CHAPTER

27

Chemotherapeutics

Maria Perno Goldie • Rebecca S. Wilder •
Sebastian G. Ciancio

INSIGHT

The dental hygienist is vital to assessing, diagnosing, and treating periodontal diseases. Many treatment options are available for controlling supragingival and subgingival plaque biofilm. The dental hygienist must stay current regarding evidence-based treatments for gingivitis and periodontitis so that appropriate decisions can be made for individual patients.

CASE STUDY 27-1 Selecting a Chemotherapeutic Agent Based on Patient Need

Ms. Chlöe Tevus, who is 39 years of age and an apparently healthy white woman, was diagnosed with localized chronic periodontitis. She denies any medical problems, takes no medication, and does not smoke. As an adolescent, she had active orthodontics and retains 24 teeth. The first premolars and the third molars were sound and were previously extracted for orthodontic reasons. She has occlusal amalgams on her molars, occlusal wear, and interproximal restorations between some of the posterior teeth.

Ms. Tevus's private law practice specializes in contract law. She is the sole caregiver for her elderly parent.

Ms. Tevus completed periodontal therapy 18 months ago and has alternately visited the hygienists at her periodontist and general dentist's offices every 3 months. She demonstrates capable technique with the toothbrush and the interdental brush. Her bleeding-on-probing percentage has varied between 23% and 32% at the 3-month intervals, generalized to interproximal sites. She has also developed a probe depth of 7 mm on the palatal of tooth #10. O'Leary's Plaque Control Record has resulted in average scores of 15% to 20%, particularly on the facial and palatal of the maxillary molars.

KEY TERMS

adjunctive therapy
antigingivitis
antimicrobial
antiplaque
bacteriocidal
bacteriostatic
biofilm
cationic
chemotherapeutic
controlled delivery
delivery system
essential oils
host modulation
host response
irrigation
locally administered antibiotics or antimicrobials
local delivery
minimum inhibitory concentration
plaque biofilm
plaque biofilm–inhibitory effect
rinsing
site-specific
substantivity
sustained-release
systemic antibiotics
triclosan

LEARNING OUTCOMES

After reading this chapter the student will be able to:

1. Discuss the rationale for chemotherapeutic treatments for reducing and controlling plaque biofilm, gingivitis, and other periodontal disease and maintaining periodontal health.
2. Differentiate among chemotherapeutic agents and delivery systems to select the optimal intervention and sequence for patient care.
3. Discuss the evidence base for selecting the various chemotherapeutic agents.
4. Discuss the available chemotherapies and the advantages and disadvantages of each.
5. Discuss the American Dental Association and the U.S. Food and Drug Administration guidelines for accepting chemotherapeutic agents for the control of plaque biofilm, gingivitis, and periodontitis.
6. Discuss the need for and methods of staying informed regarding developments and changes in the standards for using chemotherapeutic agents as adjuncts to nonsurgical periodontal therapy.

The dental hygiene process of care has five components: (1) assessment, (2) diagnosis, (3) treatment planning, (4) implementation of the treatment plan, and (5) evaluation. Although this section primarily supports the treatment phase, the other components are equally important. In defining treatment of periodontitis, mechanical therapy has been the foundation of periodontal care. Also important is daily personal plaque biofilm control and periodic professional supportive periodontal care with a dental hygienist, dentist, or periodontist. Careful, daily disruption of plaque biofilm, especially interproximally and at the gingival margins, is an essential oral health habit for health maintenance; however, this task is tedious and uninteresting for the average individual. As a result, most people do not deplaque their mouths as thoroughly as needed to maintain health. In fact, dental hygienists are probably one of the few groups excited about plaque biofilm control! However, even with good daily personal plaque biofilm control, and regular professional debridement, some periodontally involved patients are unable to attain and maintain periodontal stability.

When mechanical disruption of plaque biofilm is insufficient to control gingival inflammation, using chemotherapeutics should be considered. Chemotherapeutics and pharmacotherapeutics are broad terms encompassing agents that may affect microorganisms and hard and soft tissues in the oral cavity. **Chemotherapeutic** agents are used to eliminate, reduce, or alter the effect of microorganisms in the oral cavity, preferably the pathogenic microorganisms, or to effect a change in the host response. The term **antimicrobial** refers to agents that kill microbes or affect the growth and multiplication of microorganisms.[3]

Chemotherapeutic agents have been demonstrated to reduce gingivitis, plaque biofilm, and gingival bleeding when used daily. Evidence is still insufficient to state the magnitude of the effect that chemotherapeutics have in the deeper periodontal tissues, such as bone height and attachment level. Differences in periodontal pockets after the use of **irrigation** or chemotherapeutics have been reported, typically by attachment gain and change in the pocket microflora.[3,65,97] Currently, using pharmacotherapeutics is still considered **adjunctive therapy,** not monotherapy, or a substitute for professional debridement and daily personal plaque biofilm control. However, as these treatment modalities are studied, their use becomes a welcome and effective supplement to mechanical therapy.

A new arena for the use of chemotherapeutics in oral health care is to influence the host response to periodontal infections rather than to affect the microbial status. This task is accomplished by using a subantimicrobial concentration of certain chemotherapeutic agents (e.g., tetracycline derivatives). This concept is discussed more fully in the section on **systemic antibiotics** delivery.

When oral health clinicians speak of the benefits of chemotherapeutics, they are most often referring to the effect on the periodontal status of the mouth. Nonetheless, chemotherapeutics are useful for more than preventing and controlling periodontal diseases. For example, fluoride, chlorhexidine, essential oils, and other substances are used in controlling dental caries and their cariogenic microbes, as well as oral malodor. However, this chapter focuses on the use of chemotherapeutics in periodontal diseases—the delivery systems and the agents.

Plaque Biofilm, Host Response, and Need for Chemotherapeutics

Plaque biofilm and **host response** content are discussed in detail in Chapters 6 and 31. To understand the effectiveness of the various chemotherapeutic agents on the market, reviewing the nature of plaque biofilm, how the host response of the patient affects the disease process, and how available chemotherapeutic agents work will be helpful. Once the dental hygienist understands the science behind the use of chemotherapeutics, he or she is then able to recommend appropriate, *evidence-based products* for patients. (Read Chapter 4 to learn more about evidence-based practice.)

A **biofilm** is a complex community of bacteria adhering to an inert or living surface[26] (Figure 27-1). Biofilms are the predominant mode of bacterial growth in nature. Many microbial species not only exist as attached bacteria in the biofilms, but also discharge free-floating single-cell bacteria known as *planktonic cells*. *Plaque biofilm* is the new term for dental plaque. Plaque biofilms play an integral role in the cause and progression of dental caries and periodontal disease. The oral cavity is an ideal location for the formation of plaque biofilms because they require moist environments to provide the necessary nutrients for growth and proliferation. Plaque biofilms are difficult to eradicate. To date, scientific evidence supports physical disruption of biofilm by mechanical means (toothbrushing, flossing, hand and power instrumentation) to interrupt biofilm formation and growth. Using chemotherapeutic agents is considered adjunctive to physical disruption.

In addition to plaque biofilm, the patient's *host response* also plays a large role in the progression of the disease process (see Chapter 6). The patient's response to a microbial challenge helps determine the amount of disease the patient exhibits. The microbial challenge consists of antigens, lipopolysaccharide (LPS), and other virulence factors that stimulate the host response, resulting in the infections, gingivitis, or periodontitis.[5] If the patient is healthy and the immune defense system is competent, then the patient may be able to defend against the negative effects of the plaque biofilm's ability to produce an inflammatory response. However, if the patient has certain systemic conditions and is immunosuppressed (diabetes, respiratory illnesses, and autoimmune illness), then the host may not be able to combat the disease process.

Chemotherapeutic agents are intended to be used as adjunctive agents or in addition to evidence-based mechanical therapies such as nonsurgical periodontal therapy (scaling, root planing, and debridement) to assist in improving or maintaining a level of health. Considering that no clinician can remove all biofilm and calculus deposits from the tooth

Patient Education Opportunity

Explain to patients how the role of plaque biofilm and the patient's host response may determine their level of health or disease.

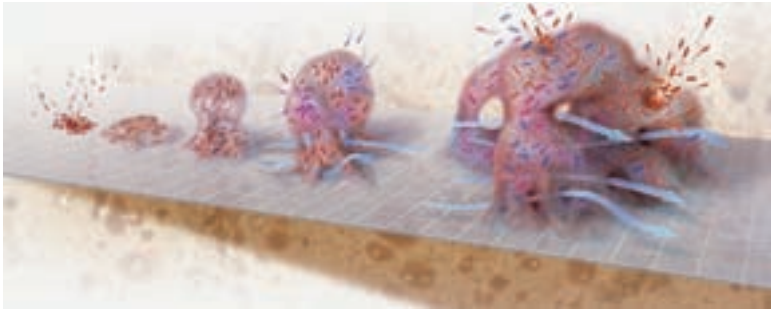

FIGURE 27-1
Different stages in a biofilm life cycle. (Images courtesy Joanna Heersink and Paul Stoodley, PhD, funded by Philips Oral Healthcare. Illustration by Keith Kasnot, Scientific American 2001, courtesy Philips Oral Healthcare.)

surface, chemotherapeutic agents are valuable home care or in-office adjuncts to treatment.[4,6] They are not intended to be used as the sole mechanism to control disease at this time, except in special circumstances in which the patient is unable to have mechanical therapy.

CONTROLLING PLAQUE BIOFILM WITH CHEMOTHERAPEUTICS

As mentioned previously, mechanical therapy is the first line of defense against dental biofilm. However, chemotherapeutic agents can be helpful adjuncts. The clinician must consider the types of bacteria being targeted, the chemotherapeutic agent being used, and the **minimum inhibitory concentration** (MIC), which represents the concentration of antibiotic required to inhibit growth of a planktonic bacterial population. The MIC has been used as a gold standard for determining antimicrobial sensitivities for animal and human pathogenic bacteria.[26] New techniques are now available to determine the types of bacteria present in the biofilm and for quantifying oral bacteria during biofilm formation.[87] New techniques using deoxyribonucleic acid–polymerase chain reaction (DNA-PCR) technology allow for DNA testing of live and dead bacteria, making timing a moot issue. Once mechanical debridement is accomplished, delivery of an adjunctive chemical agent may be accomplished in a variety of ways.

The delivery of therapeutic chemical agents to the site of infection is accomplished either systemically or locally and may be used during the presurgical, surgical, or supportive phases of periodontal care. The means by which the agent is applied or made available to the oral site is termed the **delivery system** and includes the drug carrier or vehicle, the route, and the target. Systemic or enteric delivery allows agents to flow through the body until reaching the diseased or intended site. Ingestion and intramuscular injection are common means of systemic delivery.

Topical drug-delivery systems deliver chemotherapeutic agents to the surface of mucosa or gingiva—for example with rinsing—or several millimeters below the gingival margin during supragingival irrigation. Site-specific delivery is accomplished with vehicles such as chips, powders, polymers, gels, and rinses. **Site-specific** delivery includes **sustained-release** and controlled delivery of a chemotherapeutic agent to a specified area of the mouth. Sustained release refers to systems and agents that are most active (provide drug delivery) for less than 24 hours, whereas **controlled delivery** means the agent is active longer than 1 day.[7] Controlled delivery is indicated for periodontal pockets deeper than 5 mm, and treatment is usually over a period of 7 to 28 days. In addition to rinsing, irrigation, and controlled delivery, vehicles such as lozenges, chewing gum, and sprays also have been employed to deliver chemotherapeutic agents. Irrigation with chemotherapeutic agents, as well as self-care devices, is covered in Chapter 24**.**

Antimicrobials: General Considerations and Specific Agents

QUALITIES OF THE IDEAL ANTIMICROBIAL AGENT

An ideal antimicrobial agent should possess certain qualities. The agent should be effective against specific microbes, they should inhibit the overgrowth of other organisms, and they should not cause an increase in bacterial resistance. The antimicrobial must be nontoxic to oral tissues and acceptable to the patient—for example, in taste, ease of use, and cost. A valuable quality for an antimicrobial is **substantivity,** or the persistence of antimicrobial activity[30] and the ability of an agent to remain in an area or site and resist becoming diluted or washed away by gingival crevicular fluid or salivary action. Substantivity is accomplished by adhering to the soft tissues in the oral cavity, which allows the agent to continue its antimicrobial action over a period of hours. Substantivity is assessed by measuring the changes in duration and numbers of bacteria.[30] Chlorhexidine[1] and tetracycline[71] have excellent substantivity. The usefulness of antimicrobials must be evaluated by site, concentration, and time.[20] In other words, the agent must be in a form that is capable of being delivered to the site in an effective concentration and work for a sufficient length of time.

SELECTION

Ideally, the clinician should determine the specific type of periodontal pathogens present and then select the optimal antimicrobial. In actual practice, clinicians have not readily used testing of periodontal pathogens before initiating antimicrobial

therapy. One reason is that the antimicrobial recommendations are not yet specific enough for most oral periodontal pathogens. Another reason is that specific bacteria are implicated for only a few of the various types of periodontal infections, although periodontal research efforts continue to search for putative microbes. Although the in-office tests take only minutes of the clinician's time, the cost to the patient for these tests is significant. However, the ability to identify and target oral pathogens would permit clinicians to choose an antimicrobial agent with sufficiently narrow selectivity. Antimicrobial selectivity enhances microbial effectiveness and reduces antimicrobial resistance, thus improving patient care outcomes.

PATIENT CONSIDERATIONS

Using an antimicrobial involves several patient considerations:

1. Determination of any patient sensitivity
2. Determination of the area to be treated (the entire dentition or isolated areas)
3. Informed consent, advising the patient of the following:
   - Name of the agent
   - Method of use
   - Anticipated benefits
   - Possible side effects
4. Date for follow-up evaluation of the antimicrobial therapy
5. Evaluation of the results of chemotherapeutic use

CONCENTRATION, EFFECT, AND RESISTANCE

Chemotherapeutic agents should be used in the lowest concentration that achieves maximal benefit. Concentrations that are too low may be ineffective and increase the chance of microbial resistance, whereas excessive concentrations or length of use may have untoward tissue effects and be costly. For example, **local delivery** of chemotherapeutic agents allows high concentrations to be administered with relatively few side effects yet has a seemingly effective kill rate.

Evaluation of Chemotherapeutic Agents

27-1

AMERICAN DENTAL ASSOCIATION GUIDELINES FOR SEAL OF ACCEPTANCE PROGRAM

The American Dental Association (ADA) has established guidelines for accepting chemotherapeutic products for control of gingivitis (Box 27-1), as well as guidelines for chemotherapeutic agents to slow or arrest periodontitis (Box 27- 2). According to the ADA, "For more than 125 years, the ADA has sought to promote the safety and effectiveness of dental products."[19] The

BOX 27-1

Guidelines for Chemotherapeutic Products for Control of Gingivitis

The ADA's Council on Scientific Affairs created *Acceptance Program Guidelines for Chemotherapeutic Products for Control of Gingivitis.* These guidelines maintain:

"The following guidelines are given for the design and conduct of clinical studies for the evaluation of chemotherapeutic agents to provide evidence of effectiveness and safety in the control of gingivitis and, if applicable, supragingival plaque. The clinical benefit of plaque biofilm control can best be demonstrated by a significant reduction in gingivitis.

- For products that accomplish their antigingivitis effectiveness through plaque biofilm reduction, it will be necessary to demonstrate statistically significant reductions in both plaque biofilm and gingivitis by the products.
- For products that do not exert their antigingivitis effect through plaque biofilm reduction, it will be necessary to demonstrate a statistically significant reduction in gingivitis and supporting data for the mechanism of action.

In each study, the active product should be compared with a placebo control. In addition, a positive control may be added. Designs employing either crossover or parallel groups are acceptable. Because of a possible retained effect of some agents, care must be taken in a crossover design to include an adequate latent period between study periods. Additionally, the crossover design may not be practical in the long-term studies required for adequate evaluation of product efficacy.

When the indices used allow accurate repeated measures, it is necessary to provide a measure of intra- and inter-evaluator variance. Examiners should be capable, at a minimum, of replicating their own scores to a high degree on a site-by-site basis. A Kappa statistic of 0.6 would indicate satisfactory calibration for gingivitis. An attempt should be made to assess the level of compliance of the subjects in the study."*

For these guidelines the following information is required:

- Two 6-month studies conducted at two different centers
- Plaque biofilm and gingivitis assessments
- Safety to oral soft tissues, teeth, and restorations demonstrated
- Microbiological assessments
- Appropriate statistical analysis

Long-term studies with antimicrobial agents should demonstrate that, although a shift or change in the species of these bacteria may occur, a shift to predominately gram-negative, anaerobic, and motile forms should not occur. Evidence shall demonstrate that microorganisms that have been associated with periodontitis do not develop supragingivally during the course of a clinical study. Opportunistic organisms such as yeasts and gram-negative enteric bacteria shall also not develop during the study.

These guidelines are for products that are effective in controlling gingivitis. If a product significantly reduces plaque biofilm but does not significantly reduce gingivitis, then it cannot be ADA accepted.

Examples of chemotherapeutic products accepted under these guidelines include several versions of Colgate Total Toothpaste (triclosan), Crest Pro-Health Toothpaste (stannous fluoride), Peridex (0.12% chlorhexidine), several versions of Listerine Antiseptic Mouthrinses (Original, Cool Mint, Fresh Burst, Natural Citrus, and Tartar Control) (essential oils), and many generic (private label) copies of Listerine.

*From the ADA web site. Available at: http://www.ada.org/prof/resources/positions/standards/guide_chemo_ging.pdf.

BOX 27-2

Guidelines for Chemotherapeutic Agents to Slow or Arrest Periodontitis

The ADA has also provided guidelines for studies using chemotherapeutics to slow or arrest periodontitis. They may be accessed at: http://www.ada.org/prof/resources/positions/standards/guide_chemo_perio.pdf.

The benefit of periodontal therapy is best demonstrated by stabilization of clinical parameters of periodontal health. For products that accomplish their effectiveness by antiinfective or host modulation means, demonstrating significant reductions in clinical indices of periodontitis and including supporting data for the mechanism of action are necessary. In each study, the active product should be compared with:

- A positive control (scaling and root planing)
- A placebo nonactive product plus supragingival debridement and oral hygiene control

For approval of *test agent alone* products, a negative control (e.g., supragingival debridement and oral hygiene) is compared to the test agent.

Stand-alone therapies should show at least equivalent stability of periodontal health as thorough scaling and root planing. Evaluation of periodontal stability in nontreatment arms should be ongoing. Sites that exhibit attachment level loss of 2 mm or more occurring during the trials should be exited and treated by conventional methods, if appropriate. However, the 2-mm threshold may not be appropriate for all trials and may also depend on the measurement device used. The nature of the baseline disease diagnosis and the rate of expected change should be considered. In some cases, the threshold may be more or less than 2 mm.

For these guidelines, the following information is required:

- Two 6-month or longer studies shall be conducted at two different centers.
- Studies submitted shall present a clinical picture consistent with adult periodontitis.
- Frequency of use of the product should be representative of the actual use of the product in practice.
- Primary efficacy outcomes are beneficial attachment level changes, alveolar bone changes, or both.
- Secondary outcomes may include probing depth, bleeding on probing, microbial assessment (for antiinfective agents), and biochemical and metabolic by-products.
- Safety shall be demonstrated to oral soft tissues and restorations.
- Microbiological assessments shall be made.
- Information submitted for products containing active chemotherapeutic agents shall include assessments of possible side effects of the active agent or adverse effects of the product formulation.

For microbiological assessments, evidence should be provided that the development of resistant microorganisms or emergence of periodontal pathogens does not occur with the use of the product. Evidence that microbes associated with periodontitis, opportunistic organisms such as yeasts and gram-negative enteric bacteria, do not emerge subgingivally or supragingivally during the course of the study should be demonstrated.

Chemotherapeutic products accepted under these guidelines are doxycycline (Atridox and Periostat).

In general, these ADA Guidelines follow the principles of random controlled studies that represent an important pillar of evidence-based medicine and dentistry.

first Seal of Acceptance was awarded in 1931. In 1984, President Ronald Reagan gave the Association a certificate of commendation for the outstanding self-regulatory efforts of its Seal program.

Although compliance is strictly voluntary, more than 300 companies participate in the Seal program. Participating manufacturers commit significant resources to test and market products to obtain the Seal (Figure 27-2). More than 1100 dental products carry the Seal of Acceptance. Of these, approximately 40% are products sold to consumers, such as toothpaste, dental floss, manual and powered toothbrushes, and mouthrinses. The rest are products prescribed or used by dentists and dental hygienists, such as topical in-office fluorides, antibiotics, or dental restorative materials.

An important new development exists regarding how the ADA has decided to evaluate professional dental products. Starting in July 2006, the ADA launched a quarterly *ADA Professional Product Review* [PPR] *Newsletter* to replace the Seal Program for professional products, which will terminate at the end of 2007. The PPR has several enhancements as compared with the Seal Program for professional products.

Whereas the Seal Program is voluntary on the part of manufacturers, with the PPR, the ADA will choose which products to evaluate. The Seal means that a product has met ADA criteria for safety and effectiveness, but no information is available about how products compare with others. Through focus groups and survey, ADA members have said that they want comparative product information. The PPR is designed to give the comparative information that dentists want. In each issue, many products in each of three different product categories will undergo ADA laboratory performance testing. In addition, clinical performance data will be included. Dentists can join

FIGURE 27-2
ADA Seal of Acceptance.

the ADA Clinical Evaluator (ACE) Panel and receive periodic surveys to complete on their product use experience. The PPR also includes additional information such as expert panel discussions, buyer's checklists, new technology updates, and user tips to improve product performance. The PPR is provided free to ADA members as a member benefit and is available to anyone by subscription at pprclinical@ada.org.

One more important point is that the Seal Program for consumer (over-the counter [OTC]) products will continue. It is not being replaced and, in fact, will be made even better. Surveys continue to show that dentists and consumers highly value the Seal Program for consumer (OTC) products because of what the Seal means—that a product has met the ADA criteria for safety and effectiveness.

Products to be considered for acceptance are submitted to the ADA's Council on Scientific Affairs, which reviews data on product safety and effectiveness. Because a wide variety of dental products is available, the Council often calls on one or more of its approximately 200 expert dental consultants for assistance. By doing so, the Council is assured that knowledgeable individuals have examined all aspects of the submissions. The Council's *Guidelines for Participation in the ADA's Seal of Acceptance Program* provides overall guidance for companies that wish to submit products. In addition, specific product guidelines describe the clinical, biological, and laboratory studies that are necessary to evaluate safety and effectiveness for various product categories. These guidelines are subject to revision and may be updated at any time.

Once a product carries the ADA Seal of Acceptance, dental professionals and consumers can be assured that the product has met the ADA criteria for safety and effectiveness. For non–ADA-accepted products, dental professionals are encouraged to request from manufacturers the same information required for acceptance and base their recommendation on their own evaluation of the product.

Patient Education Opportunity

Talk to patients about the ADA Seal of Acceptance and what it means so that they will have a clearer understanding when purchasing dental products.

U.S. FOOD AND DRUG ADMINISTRATION REGULATIONS

The U.S. Food and Drug Administration (FDA) is in the process of developing guidelines for the dental industry entitled *Guidance for Industry—Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention*. This document will assist sponsors of new drug applications (NDAs) with the development of drug products that treat or help prevent gingivitis in adults and children. This document will define gingivitis and clarify the distinction between gingivitis and periodontitis, as well as cover topics such as OTC versus prescription status and prevention versus treatment. The largest part of this guidance will focus on trial design issues and clinical assessments and will close with an examination of product safety determinations.[90]

Plaque Biofilm and Gingivitis Control with Chemotherapeutic Agents

Chemotherapeutic agents have been used over the years in an attempt to treat gingivitis and control plaque biofilm (Table 27-1). Dentifrices and mouthrinses are common agents used for this purpose. Typically, these agents are used for controlling supragingival plaque biofilm and gingivitis. They are usually not effective for periodontitis because they do not reach the bottom of the pocket unless they are delivered subgingivally (i.e., using irrigation). Even with subgingival application, the effectiveness for periodontitis varies. See Chapter 24 for more information on irrigation.

DENTIFRICES

Dentifrices are used to remove plaque biofilm and stains and may contain preventive or therapeutic agents that protect against oral malodor, dental caries, or periodontal diseases. Dentifrices are discussed in depth in Chapter 26, and oral malodor is discussed in Chapter 38. Two dentifrices with novel chemotherapeutic agents bear mention. The first chemotherapeutic is the antibacterial agent, **triclosan.** Triclosan can be considered to be a dual-action antiseptic because it has both antimicrobial and antiinflammatory properties. Although triclosan itself is not new, nor are dentifrices, the combination of the two products is a relatively new occurrence. Toothpastes with triclosan have been clinically proven to be effective against dental caries, gingivitis, plaque biofilm, and calculus. Triclosan has a wide spectrum of action against supragingival and subgingival bacteria found in biofilm, including many types of gram-positive and gram-negative nonsporulating bacteria, some fungi, *Plasmodium falciparum,* and *Toxoplasma gondii.* The combination of triclosan with a co-polymer in toothpaste allows the agent to remain on the tooth surface for a prolonged period, providing effective inhibition of biofilm formation and of gingivitis.[99] Triclosan with a co-polymer has been investigated in a dentifrice formulation and exhibited a 20% reduction in gingivitis and a 25% reduction in plaque biofilm formation.[27] In the United States, Canada, Europe, and other countries, Colgate Total toothpaste is available with triclosan and is ADA-accepted (Figure 27-3, A).

Prevention

Determine which of your patients might benefit from a therapeutic antimicrobial dentifrice with triclosan.

The most recent chemotherapeutic toothpaste on the market is a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice. The toothpaste combines stannous fluoride for chemotherapeutic benefits while providing additional benefits of tartar protection and inhibition of extrinsic stain through the incorporation of hexametaphosphate. The dentifrice is stabilized in a low-water formulation to prevent hydrolysis and oxidation of the ionic stannous fluoride. One study found a 21.7% reduction in gingivitis, 57% reduction in bleeding, and 6.9% less plaque than the negative control.[59a] The

Table 27-1 Comparison of Topically Applied Antigingivitis Agents

AGENT*	NUMBER OF PATIENTS STUDIED	DECREASE IN GINGIVITIS (%)	DECREASE IN PLAQUE BIOFILM SCORES (%)	VEHICLE	MECHANISM OF ACTION
Chlorhexidine[1-3]	612	18.2-43.5	21.6-60.9	Mouthrinse	Cell wall lysis, precipitation of cytoplasm
Essential oils[4-8]	866	14.0-35.9	13.8-56.3	Mouthrinse	Cell wall disruption, inhibition of enzyme production
Stannous fluoride[11-12]	450	19-22	0-6.9	Dentifrice	Alteration of cellular aggregation and metabolism
Triclosan and co-polymer[13-24]	1900	18.8-41.9	11.9-58.9	Dentifrice	Cell wall disruption, antiinflammatory
Cetylpyridinium[9-10]	230	15.4-24.0	15.8-28.2	Mouthrinse	Cell wall rupture

*A separate list of references for this table can be found under the Suggested References link for Chapter 27 on this text's Evolve site.

FIGURE 27-3
A, Triclosan-containing toothpaste. (Colgate Total, Colgate Palmolive, Inc.)
B, Stannous-fluoride–containing toothpaste. (Courtesy P&G Professional oral Health, Mason, Ohio.)

paste is approved by the ADA for anticaries, antigingivitis, antiplaque, and reduction of sensitivity and stain.

MOUTHRINSES

Rinsing is the action of swishing liquid forcefully around the mouth and between the teeth through the muscle action of the cheeks, lips, and tongue to dislodge particles and debris and to disperse agents. Antimicrobial agents reach mucosal and gingival surfaces effectively through a good rinsing pattern. However, rinsing is ineffective against the subgingival flora because the chemotherapeutic agent is not directed into the gingival margin. Additionally, some patients are able to rinse well, whereas other patients do not have adequate muscle action to move liquids around their mouth effectively.

Mouthrinses frequently contain alcohol as a common ingredient. Alcohol is used to dissolve the flavoring agents used to mask the taste of the active ingredient or to dissolve the active ingredient and stabilize the product. Some researchers believe that patients who have severely reduced salivary flow or xerostomia, alcohol-dependency problems, or tissues that are sensitive to alcohol should use an alcohol-free mouthrinse. In addition, comments have surfaced regarding an increase in oral cancer with the use of alcohol in excess of 20%. However, based on several studies reviewed by both the ADA and the FDA, conclusions were that the available data do not support a causal relationship between the use of alcohol-containing mouthrinses and oral cancer.[31] The same document states that "although some over the counter (OTC) mouthrinses contain alcohol, the potential for development of drug tolerance and addiction due to use of these products seems negligible."[31] Further, a recent review in the Journal of the American Dental Association and a meta analysis found no association between the use of alcohol in mouthrinses and oral cancer.[59a]

Mouthrinses can be cosmetic or therapeutic. Mouthrinses that are cosmetic *freshen breath* for a short period, but many have no long-lasting substantivity. Therapeutic mouthrinses are those that treat or prevent conditions or diseases, such as xerostomia, periodontal disease, and dental caries. Figure 27-4 shows various mouthrinses available for the consumer. The ADA and FDA have approved two mouthrinses, Listerine (essential oil) and Peridex (chlorhexidine), for controlling and treating plaque biofilm and gingivitis (Figures 27-5 and 27-6). Fluoride and other agents that fight dental caries are discussed in Chapter 25.

Mouthrinses fall into the following categories:

- Antimicrobial agents
- Plaque biofilm–reducing or plaque biofilm–inhibiting agents
- Anti–plaque biofilm agents; antigingivitis agents
- Antiperiodontitis agents

Mouthrinses are defined as follows:

- Antimicrobial agents: chemicals that have a bacteriostatic or bacteriocidal effect *in vitro* that alone cannot be ex-

FIGURE 27-4
Mouthrinses. **A,** Two prerinses *(left)* and several non–alcohol-containing mouthrinses *(right)*. **B,** Familiar brands of mouthrinses containing alcohol ranging from 8% to 27%. (Courtesy Dr. W. B. Stilley II, Brandon, Miss.)

FIGURE 27-5
Peridex chlorhexidine rinse; by prescription only. (Courtesy OMNII Pharmaceuticals, West Palm Beach, Fla.)

trapolated to a proven efficacy *in vivo* against plaque biofilm

- Plaque biofilm–reducing or plaque biofilm–inhibiting agents: chemicals that have been shown to reduce only the quantity or effect, or both, of plaque biofilm but may or may not be sufficient to influence disease, such as gingivitis or dental caries; also antigingivitis agents: chemicals that reduce gingival inflammation without necessarily influencing bacterial plaque biofilm (e.g., antiinflammatory agents)
- Antiperiodontitis agents: chemicals that are effective against subgingival biofilm[64]

FIGURE 27-6
Listerine antiseptic mouthwash; available OTC. (Courtesy McNeil PPC, Morris Plains, N.J.)

Table 27-2 lists several common mouthrinse agents and their adverse effects, precautions, and contraindications. The following section will provide more detailed information about the specific agents.

Control of Plaque Biofilm and Gingivitis with Chemotherapeutic Agents

27-2

Killing bacteria alone is not sufficient to prove a product or agent useful. In addition to killing bacteria or modulating the immune system, the ultimate aim of a therapeutic agent is to improve tissue response and achieve a healthy state. That being stated, the plaque biofilm–inhibitory, antiplaque biofilm, and antigingivitis properties of these antimicrobial agents are considered along with their substantivity, safety, and possible clinical usefulness. The terms *plaque inhibitory, antiplaque,* and *antigingivitis* have been defined by the European Federation of Periodontology at its second workshop.[57] They define a **plaque biofilm–inhibitory effect** as one that reduces plaque biofilm to levels that are insufficient to prevent the development of gingivitis, an **antiplaque** effect as one that produces a prolonged and profound reduction in plaque biofilm sufficient to prevent the development of gingivitis, and an **antigingivitis** effect as one that has an antiinflammatory effect on the gingival health not necessarily mediated through an effect on plaque.[29] Plaque biofilm control can be accomplished using a variety of means. The next section explores other agents that may affect bacterial plaque biofilm.

Table 27-2 Mouthrinses: Adverse Effects, Precautions, and Contraindications

GENERIC NAME	ADVERSE EFFECTS	PRECAUTIONS AND CONTRAINDICATIONS
Chlorhexidine	Allergic reaction (skin rash, hives, swelling of face), alteration of taste, staining of teeth, staining of restorations, discoloration of tongue, increase in calculus formation, parotid duct obstruction, parotitis, desquamation of oral mucosa, irritation to lips or tongue, oral sensitivity	• Permanent staining of margins of restorations or composite restorations • Should not be used as sole treatment of gingivitis • Contraindicated in patients with sensitivity to chlorhexidine
Cosmetic Mouthrinses and Mouthrinses for Halitosis	Can have a drying effect on the oral mucosa because of alcohol content in these mouthrinses, particularly in people who have low salivary flow; however, may stimulate salivary flow because of the flowing agents in them	• Should be used cautiously in young children and in people who have low salivary flow caused by age or drugs • Contraindicated in patients with allergic reactions • Contraindicated in patients with oral ulcerations • Contraindicated in patients with oral desquamative diseases
Essential Oils	Burning sensation, bitter taste, drying out of mucous membranes	• Should not be used as sole treatment of gingivitis • Contraindicated in patients with oral ulcerations or desquamative diseases • Contraindicated in children (because of high alcohol content)
Fluorides	Ulcerations of oral mucosa, fluorosis, osteosclerosis, diarrhea, bloody vomit, nausea, black tarry stools, drowsiness, faintness, stomach cramps or pain, unusual excitement if swallowed	• Chronic systemic overdose may induce fluorosis and changes in bone • Contraindicated in patients with dental fluorosis • Contraindicated in patients who exhibit fluoride toxicity from systemic ingestion • Contraindicated in patients who have severe renal insufficiency
Oxygenating Agents	Chemical burns of oral mucosa, decalcification of teeth, black hairy tongue	• Should not be used for extended periods because of possible side effects mentioned at left • Contraindicated for treatment of periodontitis or gingivitis
Prebrushing Rinses	None reported	• Negligible effects on plaque biofilm make these agents of little use in the treatment of carious lesions or periodontal diseases, including gingivitis

From Mariotti AJ, Burrell KH: *Mouthrinses and dentifrices*. In Ciancio SG, ed: *ADA guide to dental therapeutics,* 3rd ed, Chicago, 2003, American Dental Association, p 213-231. Adapted 2008 with permission.

WATER

For treating gingivitis, water has been the agent most used with irrigation. Using an intermittent (pulsed) stream of water is the least invasive procedure for supragingival and subgingival irrigation procedures. Although irrigation does not actually remove plaque biofilm, pulsed irrigation with ordinary water has been shown to alter plaque biofilm quality, rendering it less pathogenic by diluting or removing the bacterial toxins and therefore reducing bleeding and gingival inflammation.[21,23,35,65] The pulsating effect of water on bacteria in animal models has produced ruptured bacterial cell walls and production of bacterial ghosts, which are intact cell walls with no content, and imploded bacterial cell walls.[14] Research has demonstrated that a 14-day regimen of water irrigation produced therapeutic benefits in the gingiva and was accompanied by a reduction in the inflammatory cytokines in the gingival crevicular fluid.[13] Another study showed that when combined with toothbrushing, oral irrigation is an effective alternative to traditional dental floss for reducing bleeding, gingival inflammation, and plaque biofilm in some areas of the mouth.[13] In some cases, daily pulsed irrigation with water is the extra help a patient needs to achieve healthy gingiva. See Chapter 24 for further information on irrigation.

CHLORHEXIDINE

Chlorhexidine digluconate (CHX) has been used in mouthrinses and dentifrices OTC in Canada and Europe for many years. In the United States, Peridex (OMNII Oral Pharmaceuticals, West Palm Beach, Fla.) was first available for oral use as a 0.12% prescription mouthrinse (see Figure 27-5). Later, PerioGard was introduced to the market (Colgate Oral Pharmaceuticals, Canton, Mass.). Peridex was the first CHX product to receive the ADA Seal of Acceptance in 1988 for reducing supragingival plaque biofilm and gingivitis.[10] Recently, an FDA-approved alcohol-free CHX mouthrinse was introduced to the U.S. market (Sunstar Americas, Chicago, Ill.). Currently, several brand and generic names of CHX are available with Peridex carrying the ADA acceptance seal. Reductions in plaque biofilm ranged from 22-61% and for gingivitis ranged from 18-44%.[15-17]

CHX is a **cationic** bisbiguanide and the most widely studied of the oral antimicrobials. Its mechanism of action is the rupture of the bacterial cell membrane and precipitation of the cytoplasmic contents. CHX can reduce the adherence properties of *Porphyromonas gingivalis,* a known periopathogen.[42] CHX binds well to oral tissues and continues to be released in its active form for 6 hours or more.[15] *In vitro* evidence shows that 0.12% chlorhexidine is cytotoxic to fibroblasts.[75] Specific protective factors may protect the fibroblasts in the oral tissues. Because its substantivity is superior to that of other known products, CHX is the recommended positive control in oral chemotherapeutic studies.[58]

Although disadvantages exist for CHX use, not every patient exhibits all the undesirable side effects. Table 27-2 lists the reported adverse effects of CHX as a rinse. The stain and calculus accumulation can be removed professionally; the other side effects disappear when use of the product is discontinued. Rinsing concomitantly with an oxidizing agent can also reduce stain from a CHX rinse.[43] The side effects are lessened when CHX is used in an irrigant rather than as a rinse.

Patients should be instructed to rinse with 15 ml for 30 seconds twice a day.[10] CHX interacts with and is inactivated by sodium lauryl sulfate and other positively charged detergents in dentifrices. Therefore patients should wait a minimum of 30 minutes between using a dentifrice and rinsing with CHX.[12] In addition, rinsing with water immediately after rinsing with CHX should be avoided because a bitter taste results.

For professional irrigation, 0.12% chlorhexidine is generally recommended, with 0.06% for at-home daily irrigation.[35] Data shows this is effective for gingivitis but not for periodontitis.

Dilutions (based on a 0.12% concentration) that have been shown to be effective via randomized clinical trials are as follows:

- 0.02% = 5 parts water + 1 part CHX
- 0.04% = 2 parts water + 1 part CHX
- 0.06% = 1 part water + 1 part CHX[39,45]

Use of chlorhexidine has also been incorporated in the concept of whole-mouth disinfection: debridement and antimicrobial therapy of the entire mouth within a 24-hour period.[78] Unlike the familiar quadrant scaling over a series of appointments at 1- or 2-week intervals, this 24-hour approach is designed to reduce the possibility of cross-infection and reinfection in areas that were treated.

To date, chlorhexidine is the only antimicrobial that has been used for full-mouth disinfection. In studies, scaling and root planing were accomplished within a 24-hour period, and the mouth was disinfected using CHX in professional subgingival irrigation 1%, brushing of tongue with 1% CHX gel, and rinsing with 0.2% CHX for 2 minutes daily for 2 weeks. A significant improvement was observed microbiologically and clinically after 2 months. Beneficial bacteria were found in periodontal pockets, with significantly fewer spirochetes and motile rods, and probing depths in deep pockets were reduced.[78] Further studies found beneficial clinical outcomes 8 months after a 1-day full-mouth scaling and root planing and disinfection[61] and a reduction in the microbial load.[77] One reported side effect was the temporary and slight increase in temperature experienced by some patients a day or two after the therapy. Although other studies either challenge the benefits of full-mouth disinfection or challenge the beneficial effects of the addition of chlorhexidine to the regimen, it is an area that warrants further investigation.

Patient Education Opportunity

Explain to patients about the benefits and disadvantages of using CHX mouthrinse. In addition, educate them about when and how to use the mouthrinse to obtain maximal results.

ESSENTIAL OILS

Essential oils of spices and herbs have antibacterial and antifungal properties, with thyme, oregano, mint, cinnamon, salvia, and clove found to possess the strongest antimicrobial properties.[52] Rinse formulations of phenol-related essential oils include thymol and eucalyptol with menthol and methylsalicylate. Essential oil rinses have a neutral electrical charge. The mechanism of action of the phenolics is to disrupt the bacterial cell wall and inhibit bacterial enzyme production. The most familiar essential oil mouthrinse is Listerine Antiseptic Mouthwash (McNeil PPC, Morris Plains, N.J.), which was awarded the ADA Seal of Acceptance in 1988 for the control of plaque biofilm and gingivitis[9] (see Figure 27-6). Recommended use is to rinse with 20 ml full strength for 30 seconds.[80] Studies have reported plaque biofilm reductions from 14% to 56% and gingivitis reductions from 14% to 39% with twice-daily use after toothbrushing.[30] Essential oils in mouthrinses have positive effects on plaque biofilm and salivary *Streptococcus mutans* levels. One study reported an essential oil mouthrinse produced respective reductions of 69.9% and 75.4% in total recoverable streptococci and in *S. mutans* in plaque biofilm and corresponding reductions of 50.8% and 39.2% in saliva.[32] Essential oils have also been studied as a preprocedural rinse before intraoral procedures. Fine and colleagues found a 94.1% reduction in bacteria collected from aerosols produced by ultrasonic scalers.[33] After more than a century of use of essential oils, no evidence exists of the emergence of opportunistic pathogens or resistant strains with the regular use of these rinses. Some individuals experience an initial burning sensation and an unpleasant taste with essential oil mouthrinses (see Table 27-2). For these individuals, Natural Citrus Listerine Antiseptic Mouthwash may be an alternative. Most of the Listerine antiseptics have alcohol contents in the 21.6% to 26.9% range, and Listermint is alcohol free. Other essential oil products are Advanced Listerine Antiseptic Mouthwash with Tartar Protection, Cool Mint Listerine Antiseptic Mouthwash, and FreshBurst Listerine Antiseptic Mouthwash, as well as several generic versions.

Note

After review from the National Cancer Institute, the ADA has stated that insufficient evidence exists to link oral cancer and mouthrinses containing alcohol in humans. The few studies available are not consistent in the findings on the relationship between smoking and using alcohol-containing mouthrinses.[20]

Concerns over the carcinogenic potential of preparations with a high alcohol content have been expressed. Studies reporting such carcinogenic potential have been fraught with problems—for example, inclusion of pharyngeal cancer, not controlling for other use of alcohol, and frequency and length of rinsing.[21] After review from the National Cancer Institute, ADA, and FDA, the ADA has stated that insufficient evidence exists to link oral cancer and mouthrinses containing alcohol in humans. The few studies available are not consistent in the finding on the relationship between smoking and the use of alcohol-containing mouthrinses.[20]

STANNOUS FLUORIDE

Stannous fluoride (SnF_2) is available in 0.63% (rinses), 0.4% (gels), and 0.454% (dentifrices) strengths. Studies with SnF_2 have shown an adverse bacterial effect[84] and a reduction in plaque biofilm and gingivitis for a short period. The antigingivitis action of SnF_2 is believed to be primarily through the stannous (tin) ion. However, a pilot study involving 70 sites in 10 patients found positive results using a 2.0% neutral gel as part of a supportive periodontal therapy program.[24]

One study demonstrated that the use of a SnF_2 rinse twice daily significantly reduced plaque biofilm index compared with placebo in both sites that received an oral prophylaxis and those that did not (29% overall).[22] No irritation was noted, although a trend toward lower gastrointestinal scores was observed at 3 weeks for the SnF_2 group. Therefore the study concluded that the product was effective in preventing new plaque biofilm accumulation, as well as reducing existing plaque biofilm. SnF_2 as a professionally applied subgingival irrigant was studied[56,60] and found to have little benefit.

The primary disadvantage of SnF_2 is the extrinsic black stain produced when used as a mouthrinse (see Table 27-2). The stain can be removed with a dental prophylaxis.

Stannous fluoride is also the active ingredient in Crest Pro-Health toothpaste, which contains stabilized 0.454% SnF_2 plus sodium hexametaphosphate as the abrasive system to reduce calculus and stain. It is accepted by the ADA for the reduction of plaque biofilm, gingivitis, dental caries, calculus, and tooth sensitivity. Reductions in plaque biofilm range from 0% to 7% and reductions in gingivitis range from 19% to 22%.

TRICLOSAN

Triclosan is a broad-spectrum antiseptic that has been used in many products, including soaps and antiperspirants.[48] It is a bisphenol with broad-spectrum antimicrobial activity. It has been incorporated into many oral products.[28] The dentifrice Colgate Total (Colgate Palmolive, Piscataway, NJ) contains triclosan and Gantrez, a co-polymer of poly-vinylmethylether–maleic acid (PVM-MA) (see Figure 27-3). Triclosan with co-polymer has been studied as a dentifrice and found to reduce gingivitis by 19% to 42% and plaque biofilm by 12% to 59%.[27] It is the first dentifrice sold in the United States to receive the ADA's Seal of Acceptance for the reduction of plaque biofilm and gingivitis. In the United States, triclosan for oral benefit is currently available only in a dentifrice (see Chapter 26).

SANGUINARINE

Sanguinarine is an alkaloid extract obtained from the bloodroot plant *Sanguinaria canadensis* and is the active ingredient in both a rinse and a dentifrice for the treatment of gingivitis.[46] No benefits were obtained when only one of the products was used, but a decrease in plaque biofilm and gingivitis has been shown when both the dentifrice and mouthrinse were used together regularly. Reductions in plaque biofilm ranged from 17% to 42% and gingivitis reductions from 18% to 57%.[46] The only reported side effect has been a mild burning sensation when initially used.[7] It has been replaced in Viadent oral care products by zinc citrate in the dentifrice and by cetylpridinium chloride in the mouthrinse. It is found in some herbal products. Dentifrices with this herbal agent are not ADA accepted.

TETRACYCLINE AND ITS ANALOGS

The benefits of tetracycline (TCN) and its analogs, chemically modified TCN molecules (CMTs), are remarkable. TCNs can be used either as bacteriostatic agents to inhibit protein synthesis in the bacterial cells or, at subantimicrobial (lower) concentration, to modulate the host response.[93] Two useful properties of TCN are its ability to concentrate in gingival crevicular fluid and its long-established safety record in low systemic doses. The CMTs inhibit the destructive activity of mammalian collagenases and possess a powerful ability to inhibit osteoclastic activity, thus reducing bone loss.[94] TCN should not be administered to pregnant women or young children whose teeth are still calcifying because TCN's affinity for mineralizing tissue causes intrinsic staining in teeth.

As an irrigant, TCN (250-mg capsule in distilled water at 53° C) was reported to achieve clinical healing similar to scaling and root planing with an average attachment gain of 1.3 mm when the irrigant was delivered for 5 minutes per site.[18,85] If the entire mouth is periodontally involved, then using TCN as an antimicrobial irrigant is not practical because of the long application time. However, in an isolated site, the authors suggested this amount of time and concentration of TCN irrigant.

OXYGENATING AGENTS

Oxygenating agents such as urea peroxide, hydrogen peroxide, gaseous oxygen, and redox agents release oxygen for the resulting deleterious effect on anaerobic pathogens.[83] For periodontal problems, oxygenation is not retained sufficiently long in the pockets and produces untoward side effects. Oxygenating agents alter normal healing, have produced soft tissue lesions, and have been co-carcinogenic in an animal model.[20] The general belief is that overuse of oxygenating rinses, hydrogen peroxide in particular, causes the overgrowth of opportunistic organisms such as *Candida* species. In most studies, results of using oxygenating agents are similar to those of the placebo. However, using the redox agent methylene blue in a slow-release (controlled-delivery) device showed improvement in clinical and microbial pocket parameters beyond debridement alone[68] (see Table 27-2).

Rather than releasing oxygen, some oral antimicrobial agents such as Listerine, doxycycline, TCN hydrochloride (HCl), and

sanguinarine have an antioxidant effect in the tissue, thus decreasing gingival inflammation.[34] This concept is not the same as that of oxygenation. Periopathogenic microbes produce oxygen free radicals (O^-) that are toxic to the gingival tissues. An antioxidant chemically reacts with these oxygen free radicals, thus reducing the inflammatory tissue response.

BAKING SODA, SALT, AND HYDROGEN PEROXIDE

Products that contain baking soda, salt, and hydrogen peroxide have been used together with hydrogen peroxide in a modality called *Keyes' technique*.[8] After mechanical instrumentation, a paste of baking soda, salt, and hydrogen peroxide were used as a dentifrice, and irrigation was performed with a saturated salt solution. Studies comparing this technique with other procedures showed no statistically different improvements in clinical efficacy.[41] Baking soda is also used in dentifrices as a cleaning agent.

QUATERNARY AMMONIUM COMPOUNDS

Agents that contain quaternary ammonium compounds are anionic and strongly positively charged and bind easily to oral tissues.[70] The most common quaternary ammonium compound is cetylpyridinium chloride (CPC) 0.05%. This cationic surface-active compound binds to oral tissues but less strongly than CHX. Its mechanism of action ruptures cell walls and alters cytoplasmic contents. Reported side effects are some staining, increased calculus formation, and an occasional burning sensation and epithelial desquamation.[24] Their activity is altered by anionic substances, such as flavoring agents, abrasives, and other charged particles sometimes found in dentifrices. Therefore, compliance could be problematic since a water rinse is recommended following use of traditional dentifrices to maximize their effect, which removes anionic substances. Cēpacol 0.05% CPC (Merrell Dow Pharmaceuticals, Inc., Kansas City, Mo.), Scope 0.045% CPC, Viadent 0.05% (Colgate Palmolive, Piscataway, NJ), and Crest Pro-Health Rinse 0.7% CPC (Procter & Gamble, Cincinnati, Ohio) are familiar brands. Six-month studies of CPC showed a 16% to 28% reduction in plaque biofilm and a 24% reduction in gingivitis.[59]

POVIDONE-IODINE

Povidone-iodine has been used for many years as a surgical hand-scrubbing agent. It is effective against many types of bacteria, viruses, and fungi.[76] A low concentration of povidone-iodine has been shown to be effective as a mouthrinse (in combination with hydrogen peroxide), a subgingival irrigant, and a preprocedural rinse.[38] Clinicians have generally avoided iodine preparations for their known caustic effect on tissue, staining, and the possibility of a sensitivity reaction to iodine. This agent should not be used in patients with known allergies to povidone-iodine or shellfish, with thyroid dysfunction, or who are pregnant or lactating.

PREBRUSHING RINSES

Plax (Johnson & Johnson, Morris Plains, NJ) is a detergent–sodium benzoate mixture sold as a prebrushing rinse. Generally, no benefit accrues because results from using the prebrushing rinse appear to be similar to placebo use [62] (see Table 27-2).

In summary, evidence suggests that some chemotherapeutic agents can control plaque biofilm and gingivitis or provide an effective adjunct to traditional therapies. Research efforts continue in the arena of antimicrobials in patient care, with the result that formulary changes, newer antimicrobials, new uses of familiar antimicrobials, and recommendations about how chemotherapeutics should be used are evolving and changing; thus the dental hygienist must stay up to date in this dynamic area of care.

Controlled Drug-Delivery Systems for Treating Chronic Periodontitis

Locally or controlled delivery products are a combination of antimicrobials or antibiotics and devices that deliver a drug directly to a periodontally diseased pocket. The term *controlled* is used to imply that the drug is released in the pocket at a controlled concentration over a period of time. The current products on the market deliver the drug from 7 to 14 days at a very low dose compared with a systemic antibiotic. In addition, the side effects are essentially nonexistent.

The effect of **locally administered antibiotics or antimicrobials** (LAAs) has been shown to produce better periodontal health effects than mechanical debridement alone. Although the effect of mechanical interventions may produce a positive change in the health of the periodontium, sites may attain a better response if an LAA is placed at the time of initial therapy or shortly thereafter. LAAs are designed to be used in periodontal pockets of 5 mm or greater that bleed on probing. They are not intended for patients with more aggressive forms of periodontal disease who might need more invasive procedures or systemic antibiotics to control the disease. They may be placed numerous times, if warranted.

What is the evidence supporting LAA? The Cochrane Oral Health Group (http://www.cochrane-oral.man.ac.uk/) conducts systematic reviews and develops protocols for treatment. *Protocols* are the introduction, objectives, materials, and methods for reviews currently being prepared and do not yet have abstracts. Local delivery of antimicrobials for chronic periodontitis is one such Cochrane protocol.[25] In addition, the Agency for Healthcare Research and Quality published a report in March 2004: *Effectiveness of Antimicrobial Adjuncts to Scaling and Root-Planing Therapy for Periodontitis.*[1] Conclusions reached were that "the difference in measurements between the treatment and control groups typically favored the treatment group, but was relatively modest. . . . Of the antimicrobials investigated, studies of locally applied tetracycline and minocycline—and locally delivered chlorhexidine—have fairly consistent results in moderately large studies that often reach statistical significance; improvements [in probing depths (PD)] observed in these studies typically average in the neighborhood of 0.3 mm to 0.6 mm. The other agents and delivery modes produced less consistent outcomes and fewer outcomes that reached statistical significance; the majority of studies showed small, statistically nonsignificant PD improvements. [Clinical attachment level (CAL)] outcomes were not as positive as those for PD. The question

remains, the authors note, whether such improvements are clinically meaningful."[1]

The area of clinical significance has become a topic of interest to clinicians. Although knowing whether statistical significance has been achieved is important (to determine that a result did not happen by chance), it can provide little meaning when making clinical decisions. Killoy suggested that if a product or procedure achieved an improvement of 2 mm or more in probing depth or attachment gain, it might be deemed clinically significant.[53] All of the LAA products in the U.S. market have published the clinically significant results of their clincal trials.

The first LAA on the U.S. market was a TCN fiber called Acticite. The fiber consisted of a woven tube made of the polymer ethylene vinyl acetate saturated with 25% TCN HCl. Even though the product was effective, placing it in a timely manner and retaining it in place for the duration needed was difficult. Currently, CHX (PerioChip), doxycycline hyclate (Atridox), and minocycline microspheres (Arestin) are the three controlled drug-delivery systems available in the United States. Products available in other countries include metronidazole gel, minocycline gel, and minocycline ointment.

ADVANTAGES

A controlled drug-delivery system has several advantages.

- Compliance with self-care is not an issue, and patients do not have to remember to take the medication because the dosing and timing are part of the delivery system.
- Dose concentration can be much greater, permitting a greater microbial kill rate and less opportunity for microbial resistance to develop.
- Side effects are often reduced because the agent is delivered to a particular site and not distributed throughout the mouth.
- The systemic effect on the body is also lessened because the agent is delivered locally rather than systemically.

CAUTIONS

Although an LAA is not typically used for generalized periodontitis, it is not contraindicated if a person has multiple pockets and will not or cannot undergo surgical therapy. The contraindication may be the result of medical or financial considerations or fear. Additionally, controlled drug-release delivery is not recommended for pockets less than 5 mm because retention may be an issue. Clinical trials have not included children younger than 18 years of age, pregnant women, and medically compromised individuals; therefore using controlled drug-delivery therapy in these population groups would be considered an *off label* use. Finally, individuals may respond differently to controlled drug-delivery systems, ranging from a worsened condition (infrequent) to a mild, moderate, or marked improvement. No single therapy is guaranteed, and all therapy should be monitored and evaluated.

CHLORHEXIDINE GLUCONATE

In 1998 the first subgingival sustained-release delivery system containing CHX became available to U.S. practitioners. PerioChip (manufactured by Dexcel Pharma and distributed by OMNII Oral Pharmaceuticals, West Palm Beach, Fla.) is a small orange chip, 4 mm × 5 mm × 350 mcm, weighing 7.4 mg (Figure 27-7, *A*). The prescription chip contains 2.5 mg of CHX, a broad-spectrum antimicrobial, in a biodegradable matrix of hydrolyzed gelatin cross-linked with glutaraldehyde, glycerin, and water. Gingival crevicular fluid concentration appears to be biphasic and varies among patients, peaking at 4 hours (more than 1000 mcg/ml) after insertion of the chip into the pocket, and then again at 72 hours (more than 480 mcg/ml) (Figure 27-7, *B*). Release of CHX lasts from 7 to 10 days. In patients with 5- to 8-mm pockets, depth reductions of 2 mm or more over scaling and root planing alone were reported in a 9-month period.[50]

Inserting the chip with forceps is simple, quick, and comfortable. Bacterial resistance to CHX in studies up to 2 years has not been observed.[15] Additionally, the customary side effects of CHX are not evident, most likely because CHX is released below the gingival margin.[11] This product is active in the pocket for 7 to 10 days. The patient is instructed to avoid brushing or flossing the area for 7 days.

DOXYCYCLINE HYCLATE

Doxycycline gel (Atridox) is a 10.0% concentration of doxycycline hyclate for controlled delivery subgingivally in treating chronic adult periodontitis. It is a liquid biodegradable polymer that hardens shortly following exposure to the fluid in the periodontal pocket. Marketed in the United States since 1998, Atridox is available by prescription and carries the ADA Seal of

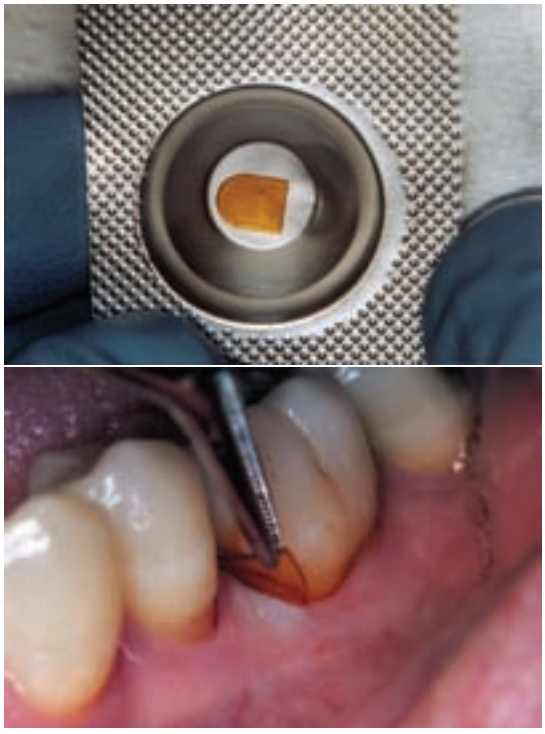

FIGURE 27-7
A, The PerioChip is a biodegradable film of hydrolyzed gelatin 0.35 mm in thickness and 4 × 5 mm, containing 2.5 mg chlorhexidine gluconate. **B,** The PerioChip is inserted into a 6-mm pocket on the mesial surface of tooth #19. (From Rose LF et al: *Periodontics: medicine, surgery and implants,* St Louis, 2004, Mosby.)

Acceptance. The polylactic acid gel and drug are mixed at chairside and delivered to the bottom of the pocket via a small cannula (Figure 27-8). The gel then solidifies, releasing doxycycline for a period of 7 days. Clinical trials have resulted in an increase in clinical attachment averaging 0.8 mm and a reduction of probe depths averaging 1.3 mm in a 9-month study.[37] Headache, common cold symptoms, and some toothache and gingival discomfort were the most common side effects. Interestingly, the difference in improvement between two groups, smokers and nonsmokers, was not evident when Atridox was used.[81] This product is active in the pocket for 7 to 10 days and usually dissolves in 28 to 30 days. The patient should be instructed to avoid brushing, flossing, or eating in the area of placement for 7 days.

MINOCYCLINE MICROSPHERES

Minocycline HCl is available in a controlled drug-delivery system with the brand name of Arestin (OraPharma, Inc., Warminster, Pa.). This TCN derivative is incorporated in a bioresorbable polymer in the form of a powder of bioadhesive microspheres and marketed in 1-mg unit-dose cartridges with accompanying delivery syringes. Minocycline is a member of the TCN class of antibiotics and has a broad spectrum of activity.[86] Minocycline inhibits protein synthesis in the bacterial cell wall that causes leakage and destroys the cell. At higher concentrations, minocycline is bacteriocidal, killing the bacteria. Laboratory testing has shown minocycline to be effective in eradicating the organisms that are associated with chronic periodontitis. *Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Eikenella corrodens,* and *Actinobacillus actinomycetemcomitans* are susceptible to minocycline at concentrations of up to and including 8 mcg/ml. A 2001 study reported the results of a 9-month multicenter trial on Arestin. The study compared scaling and root planing (SRP) alone, SRP plus minocycline microspheres, and SRP plus the placebo microspheres (not containing minocycline). The results showed a greater therapeutic effect of the SRP plus minocycline microspheres compared with the other treatment groups.[98]

Arestin has also been shown to maintain effective MIC of the drug for up to 14 days and, in some cases, 28 days.[17] The levels found were well above the MIC levels for common periodontal pathogens. Although the product maintains high local levels of drug, the systemic levels are minimal. In a pharmacokinetic study, results found mean dose saliva levels to be approximately 1000 times higher than serum levels (blood), indicating minimal absorption of the drug through the periodontal pocket into blood.[69]

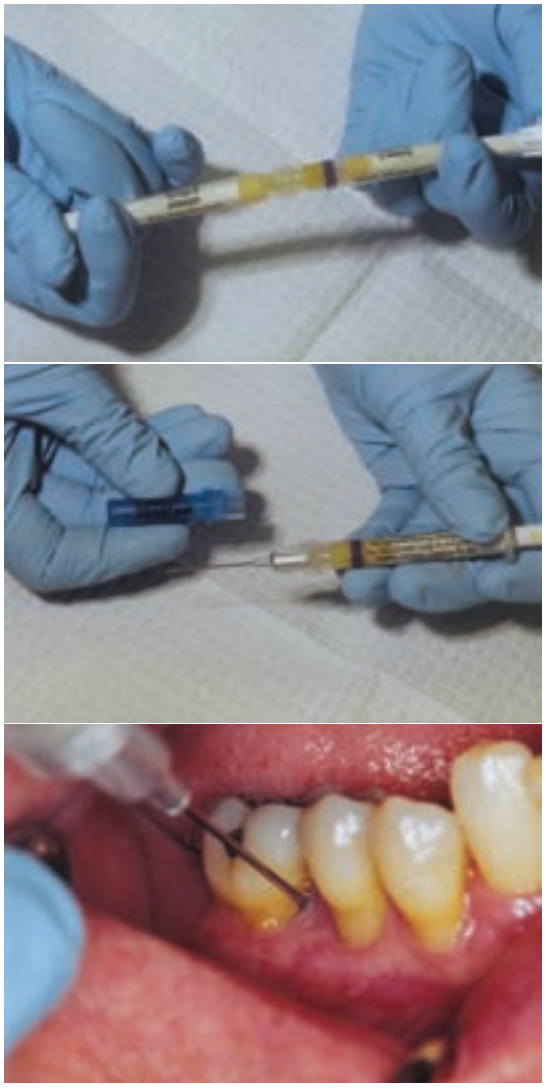

FIGURE 27-8
A, Atridox in two syringes that are coupled together for mixing. Atridox also comes in a single-syringe, premixed formulation. **B,** After mixing, the delivery syringe is attached to a blunt cannula. **C,** Atridox is placed into a 7-mm pocket on the mesial surface of tooth #30. (From Rose LF et al: *Periodontics: medicine, surgery and implants,* St Louis, 2004, Mosby.)

BOX 27-3

TIPS FOR ARESTIN TIP PLACEMENT

- Ease of insertion may be facilitated by aligning the cartridge tip parallel to the long axis of the tooth, similar to a periodontal probe.
- In a pocket with *tight* tissue (smokers or maintenance patients), a probe may be inserted to retract the tissue before inserting the tip of the cartridge.
- For tight tissue, the orifice of the tip may be altered from a circle to an elliptical or flatter shape. Start at the end of the tip and run the end of the mirror handle up to the ring on the cartridge. Do this a few times.
- In a difficult-to-access pocket (i.e., distal of molars), the cartridge may be slightly bent to increase the angle at the existing angle of the cartridge, approximately 12 mm from the end of the tip. Do not bend the tip in the first 6 mm from the end of the tip because the plunger may rupture the cartridge and puncture the barrel wall.
- When inserting the cartridge tip, use a light grasp and an exploratory motion. When the pocket morphology or best access is identified, align the cartridge tip as parallel as possible to the long axis of the tooth; express the cartridge contents into the pocket.

Modified from Wilder RS: A new option for local delivery, *Dimens Dent Hyg* 1(2):24-27, April/May 2003.

The microspheres are dispensed subgingivally using a disposable premeasured plastic cartridge in a stainless steel handle. The tip is inserted to the base of the pocket and the material is activated into the pocket (Figure 27-9). Posttreatment instructions include avoiding eating hard, crunchy, or sticky foods for 1 week and postponing brushing for a 12-hour period and interdental cleaning for 10 days. Box 27-3 lists suggestions on Arestin placement.

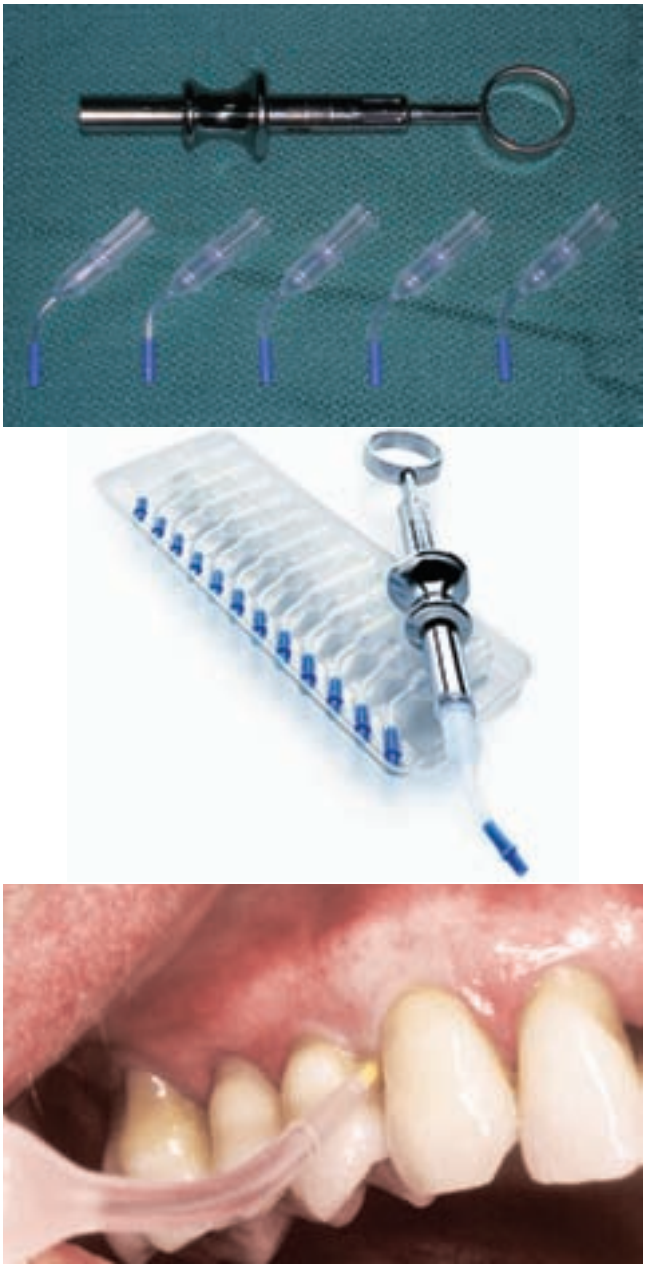

FIGURE 27-9
Minocycline microspheres (Arestin). A, Handle and premeasured cartridges. B, Handle with attached cartridge. C, Arestin is placed into a 6-mm pocket on the mesial surface of tooth #5. (**A** and **B** courtesy OraPharma, Inc.; **C** from Rose LF et al: *Periodontics: medicine, surgery and implants,* St Louis, 2004, Mosby.)

METRONIDAZOLE GEL*

Metronidazole gel contains 25% metronidazole in a glycerin mono-oleate and sesame oil base and is applied to the pocket using a syringe with a blunt cannula. This agent is not currently available in the United States. It is easy to place but may require multiple applications to achieve desirable results. Studies using metronidazole gel as a monotherapy show similar results compared with scaling and root planing.[2,39,73] When metronidazole gel was used in studies with two other adjunctive treatments to SRP and compared with SRP alone, all treatments improved over 6 months with no significant differences among treatment groups.[54,79]

MINOCYCLINE OINTMENT AND GEL

Minocycline ointment contains 2% minocycline HCl and is applied using a syringe with a blunt cannula. This agent is not currently available in the United States. A 2% minocycline gel has also been used in several studies. In a multicenter study of patients with moderate to severe periodontitis, results of treatment with minocycline ointment combined with SRP were found to be statistically significant when compared with treatment with a vehicle control with SRP.[91,92] When subgingivally applied minocycline gel was used as one of three adjunctive treatments to SRP compared with SRP alone, all treatments showed improvements with no significant differences among groups.[54,79]

Systemic Antibiotics

Antibiotics are organic substances that have the ability to destroy or inhibit the growth of bacteria and other microorganisms. Most antibiotics have been isolated and purified from their natural source and are prepared synthetically or semisynthetically. In contrast to antiseptics, they are administered orally, parenterally, and rarely topically. The topical route is not widely used because this route of administration may sensitize the patient to these agents, particularly when penicillin is concerned.

An ideal antibiotic should:

- Be selective and effective against microorganisms without injuring the host
- Destroy microorganisms (bactericidal action) rather than retard their growth (bacteriostatic)
- Not become ineffective as a result of bacterial resistance
- Not be inactivated by enzymes, plasma proteins, or body fluids
- Quickly reach bactericidal levels throughout the body and be maintained for long periods
- Have minimal adverse effects

Currently an ideal antibiotic for the treatment of periodontal disease does not exist. Depending on the antibiotic, several mechanisms of action are inherent. These mechanisms include the following:

*Text on metronidazole gel and minocycline ointment and gel borrowed with permission from Hill M and Moore R. In Rose LF et al: *Periodontics: medicine, surgery, and implants,* St Louis, 2004, Elsevier.

- Inhibition of bacterial cell wall synthesis
- Alteration of bacterial cell membrane permeability
- Alteration of bacterial synthesis of cellular components
- Inhibition of bacterial cell metabolism

Antibiotics are either bacteriostatic or bactericidal. **Bacteriostatic** antibiotics inhibit the growth and multiplication of microorganisms, whereas **bactericidal** antibiotics kill or destroy microorganisms. In general, bacteriostatic antibiotics alter the metabolic pathways or synthesis of cellular components. In contrast, bactericidal drugs interfere with the synthesis or function of the cell wall, the cell membrane, or both.

When two bactericidal antibiotics are given together, they may exert a greater effect than when each is given separately. This effect is called *antibiotic synergism.* Sometimes, however, when a bacteriostatic and a bactericidal antibiotic are given together, their effectiveness is negated or reduced. This effect is called *antibiotic antagonism.*

Their antimicrobial activity varies according to the agent selected, dose level, and route of administration. Some antimicrobials are effective against selected gram-positive and gram-negative bacteria, some are most effective against aerobic bacteria (although others act better on anaerobes), a few are effective against fungi, and most have no effect on viruses.

Susceptibility of various microorganisms to antibiotics is initially determined by laboratory tests. However, as with antiseptics, although an agent may be found to be active in laboratory tests, it may prove clinically ineffective if the dose is inadequate, a patient's resistance to infection is poor, or the wrong pathogen has been determined as the etiologic agent.

The advantage of a systemic antibiotic, assuming patient compliance in taking the oral medication, is that the drug reaches bacteria in deep periodontal pockets, gingival tissue, and other oral sites and leaves no reservoir or niche of microbes. The disadvantages of systemic delivery are the adverse side effects, such as gastrointestinal imbalance, nausea, diarrhea, and rash; the risk of producing antimicrobially resistant microbes; and patients not taking the pills as prescribed.[93] Another concern is that systemic antibiotics used to treat periodontal infections are not sufficiently narrow. Ideally, the putative organism should be identified so that the appropriate antibiotic can be selected. Because the causative organism or organisms and the destructive processes in periodontal diseases are not yet fully understood, selecting an antibiotic with a sufficiently narrow spectrum is difficult. Because antibiotics can produce adverse effects, knowledge of these side effects is essential for dental professionals because they may observe these side effects in their patients.[20] A major concern with antibiotics is the development of resistant strains of bacteria with the emergence of resistant strains considered to be one of the major therapeutic challenges facing practitioners in the next decade[63,89] (Box 27-4).

> *Note*
>
> Antibiotics are either bacteriostatic or bactericidal. Bacteriostatic antibiotics inhibit the growth and multiplication of microorganisms, whereas bactericidal antibiotics alter the metabolic pathways or synthesis of cellular components.

Antibiotics most often prescribed for dental therapy are shown in Box 27-5 and include penicillins, TCNs, metronidazole, and clindamycin. Other less often prescribed antibiotics that have been reported in the dental literature are ciprofloxin (alone or in combination with metronidazole) and azithromycin. Selecting an antibiotic for a patient may be based on microbiological evaluations of periodontal pathogens present in the patient, the clinical diagnosis, or both.

Antibiotic therapy should be an adjunctive treatment in managing periodontal diseases and not used as a monotherapy. This therapy should include SRP, optimal oral hygiene, and, as needed, surgical therapy.[51]

Systemic antibiotics have shown to be of minimal value in treating chronic periodontitis. However, they have been shown to be of value in treating localized aggressive periodontitis, generalized aggressive periodontitis, and unresponsive forms of periodontitis.[47,55,72,96]

BOX 27-4

Potential Concerns with Systemic Antimicrobials

- Interference with the body's normal microbial flora
- Side effects
- Drug pharmacokinetics (absorption, distribution, metabolism, and excretion)
- Drug pharmacodynamics (how the drug affects the body)
- Potential for development of microbial resistance
- Drug interactions
- Concerns with special populations (pregnant women, children, elderly, ethnicity, gender, general health status)
- Likelihood of increasing drug sensitivity
- Adherence and compliance to daily medication regimen

BOX 27-5

Most Commonly Prescribed Antibiotics in Dentistry

- Amoxicillin
- Amoxicillin plus clavulanic acid
- Tetracyclines
- Tetracycline HCl
- Minocycline HCl
- Doxycycline HCl
- Metronidazole
- Clindamycin
- Combination of metronidazole and penicillins

HCl, Hydrochloride.

ADVERSE EFFECTS OF ANTIBIOTICS

The adverse effects of the various antibiotic groups most commonly used as adjuncts to periodontal therapy are summarized in the following sections.

Amoxicillin

Amoxicillin toxicity is extremely low and, except for allergic reactions, it is one of the safest drugs known. Patients who are hypersensitive to one penicillin are most likely hypersensitive to all other penicillins. In addition, patients with a history of hypersensitivity to cephalosporins, griseofulvin, or penicillamine may show a similar response to penicillins. Moreover, the combination of amoxicillin and clavulanic acid (Augmentin) may produce diarrhea.

Tetracyclines

The side effects associated with TCN therapy are varied. These side effects and toxicities include photosensitivity, gastrointestinal upset, lymphoepithelioma, fetal tooth staining, and simulated lupus erythematosus. In addition, reports indicate that long-term TCN therapy with minocycline (as used for patients with acne) may discolor adult teeth and gingival tissue.[74,82]

Metronidazole

The main adverse effects of metronidazole are an interaction with alcoholic beverages, which can result in severe nausea and vomiting, metallic taste, gastric discomfort, and diarrhea.

Clindamycin

The main adverse effects of clindamycin are diarrhea and gastric upset. Therefore clindamycin should be taken with food. Pseudomembranous colitis has occurred during therapy with clindamycin, but its frequency of occurrence is less than that seen with ampicillin or the cephalosporins.

Table 27-3 U.S. Food and Drug Administration Pregnancy Classifications

CLASSIFICATION	DEFINITION
A	No risk demonstrated to the fetus in any trimester
B	No adverse effects in animals; no human studies available—amoxicillin, amoxicillin plus clavulanic acid, clindamycin, metronidazole, azithromycin, erythromycin, cephalosporin
C	Only given after risks to the fetus are considered; animal studies have shown adverse reactions; no human studies available—clarithromycin
D	Definite fetal risks; may be given in spite of risks if needed in life-threatening situations—all tetracyclines
X	Absolute fetal abnormalities; not to be used at any time during pregnancy

PREGNANCY CLASSIFICATION OF ANTIBIOTICS

All prescription medications are categorized according to their potential to produce adverse effects on the fetus.[19] These medications are listed in Table 27-3.

Host Modulation

Dentistry has had a long history of research into clarifying the role of the host in the pathogenesis of periodontal disease. Although the profession has long understood the importance of bacteria in disease causation, the understanding of how the host contributes to the periodontal disease process has emerged only since the 1970s. Although investigators have identified specific pathways and mediators of tissue destruction, logically, research effort has been undertaken into **host modulation** treatments that block or modulate these destructive pathways and mediators as a potential adjunctive way to treat periodontal disease. The following discussion is a summary of host modulation treatments for patient use.

PROTEASE INHIBITORS

Subantimicrobial dose doxycycline (SDD), 20 mg doxycycline twice daily over 6 to 9 months, has been proposed as an adjunctive treatment for periodontitis.[40] A recognized feature of doxycycline is its ability to downregulate the activity of matrix metalloproteinases (MMPs), which are active in tissue breakdown during periodontitis. The current understanding of periodontal pathogenesis suggests that MMPs play a major role in inflammation, tissue remodeling, and the destruction of collagen and bone within the periodontium, leading to clinical signs of periodontitis such as attachment loss, bone loss, and tooth mobility. Currently, multicenter clinical studies support the hypothesis that downregulation of MMPs by SDD confers measurable benefits to patients with periodontitis.

Caton and colleagues[16] reported on a 190-patient, placebo-controlled trial in which all patients received SRP; one half of these patients also received adjunctive SDD (20 mg doxycycline twice daily). Patients were examined every 3 months over a 9-month period, and for those receiving SDD, an improvement in attachment gain of 18% was noted (in patients with 4- to 6-mm pockets at baseline). The differences for SDD over SRP alone were greater in pockets of 7 mm or more, for attachment gain (33%), and for pocket depth reduction (40%). Thus the literature suggests that SDD, when prescribed as an adjunct to SRP, results in statistically significant gains in attachment levels and reduction in probing depth when compared with SRP alone. Although the adjunctive use of SDD in addition to mechanical therapy may provide statistically significant improvement in attachment gain when compared with mechanical therapy alone, many researchers have questioned the clinical significance of the differences, which average less than 0.5 mm.[40] One concern that arises with any antimicrobial usage is the emergence of resistant microbial strains, but research implies that SDD is not antibacterial at this dosage (20 mg), and it does not lead to the development of resistant strains or the acquisition of multi-antibiotic resistance.[88] The drug is well

tolerated by the body, and clinical trials have established that the incidence of unwanted effects is similar to that of the placebo. Walker and colleagues[95] concluded that SDD and placebo did not produce effects on vaginal or intestinal flora over 9 months of use. SDD is designed to be given over many months and may therefore suffer from compliance problems similar to other long-term medications used to treat chronic systemic conditions.[95]

SDD was evaluated as part of a systematic review and consensus report from the American Academy of Periodontology. SDD received the highest level of rating possible from a panel of periodontal thought leaders. The rating supported the efficacy and safety of SDD as an adjunct to conventional therapy in managing chronic periodontitis.[49]

NONSTEROIDAL ANTIINFLAMMATORY DRUGS*

Nonsteroidal antiinflammatory drugs (NSAIDs) are generally used in dentistry for treating pain. However, because these drugs inhibit antiinflammatory processes related to the cyclooxygenase pathway, such as prostaglandin, thromboxane, and prostacyclin production, they also have the potential to be beneficial as adjuncts in periodontal therapy. Researchers have recognized that prostaglandin E_2 and other arachidonic acid metabolites are important proinflammatory mediators in bone resorption and the various manifestations of periodontal disease.

NSAIDs are certainly of use after surgical periodontal procedures in reducing postoperative pain and inflammation. Ibuprofen, for example, has been shown to successfully inhibit prostaglandin E_2 production in the periodontal tissues after surgery, contributing to the healing process.[67] Ibuprofen as an adjunct for SRP, however, has not been demonstrated to be effective. Ng and Bissada,[66] for example, showed that ibuprofen (800 mg/day) administered as an adjunctive treatment to SRP did not improve the results on probing depth and clinical attachment levels when compared with SRP alone. Other drugs such as meclofenamate sodium (Meclomen) have been shown to produce positive results in patients with aggressive periodontitis. The use of systemically administered acetylsalicylic acid (aspirin; 500 mg daily for 6 weeks after mechanical debridement) has also been reported to be an effective adjunct in periodontal therapy.[36]

An important factor that must influence the decision on whether to use NSAIDs on a long-term basis is the gastrointestinal complications that may arise. Some cases may result in considerable ulceration of the gastric mucosa. Newer NSAIDs that selectively inhibit cyclooxygenase 2 (COX-2) inhibitors are much better tolerated by the gastric mucosa and may one day prove beneficial in modulating the host response in periodontitis.

Evaluation of Success

Evaluating the efficacy and the effects of chemotherapeutics is ultimately the responsibility of the clinician. Patients should be placed on a chemotherapeutic agent for a finite period and then return to the office for an evaluation. Currently accepted clinical signs of a healthy periodontium include the absence of inflammatory signs of disease such as redness, swelling, suppuration, and bleeding on probing; maintaining a functional periodontal attachment level; minimal or no recession in the absence of interproximal bone loss; and functional dental implants.[4] If these effects are not demonstrated when the use of irrigation and antimicrobials has been added to the patient's regimen, then the clinician should consider a sizeable number of possibilities, including the following:

- Was the agent used as directed?
- Did exudates, blood, calculus, or debris inactivate or block the action of the antimicrobial?
- Would a different chemotherapeutic agent be more effective?
- Is referral indicated?

If these questions do not provide the needed information, then the clinician must reinvestigate the oral condition, as well as the patient's general health and well-being. Adverse personal circumstances such as an increase in patient stress, a change in health status not reported by the patient, or an undiagnosed medical condition may contribute to the regression of the oral status. Although people are able to maintain their teeth longer—even seriously involved periodontal teeth—not every case always results in complete absence of bleeding and absence of attachment loss. The clinician must keep abreast of the patient's clinical signs and symptoms of health and treat the patient according to the best options available.

CASE APPLICATION 27-1.1

Treatment Planning

What areas of concern do you have for Ms. Tevus's oral health? What treatment options might you offer her? Use a decision-tree diagram to illustrate your choices. (A decision tree is a pathway or diagram of lines indicating, at each problem point, the available choices or paths.) Some considerations to guide your thoughts may include the following:

- Does an adequate level of plaque biofilm control exist?
- What type of therapy you would recommend?
- Which chemotherapeutic agent would you recommend for the treatment of tooth #10?
- If SRP of tooth #10 does not improve the probing depth, what options will you suggest for that site?

Conclusion*

Using locally acting chemotherapeutic agents can be a valuable adjunct to conventional mechanical therapeutic treatments. Topically applied agents such as dentifrices and mouthrinses are useful in controlling gingivitis in patients who cannot perform traditional methods to control plaque biofilm or in patients who

*Adapted from Kinane DF: Systemic chemotherapeutic agents. In Rose LF et al: *Periodontics medicine, surgery, and implants,* St Louis, 2004, Elsevier.

*This section was adapted from Hill M, Moore R: Locally acting oral chemotherapeutic agents. In Rose LF et al: *Periodontics medicine, surgery, and implants,* St Louis, 2004, Elsevier.

need an adjunctive method to brushing and flossing. Although mouthrinses and dentifrices have been successful with gingivitis treatment, they have limitations for periodontitis cases because of issues with substantivity. In patients with chronic periodontitis, mechanical treatments with hand or powered instrumentation can provide an excellent clinical response in the majority of patients. However, locally delivered drugs placed subgingivally also represent a valuable adjunctive therapy for patients with chronic moderate periodontitis (5 to 8 mm) who have bleeding on probing. Locally delivered drugs can be used at the time of SRP or when the posttreatment evaluation indicates that the patient has not responded to mechanical therapy. A recent comprehensive meta-analysis demonstrated a statistically significant improvement in probing depth reduction and clinical attachment gain when these products were used as adjuncts to SRP.[45]

In some patients, adjunctive systemic agents will be indicated. In patients with aggressive forms of periodontitis and those who do not respond to mechanical therapy alone, adjunctive systemic agents may be indicated and should be considered as a viable therapeutic intervention.[44] Host response modulation using protease and inflammatory inhibitors may become widely accepted in the future as an adjunct to periodontal therapy. Furthermore, periodontal risk factor modification such as smoking cessation and simpler measures such as oral hygiene advice and motivation will continue to be crucial in the comprehensive treatment of periodontitis.

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