications, smoking, and alcohol and drug abuse. Males have a higher prevalence of moderate periodontal disease than females. Low socioeconomic status and education level correlate with an increased prevalence of disease.

One of the greatest risk factors is tobacco smoking. Higher levels of cigarette smoking (heavy versus light smoker; 10 cigarettes per day is a common cutoff point) are associated with increased severity of periodontal disease. Smokers also experience deeper periodontal pockets than nonsmokers.¹⁷ Based on a recent longitudinal study spanning 26 years, the investigators concluded that the two factors most predictive of periodontal disease progression were smoking and increased levels of calculus.¹⁸ Stress has also been found to influence periodontal disease status; periods of stress cause increased levels of adrenaline and noradrenaline, which are known to influence bacterial growth. Based on in vitro testing, increased and decreased growth of different bacterial species were found following exposure to increased levels of these hormones. The investigators concluded that such stress-related changes could influence periodontal disease status.¹⁹ Sex hormones may also influence gingivitis and periodontal disease, as demonstrated in studies on increased levels of ovarian sex hormones in women.²⁰ Ethnicity (race) also plays a role; non-Hispanic blacks had the highest prevalence in the NHANES III data.²¹

Genetic makeup is now understood to play a significant role in the severity of periodontal disease. Studies of monozygotic and dizygotic twins have shown that 50% of the variance in periodontal disease may be attributed to genetics.²² The host response

Figure 2. Pathogenesis: destructive and protective factors



demonstrates an influence of genetics on periodontal disease and its progression. People who are genotype positive for IL-1 (IL-1A and IL-1B) genes were found in one study of more than 100 patients to harbor higher levels of virulent bacterial complexes (red and orange complexes) than did genotype-negative patients. In addition, genotype-positive patients were found to have higher mean counts of individual virulent bacterial species in pockets deeper than 6 mm, including *T. forsythia* (*B. forsythus*), *P. gingivalis* and *T. denticola*.²³ The importance of genetics is also suggested by experimental studies on the influence of the balance between protective and destructive chemical mediators as well as signaling pathways and gene expression.^{24,25} Over the years, there has been significant interest in the genetic component of localized aggressive periodontitis (LAP, formerly known as localized juvenile periodontitis). As study populations have been refined, it appears that predisposition to this disease is passed as an autosomal dominant trait. In addition, there is evidence to suggest that the macrophages are in a hyperimmune state, producing increased amounts of TNF- α , which may contribute to early and rapid bone loss in these individuals.

Local risk factors include the presence of carious lesions at gingival margins, overhanging and defective restorations, and interdental areas subject to food impaction. Finally, systemic disease – including uncontrolled or poorly controlled diabetes, autoimmune disease and hematological cancers – and drug use can impact the progression of periodontal disease.

Table 1. Risk factors for periodontal disease

Intrinsic	External Acquired
Gender	Smoking
Race	Alcohol abuse
Socioeconomic status	Drug abuse
Education level	Medication use
Age	Stress
Hormonal changes	Local
Genetics	Poor oral hygiene
Auto-immune disease	Increased levels of calculus
Diabetes mellitus	Overhanging/defective restorations
Hematological cancers	Carious lesions and margins
Other systemic conditions	Areas subject to food impaction

Standard nonsurgical treatment

The key goal of periodontal treatment is the removal of pathogenic bacteria, correction of reversible risk factors, and then the prevention of recolonization in order to prevent disease recurrence. The desired clinical outcomes are to favorably influence clinical attachment levels, pocket probing depths and other clinical parameters such as bleeding on probing, mobility and furcation involvement. The standard nonsurgical treatment for periodontal disease is scaling and root planing (SRP). Meticulous removal of bacteria is required, together with removal of calculus and debris from the periodontal tissues and tooth surfaces to minimize bacterial retention. Recently, lasers have been advocated as an alternative or

adjunctive therapy to reduce levels of periodontal bacteria and for “pocket disinfection.”²⁶

While it has been demonstrated that it is the removal and reduction of bacteria that are key,²⁷ removal of calculus reduces the opportunity for bacterial reattachment and colonization and also removes the bacteria and toxins contained in the calculus. Certain bacteria may remain in the soft tissues and anatomical niches following scaling and root planing. It is difficult to completely remove bacteria, calculus and debris, given the anatomy of periodontal pockets. Virulent bacteria, which are more prevalent in deeper pockets, can rapidly recolonize periodontal sites, with the potential for recurrence of active periodontal disease and renewed tissue destruction.^{28, 29} Quantitative polymerase chain reaction (PCR) in one study found an association between the *P. gingivalis* count and both pocket depth and attachment loss, but no such relationship for *P. intermedia* or *A. actinomycetemcomitans*. Nonsurgical scaling and root planing were found to substantially reduce the levels of all three bacteria but did not eliminate any of them completely.³⁰ Scaling and root planing have been found to effectively reduce the levels of IL-1-B, MMPs and elastase activity in gingival crevicular fluid in both healthy and diabetic patients, although the diabetic group had less reduction of elastase activity.³¹ Scaling and root planing are effective at reducing the levels of bacteria and improving clinical parameters in responsive patients.

Responsiveness to treatment

The presence and level of virulent periodontal bacteria influence treatment outcomes. Smoking status in particular influences responsiveness. Following periodontal therapy, probing depth reductions and clinical attachment level gains are less in smokers than nonsmokers.³² Darby et al. found that the reduction in periodontal bacteria was less in smokers than nonsmokers following scaling and root planing therapy, possibly a result of the deeper pockets found in the smokers’ group prior to treatment.³³ Smokers account for the majority of cases of refractory periodontitis.³⁴ In investigating the effects of nonsurgical scaling and root planing over a nine-month period post-treatment, Haffajee et al. found significant decreases in the levels of *P. gingivalis*, *T. denticola* and *T. forsythia* (*B. forsythus*) as well as their prevalence in the 57 subjects, and increases in *A. viscosus*, in particular, at the deepest pocket sites. In the responders, they found that modest reductions in periodontal bacteria were sufficient for clinical improvement.³⁵ The greatest improvements following scaling and root planing were at the sites that were most severe and had the highest periodontal bacterial loads.³⁶ A recent study of type 2 diabetics found that while clinical parameters improved following SRP, the levels of TNF- α and IL-6 actually increased.³⁷ Type 1 diabetics with poor disease control experience more attachment loss as a result of periodontal disease than diabetics with moderate and good control.³⁸ As discussed earlier, genetics and genotype influence responsiveness by influencing the presence of specific bacteria; the immune response, involving signaling pathways; and chemical inflammatory mediator production.

The importance of obtaining a response and an improvement in periodontal clinical and bacterial parameters has been heightened with the increasing amount of research demonstrating an association between periodontal and systemic disease.

Oral-systemic associations

The body of research in support of oral-systemic associations between periodontal disease and systemic disease includes studies on associations between periodontal status and cardiovascular disease, diabetes, pulmonary disease, renal disease and osteoporosis. Research suggests that the presence of periodontitis may increase the risk of cardiovascular events and severe periodontitis may increase the risk of cerebral ischemia (stroke). Periodontal bacteria, and antibodies to these, have been found in the bloodstream. Elevated C-reactive proteins, inflammatory mediators associated with inflammation, are associated with periodontal disease, and long-term exposure to C-reactive proteins has been found to be associated with a threefold risk of cardiovascular disease. Bahekar et al., in their meta-analysis, found a significant association between periodontal disease and cardiovascular disease after controlling for major co-contributors of cardiovascular disease.^{39, 40, 41, 42, 43}

With respect to renal disease, it has been hypothesized that severe periodontitis may be a contributing factor to morbidity and mortality, and it was found in one study to be predictive for end-stage renal disease. Investigators have recently found that serum antibodies to periodontal bacteria, as well as increases in C-reactive protein levels, may be associated with impaired renal function.^{44, 45, 46, 47} Diabetes and periodontal disease are also linked. There is a strong association between untreated periodontal disease and poor glycemic control. Conversely, uncontrolled diabetes has been found to be a risk factor for a number of inflammatory conditions, including periodontal disease. Some studies suggest that treating periodontal disease can help improve glycemic control.^{48, 49, 50} Regarding pulmonary disease, research has also found that reducing the levels of oral bacteria prior to hospitalization reduces the rate of hospital infections associated with oral bacteria in heart surgery as well as head and neck surgery patients.⁵¹

The previously mentioned studies and others must be interpreted with caution. While we now know that there are associations and statistical correlations between periodontal disease and many systemic conditions, no causal relationship has been proven for oral-systemic associations. The criteria that must be satisfied to prove a causal relationship are: biologic plausibility, specificity of the association, strength of the association, dose-response effect, temporal consistency and consistency of the findings.

Many of the pronouncements regarding the possible causal effects of periodontal inflammation and systemic disease are based on biologic plausibility arguments. For a causal relationship to be established, it would be necessary to conduct controlled interventional studies in which the elimination of periodontal inflammation would lead to a decrease in the systemic disease in question. As was seen in the two largest preterm birth studies, Obstetrics and Periodontal Therapy⁵² and Maternal Oral Therapy to Reduce

Obstetric Risk,⁵³ biologic plausibility alone is not sufficient to prove causality, as neither study showed an improvement in birth outcomes when periodontal oral inflammation was eliminated during pregnancy. Nonetheless, the associations discussed above do imply that periodontal disease status and treatment have implications beyond oral health. In fact, the American Academy of Periodontology recently completed a consensus conference with editors of the American Journal of Cardiology. A consensus statement has been published, focusing on treatment or referral recommendations for patients with periodontal disease, cardiovascular disease or both.⁵⁴

Systemic and local treatment adjuncts

Adjunctive systemic and/or local antibiotic/antimicrobial treatment has been found to positively impact periodontal therapy outcomes. Indications include when a patient's risk factors suggest that he or she may otherwise be nonresponsive, when a patient has received periodontal therapy and the response was unfavorable, or when there is a recurrence of disease. With increasing evidence of the role of genetics and inflammatory mediators, biomarkers may in the future offer definitive predictive value for responsiveness and aid preemptive case selection or adjunctive therapy. Systemic therapy can be utilized for host modulation or bacterial elimination (control), while local treatments have been shown to be successful at controlling the bacterial environment.

Systemic Therapy – Host Modulation

Host modulation is the purposeful redirection of the inflammatory host response. Nonsteroidal anti-inflammatory drugs, bisphosphonates and antibiotics have all been explored as host modulation agents. Due to complications of long-term use of the first two classes of drugs, to date only systemic doxycycline has had any clinical utility. Subantimicrobial-dose doxycycline (SDD) has been used adjunctively in periodontal disease therapy for almost two decades. Doxycycline hyclate at a dose of 20 mg twice daily (Periostat[®]), is effective at reducing pocket depths and gingival indices and has been found to help prevent collagen breakdown and influence the levels of inflammatory mediators. Doxycycline inhibits the enzyme collagenase, helping to prevent collagen breakdown. It has been shown to reduce pocket depths by up to 79%, depending on the pre-treatment depth of the pockets.^{55, 56} Low-dose doxycycline also modulates the host response in other ways. A randomized, double-blind, placebo-controlled study found that low-dose doxycycline given twice daily (20 mg per dose) resulted in greater pocket depth reductions and gingival indices than were seen in the control group. Levels of MMP-8 have been found to be lower compared to a control group. The levels of Ln-5 gamma2 chain fragments of laminin-5, which are mediated by MMPs and have been found to aid pocket development, are also lower with adjunctive low-dose doxycycline. Another study found increases in the level of growth factor-B1 in the gingival crevicular fluid in the adjunctive low-dose doxycycline test group compared to the control group, which received only scaling and root planing and a placebo.^{57, 58, 59} A combination of low-dose doxycycline and

NSAIDs has been found to suppress MMP activity more than low-dose doxycycline alone.⁶⁰

Bacterial resistance associated with low-dose doxycycline therapy has not been seen.⁶¹ Studies of up to 12 months' duration have been completed. One common clinical question is, How long should a patient be on this medication? As host modulation is used when all other approaches have failed to control attachment loss, the answer is probably for an indefinite period. Some clinicians suggest placing patients on SDD for a time, next having them enter a "resting" phase and then reinstating host modulation therapy.

Systemic Therapy – Antimicrobials

Systemic antibiotics have been used to treat periodontal disease. One of the first was metronidazole (Flagyl®), used for three days to treat what was then known as acute ulcerative gingivitis and is now known as acute necrotizing ulcerative gingivitis. Systemic antibiotics proven to help periodontal disease include amoxicillin, ciprofloxacin, metronidazole, tetracyclines/doxycyclines, erythromycin and clindamycin. Indications for the use of systemic antibiotics include the following: the treatment of aggressive forms of periodontitis, especially when *A. actinomycetemcomitans* is present; treatment of recurrent/refractory disease forms of periodontitis, especially when multiple sites are involved; treatment of patients prone to infection, such as unstable diabetics and patients with other immune compromise such as chemotherapy or HIV infection. One disadvantage of using systemic antibiotics is that the level needed to treat periodontal disease is high, because the concentration that reaches the periodontal tissues after systemic ingestion is low; additionally, overuse of systemic antibiotics to treat disease has contributed to an increasing level of antibiotic resistance worldwide. These disadvantages are absent with the use of locally applied antimicrobials. Systemic antibiotics have been used to treat aggressive forms of periodontitis and recurrent/refractory disease in brittle diabetics and empirically when the amount of inflammation is severe compared to the amount of etiology present, as well as for the current prophylaxis indications. It is critical to remember that biofilm throughout the mouth must be disrupted at the onset of systemic or local antibiotic therapy.

Specific dosing is at the practitioner's discretion. The American Academy of Periodontology has published suggested systemic antibiotic dosages.⁶² Pallasch has presented criteria for antibiotic dosing and suggests employing high doses for a short duration, using an oral antibiotic loading dose, frequent dosing intervals, achieving blood levels of the antibiotic at two to eight times the minimum inhibitory concentration and determining the duration of therapy by the remission of disease.⁶³

Local Therapy – Locally Applied Antimicrobial Agents

Locally applied antimicrobial agents (LAAs) enable targeted use of antimicrobials, with a lower dose than would be required if given systemically, and release the antimicrobial in a controlled manner at or above the minimum inhibitory concentration (MIC) over a period of several days. In addition to being effective at a lower dose,

no antibiotic resistance has been found following the use of LAAs. Studies have found improved clinical parameters with the use of LAAs.⁶⁴ Available agents in the United States include doxycycline hyclate, minocycline hydrochloride and chlorhexidine gluconate. In a comparative study of doxycycline hyclate, chlorhexidine gluconate chip and Elyzol® (metronidazole gel, available in Europe), it was found that all three resulted in a statistically significant reduction in pocket probing depths, while only doxycycline hyclate resulted in a statistically significant improvement in clinical attachment level.⁶⁵ Killoy addressed five requirements for a local delivery system to be effective. These are that the agent must reach the site to be treated, have an adequate concentration at the site, remain at the site long enough to be effective, inhibit or kill the putative bacteria and, lastly, do no harm.⁶⁶ These requirements should be considered when selecting an agent.

Doxycycline hyclate

Ten percent doxycycline hyclate (ATRIDOX®) is applied as a gel directly to the pockets, using a syringe. Upon application, the polymer sets in the presence of moisture, releases the antimicrobial for 21 days at doses higher than the MIC and is bioabsorbable. Novak et al. conducted a multicenter, randomized, blinded study on SRP plus adjunctive use of both low-dose systemic doxycycline hyclate and 10% doxycycline hyclate gel (ATRIDOX®). The combination of SRP and both adjuncts resulted in greater reductions in bleeding upon probing and greater gains in clinical attachment levels than SRP alone, and based on other studies it was also concluded that this combination was more effective than using SRP plus low-dose systemic doxycycline hyclate or SRP plus 10% doxycycline gel.⁶⁷ Ten percent doxycycline hyclate has been found to be effective as an adjunct to SRP in both smokers and nonsmokers. It has also been found to be effective in smokers in the absence of scaling and root planing. ATRIDOX® is approved for application prior to, during or after SRP. In smokers and type 1 diabetics, the use of 10% doxycycline hyclate has resulted in improvements in post-therapy clinical parameters.⁶⁸ In one study of smokers, the level of *P. gingivalis* three months post-therapy was significantly reduced with SRP and use of doxycycline hyclate compared to only SRP.⁶⁹ At 18 and 24 months following therapy using SRP and doxycycline hyclate, greater reductions in pocket depth and improved clinical attachment levels were found compared to the control group receiving only SRP, with the magnitude of change depending on the initial depth of the pockets. At 24 months, relative attachment gains of 2 mm or greater were observed in 34.4% of sites receiving doxycycline hyclate, compared to 18.1% of sites in the control group.⁷⁰ In 16 patients who were smokers, the proportion of sites with no remaining *T. forsythia* (*B. forsythus*) three months following adjunctive treatment with doxycycline hyclate was 53% versus 9% for SRP alone, and for *P. gingivalis* 82% versus 40%.⁷¹ A trial comparing doxycycline hyclate use with SRP found the clinical results of both protocols to be the same, with no statistical differences. Probing depth reductions of at least 2 mm were found in 41% of sites treated with doxycycline hyclate and in 43% of SRP sites.⁷² From a clinical perspective, it is interesting to note that the doxycycline gel penetrates the topographical complexities

of the periodontal pockets. If the material is removed after 10 days instead of being left to resorb, the complexities of the pocket wall are evident in the residual polymer. In addition to adaptation of the polymer to the pocket wall, one syringe of ATRIDOX® may be used to treat several pockets.

Minocycline hydrochloride

Minocycline hydrochloride 1 mg (Arestin®), which is also applied in a syringe (one syringe per site pocket), consists of microspheres that are applied as a dry powder that hydrolyzes and sets when exposed to gingival crevicular fluid and remains in the pocket for 14 days. Minocycline hydrochloride is used adjunctively with SRP. Williams et al. found a 22% greater reduction in mean pocket probing depths (with a mean clinical difference of 0.24 mm) with its use compared to SRP only.⁷³ Minocycline hydrochloride use has been found to result in improved clinical parameters nine months following treatment in smokers compared to SRP only, with a 32% greater reduction in pocket depths.⁷⁴ Adjunctive use of minocycline hydrochloride together with mechanical debridement of peri-implantitis sites has been found to result in reduced probing depths compared to the control treatment without adjunctive LAA therapy, when repeated application of LAA was provided at baseline, 30 and 90 days.⁷⁵ In smokers and nonsmokers, adjunctive therapy with minocycline hydrochloride resulted in reduced levels of red complex bacteria for up to one month. In the same study, SRP alone did not reduce the levels of red complex bacteria in smokers.⁷⁶ In one study, in type 1 diabetics, adjunctive application of minocycline hydrochloride resulted in greater reductions in pocket probing depths and improved gains in clinical attachment level compared to SRP alone.⁷⁷

Chlorhexidine gluconate

Chlorhexidine gluconate is used as an LAA in the form of a 2.5 mg hard chip that is a biodegradable matrix of gelatin and glutaraldehyde inserted into the periodontal pocket. While it is also a controlled-release vehicle, it releases the first 40% of the chlorhexidine within 24 hours and the remainder over the one-week treatment period. The released cationic chlorhexidine has a broad antimicrobial effect and, as with chlorhexidine rinses, adheres to the cell wall surfaces, which are anionic, and causes cell apoptosis and death. The use of chlorhexidine gluconate chips has been found to be superior to only SRP.⁷⁸

Case treatment

Considerations in the decision to use adjunctive LAAs include the patient's predicted responsiveness – whether the patient is a smoker or diabetic, has a genotype favoring periodontal disease, or did not respond to prior therapy. Further considerations in determining which LAA to use include clinical preference, efficacy, ease of application, and number of sites that can be treated with one packet or syringe. The case below shows the use of doxycycline hyclate.

The patient was a 38-year old woman. There was nothing abnormal in her medical history and she did not smoke. On examination and probing, twelve sites with probing depths greater than 5 mm were found. Following scaling and root planing, a number of sites required adjunctive therapy.

Figure 3. Prior to adjunctive use of doxycycline hyclate



Case courtesy of Drs. Norman Stoller and Lonnie Johnson

Prior to use, the polymer and doxycycline components must be mixed. When this is accomplished, a blunt end cannula is attached to the syringe and the material is slowly applied into the pocket. As moisture acts as the catalyst to set the polymer, it may be helpful to have an instrument handy to separate the last of the material from the cannula.

Figure 4. Syringe ready for use



Figure 5. Doxycycline hyclate in the pocket



Figure 6. Site at reevaluation following resorption of doxycycline hyclate



At baseline, CAL were 12.5 mm mesiolingually (ML) and 3 mm mesiobuccally (MB), and at 9 months 7.5 mm (ML) and 1mm (MB). Probing depths reduced from 10 mm to 2 mm (ML), and from 6 mm to 3 mm (MB). Significant improvements in probing depths and CAL were achieved.

Summary

Both systemic and local antibiotic/antimicrobial approaches have their place in periodontal therapy. The main questions faced by clinicians are: when are systemic and local antibiotic/antimicrobial approaches indicated, at what dose and for how long, and which

drug/product to choose. While there is no one answer to each of the above questions, basic principles and experiences can guide the decision-making process. Indications for the use of local antibiotic/ antimicrobial therapy include the presence of one or several areas that have either not responded to therapy or have been discovered during a maintenance appointment to be breaking down; and, the number of sites to be treated and the cost of material to treat the selected sites. The availability of locally-applied antimicrobials and subantimicrobial doses of antibiotics has increased the therapeutic options available to treat patients with periodontal disease.

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Dr. Francis G. Serio is Professor and Chairman of the Department of Periodontics and Preventive Sciences at the University of Mississippi School of Dentistry, and a Diplomate of the American Board of Periodontology. Dr. Serio completed his undergraduate studies at The Johns Hopkins University and received his DMD from the University of Pennsylvania. He earned his MS and certificate in Periodontics at the University of Maryland and his MBA from Millsaps College. Dr. Serio has presented over 120 lectures and continuing education courses in the U.S. and around the world, and is founder and director of the Dominican Dental Mission Project, which received The President's Volunteer Action Award in 1991. Dr. Serio has written or co-authored over 35 scientific articles and four books. The most recent book, the *Manual of Clinical Periodontics*, was written with Dr. Charles E. (Bud) Hawley.

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Ms. Teresa Duncan is an Instructor in Dental Hygiene at the School of Health Related Professions, University of Mississippi Medical Center and has been a dental hygienist since 1979. She has worked in private practice, taught in dental hygiene programs, lectured widely to dental hygienists and worked as a professional programs area manager. She has been involved in developing the Caries Management by Risk Assessment (CAMBRA) program that is used at the University of Mississippi School of Dentistry.

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Questions

- It has been estimated from the 1999-2004 III (NHANES III) data that the prevalence of moderate and severe periodontal disease combined is approximately _____ in the 75-and-older age group.
 - 15 percent
 - 20 percent
 - 25 percent
 - 30 percent
- Mature subgingival biofilm takes up to 12 weeks to develop.
 - True
 - False
- Mature subgingival biofilm enables the migration and colonization of periodontal bacteria _____.
 - at adjacent periodontal sites
 - in periodontal tissues
 - only in smokers
 - a and b
- Biofilm disruption is a necessary step when using either local or systemic antibiotic therapy.
 - True
 - False
- The inflammatory response in periodontal disease includes the _____.
 - activation of leucocytes, neutrophils, T-lymphocytes and plasma cells
 - release of antibodies, lipopolysaccharides and chemical inflammatory mediators
 - release of antibodies
 - all of the above
- Virulent periodontal bacteria are commonly found in patients with periodontal disease and rarely found in patients with a healthy periodontium.
 - True
 - False
- TNF- α is responsible for _____.
 - increased osteoblast activity
 - increased osteoclast activity resulting in bone resorption
 - reduced collagen production
 - b and c
- Matrix metalloproteinases (MMPs) _____.
 - activate cytokines and chemokines, exacerbating the destructive process
 - are responsible for increased collagen breakdown
 - are secreted by polymorphonuclear neutrophils
 - all of the above
- The initiation and progression of periodontal disease depend on the presence of pathogenic bacteria, host response and risk factors.
 - True
 - False
- Smoking is a risk factor for periodontal disease, and smokers experience _____.
 - slower but more severe progression of periodontal disease
 - more severe periodontal disease but are more responsive to therapy
 - more severe periodontal disease and deeper periodontal pockets
 - ulcerative periodontitis
- Risk factors for periodontal disease include _____.
 - external and systemic influences
 - intrinsic factors such as gender and ethnicity
 - local factors
 - all of the above
- Periods of stress cause increased levels of adrenaline and noradrenaline, which are known to influence bacterial growth.
 - True
 - False
- The standard nonsurgical treatment for periodontal disease is scaling and root planing.
 - True
 - False
- Genetic makeup is now understood to play only a minor role in the severity of periodontal disease.
 - True
 - False
- During scaling and root planing, it is difficult to completely remove bacteria, calculus and debris, given the anatomy of periodontal pockets.
 - True
 - False
- Haffajee et al. found that the greatest improvements following scaling and root planing were at periodontal sites that were the _____.
 - least severe and had the lowest periodontal bacterial loads
 - most severe and had the highest periodontal bacterial loads
 - least severe and harbored only nonpathogenic bacteria
 - none of the above
- Genotype influences an individual's responsiveness to therapy by influencing the presence of specific bacteria.
 - True
 - False
- Research has found associations between periodontal status and cardiovascular disease, diabetes, pulmonary disease, renal disease and osteoporosis.
 - True
 - False
- Indications for adjunctive systemic and/or local antibiotic/antimicrobial treatment include _____.
 - risk factors suggesting a lack of responsiveness to scaling and root planing
 - an unfavorable response to periodontal therapy received
 - recurrence of disease
 - all of the above
- Subantimicrobial-dose doxycycline hyclate at a dose of 20 mg twice daily (Periostat®) is effective at reducing pocket depths and gingival indices and has been found to help prevent collagen breakdown.
 - True
 - False
- Doxycycline inhibits the enzyme _____, helping to prevent _____ breakdown.
 - protease; collagen
 - transferase; elastin
 - collagenase; collagen
 - none of the above
- Bacterial resistance associated with low-dose doxycycline therapy has not been seen.
 - True
 - False
- Indications for the use of systemic antibiotics include _____.
 - the treatment of aggressive forms of periodontitis
 - the presence of recurrent/refractory disease forms of periodontitis
 - the treatment of patients prone to infection
 - all of the above
- Ten percent doxycycline hyclate given as a locally applied antimicrobial has been found to be effective as an adjunct to scaling and root planing in both smokers and nonsmokers.
 - True
 - False
- Locally applied antimicrobial agents (LAAs) _____.
 - release the antimicrobial in a controlled manner at or above the minimum inhibitory concentration (MIC)
 - require a lower dose than would be required if given systemically
 - enable targeted use of antimicrobials
 - all of the above
- Doxycycline gel penetrates the topographical complexities of the periodontal pockets.
 - True
 - False
- In smokers and nonsmokers, adjunctive therapy with minocycline was found in one study to result in reduced levels of red complex bacteria for up to one month.
 - True
 - False
- Williams et al. found a 27% greater reduction in pocket probing depths (with a mean clinical difference of 0.3 mm) with the use of minocycline compared to scaling and root planing only.
 - True
 - False
- In one study of smokers, the level of *Porphyromonas gingivalis* three months post-therapy was significantly reduced with scaling and root planing and use of doxycycline hyclate compared to only scaling and root planing.
 - True
 - False
- The availability of locally applied antimicrobials and subantimicrobial doses of antibiotics has increased the therapeutic options available to treat patients with periodontal disease.
 - True
 - False

The pathogenesis and treatment of periodontal disease

Name: _____ Title: _____ Specialty: _____
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Educational Objectives

- Understand the pathogenesis of periodontal disease
- Know the risk factors for periodontal disease and the factors that may play a role in responsiveness to periodontal therapy
- Understand the adjunctive therapeutic options available in the treatment of periodontal disease and their utility
- Know the factors involved in selecting locally applied antimicrobials.

Course Evaluation

Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

1. Were the individual course objectives met?	Objective #1: Yes	No	Objective #3: Yes	No		
	Objective #2: Yes	No	Objective #4: Yes	No		
2. To what extent were the course objectives accomplished overall?	5	4	3	2	1	0
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5. How do you rate the author's grasp of the topic?	5	4	3	2	1	0
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AGD Code 495

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