Localized Therapy with Controlled-Release Antimicrobials

**Faculty**

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Dr. Frey retired from the United States Army Dental Corps in 1989 after 22 years of service. Throughout the course of his professional career, he has continuously practiced dentistry, the first 7 years as a general dentist and the past more than 30 as a periodontist. His military experience included the command of a networked Dental Activity consisting of five dental clinics. In his last assignment, he was in charge of a 38-chair facility. Colonel Frey was selected by the Army to serve on two separate occasions as the Chair of the Periodontal Department in Army General Dentistry Residency Training Programs.

Dr. Frey currently maintains a practice limited to Periodontics in Jackson, California, and is the founder and president of Perio Plus, a practice management firm specializing in creating individually-designed hygiene and periodontal care programs for general dentists. He is also the creator of the Inspector Gum patient education series.

**Faculty Disclosure**

Contributing faculty, William E. Frey, DDS, MS, FICD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

**Audience**

This course is designed for dentists, dental hygienists, and dental assistants involved in the treatment and care of patients in need of localized therapy with controlled-release antimicrobials.

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**Course Objective**
The purpose of this course is to familiarize dentists and their staff with site-specific therapy utilizing controlled-release antimicrobials and assist them in developing a protocol for clinical utilization.

**Learning Objectives**
Upon completion of this course, you should be able to:

1. Describe the microbiologic etiology of periodontal disease.
2. Outline the diagnostic criteria and techniques used to identify periodontal disease.
3. Discuss the role of biofilms in the development of periodontal disease and their impact on treatment.
4. Explain the role of gingival crevicular fluid in the use of locally applied agents.
5. Compare available antimicrobial agents, the pharmacokinetics of their activity and delivery, and their handling characteristics.
6. Assess appropriate utilization of agents in a variety of clinical situations.
7. Establish a clinical protocol for agent use.
INTRODUCTION

MICROBIOLOGIC ETIOLOGY

Periodontal disease is one of the world’s most prevalent chronic diseases. It is estimated that up to 50% of adult Americans manifest some aspect of the disease’s presence [1]. Periodontitis is a multifactorial infection with complex and interconnected mechanisms of pathogenesis [2]. The interplay between bacteria within the sulcus and periodontal pocket and the response they elicit in the host defense mechanisms, which in turn can be modified by genetic and acquired risk factors, produces the prospects of a large number of possible permutations of how the disease might present clinically and how it might progress [3; 4]. Bacteria have long been established as the etiologic agents [5]. More than 700 species of aerobic and anaerobic bacteria have been identified in the oral cavity [6]. Only a few, however, have been associated with the connective tissue dissolution, apical migration of the epithelial attachment, and alveolar bone loss that characterize the disease process [7].

Bacteria and other micro-organisms establish themselves in the environment of the periodontal pocket through a complex, sequential colonization, interacting with each other in a variety of ways [6]. The presence and growth of some species may assist others in colonization. For example, among the first bacteria to populate a site and establish themselves are gram-positive, aerobic streptococci. As they proliferate, more and more oxygen is consumed, eventually producing conditions where anaerobic species can establish themselves. Conversely, some species are directly antagonistic to the colonization of others, often competing for similar nutritional and growth factors. Thus, each of the 700 or more bacterial species has its own specific environmental and nutritional requirements, some of which may be in competition with other species also attempting to establish colonies, and some of which may assist others in colonization [8].

Once established, this complex combination of interacting species, bathed in the contents of the gingival crevicular fluid (GCF) and impacted by the mechanisms of the host’s defense, accounts in part for the variability of disease manifestation from tooth to tooth and from site to site on the same tooth. On the same tooth surface within the periodontal pocket, different combinations and relative proportions of bacteria within the plaques can be present. Each combination has the potential to produce a different response from the host in a broad range from slight to significant. These responses may lead to varying magnitudes and degrees of tissue destruction. This may result in localized or generalized destruction, producing either an aggressive and rapid loss or a more chronic problem [4].

In general, chronic adult periodontitis may be defined as a mixed anaerobic infection where the overgrowth of potential pathogens is influenced by local factors within the bacterial community and the impact of host defense mechanisms elaborated within the pocket. Some of the most commonly implicated micro-organisms associated with periodontal destruction are Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, and Actinobacillus actinomycetemcomitans [6; 9; 10]. This group of micro-organisms has been shown to be strongly associated with the progression of the disease as measured by clinical assessment parameters. It is now apparent that even within a given pathogenic species, only certain subsets or clonal types may be pathogenic. It is postulated that these pathogenic microorganisms produce tissue destruction through the release of virulence factors that induce the elaboration of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1B) and tumor necrosis factor-alpha (TNF-a). These agents bind to fibroblast receptor sites, inducing the secretion of prostaglandins (PGE), culminating in the release of matrix metalloproteinases (MMPs) that degrade connective tissue and cause bone resorption, producing the clinical manifestations of pocket depth, bone loss, and bleeding on probing [10; 11].
Association with Systemic Conditions

Epidemiologic and experimental evidence points to the possible interaction between periodontal and systemic health. A number of medical conditions, including myocardial infarction, stroke, diabetes, and the birth of premature low weight infants, have been linked with the presence of advanced periodontal disease [12; 13; 14; 15; 16]. The basis of this potential relationship is that the periodontal pocket environment provides a prospective “two-way street” for bacterial products and the cytokines they induce the host tissue to produce to influence the patient’s systemic health. Once bacterial colonies have established themselves in the periodontal pocket, bacteremia can result from many activities, such as chewing or tooth-brushing, as well as from the circumstances produced by dental treatment, which are familiar to dental practitioners. The periodontal pocket environment provides a potential open door to the rest of the body. Conversely, it has also been long established that certain systemic conditions and influences, such as diabetes and smoking, place the patient at an increased risk for periodontal disease progression [17; 18]. With an increasing appreciation of the “two-way street” nature of this periodontal-systemic connection and its underlying mechanisms comes an enhanced realization of the importance of developing and implementing effective strategies for dealing with the microorganisms involved and for effective treatment of periodontal disease.

ANTIMICROBIAL THERAPY

Traditional approaches to periodontal therapy, whether surgical or nonsurgical (i.e., scaling and root planing [SRP]), have been shown to significantly reduce the bacterial population in treated sites without the use of supplemental antimicrobial agents. In an attempt to enhance the effect due to mechanical therapy, antibiotics such as penicillin, members of the tetracycline family, and metronidazole have all been given systemically. The members of the tetracycline family (e.g., tetracycline, doxycycline, minocycline) are good candidates for use as these drugs concentrate in the GCF by a factor of four to eight, depending on the agent employed. Thus, every systemic application of a member of the tetracycline family will produce a topical application of the agent within the periodontal pocket in a concentration several times greater than that produced in the serum. Clinical studies have failed, however, to demonstrate any significant benefit of the routine use of systemic antibiotics alone or in combination with mechanical therapy over mechanical therapy alone for patients diagnosed with adult periodontitis [19; 20; 21; 85]. The use of supplemental systemic antibiotics seems indicated, however, in the treatment of patients diagnosed with aggressive manifestations of periodontal disease, such as those associated with juvenile and refractory periodontitis [22; 86].

The decision to use systemic antibiotics also has a number of factors that may adversely affect treatment outcomes for the clinician to consider. Factors such as the development of resistant strains of microorganisms both within the periodontal pocket and systemically, the interaction of these drugs with other medications that the patient may be taking, side effects of the drug, and patient compliance all have the potential to impact therapeutic outcome and should be considered before employing systemic antibiotics [23; 86]. In an attempt to circumvent the potential for adverse responses, these antibiotics have been applied locally to the
periodontal pocket through topical application and irrigation. In addition, other antibacterial and chemotherapeutic agents, such as sanguinarine and the biguanides (including chlorhexidine gluconate), have been locally applied in an attempt to enhance therapeutic results.

When agents are locally applied, the problem is in getting the agent to the site of activity in sufficient concentration to have an effect on the pathogenic micro-organisms present and then keeping it there for a long enough period of time to permit the agent to have optimal impact. Very few agents are substantive enough to remain within the periodontal pocket for more than just a few minutes. Few, if any, are potent enough to have more than a transient effect. Only chlorhexidine gluconate, stannous fluoride, and members of the tetracycline family have been shown to be present for any significant period of time after application. It soon became evident in developing a strategy for the local application of antimicrobials that there was a need for agents to be used after initial periodontal therapeutics were completed in an otherwise controlled patient in order to treat remaining isolated sites of persistent disease activity that did not satisfactorily respond to initial therapy or to enhance and stabilize these outcomes, particularly in those patients who are not good candidates for surgical therapy. Controlled-release antimicrobials were developed as a response to meet this need [24].

DIAGNOSTIC CRITERIA

The formation of the periodontal pocket, characteristic of periodontal disease, is the direct result of connective tissue destruction of the periodontal ligament fibers. In health, these fibers insert into the root surface at the cemento-enamel junction and apically. Dissolution of these fibers from their root surface attachment permits the apical migration of epithelial cells onto the root surface and the subsequent exposure of the root surface to bacterial colonization and the contents of the developing periodontal pocket [25]. The amount of periodontal destruction, defined in terms of connective tissue loss and root surface exposure, can thus be calculated as a clinical attachment loss (CAL) measured from the cemento-enamel junction. In areas of hyperplasia, sulcular depth may be greater than the customarily accepted norm of 1–3 mm, but until connective tissue fibers are dissolved and the root surface is exposed, periodontal disease is not present. This affects the clinician's choice of therapeutic measures to employ once a diagnosis has been made. A 7-mm sulcular depth on the distal of a second molar may be completely hyperplastic with no connective tissue dissolution present, no root exposed, and no periodontal disease present. The enamel surface may be scaled, but it is not feasible to root plane when no root is exposed to treat. Concurrent with the dissolution of connective tissue attachment on the root surface, the alveolar bone may also be resorbed.

Disease progression, once thought to be a steady ongoing process, has now been established to be variable and episodic [26]. Disease progression is characterized by periods of quiescence and spurts of activity. Diagnostic criteria include [26; 27; 28; 29]:

- Clinical signs of inflammation (e.g., redness, tissue edema)
- Gingival bleeding upon probing
- Probing depth
- Furcation involvement (based upon radiographic evidence)
- Tooth mobility
- Clinical attachment loss
- Medical and dental histories
- Periodontal risk factors (e.g., age, gender, medications, smoking, systemic disease, oral hygiene)
- Other clinical signs and symptoms (e.g., pain, ulceration, plaque, and calculus)
A classification system for periodontal diseases has existed for decades. The first system was established in 1977 and included only two categories of disease; however, as research and clinical practice continues to advance, the classification system continues to be refined. Although newer systems were developed in 1986 and 1989, a reclassification of plaque-induced periodontal diseases was developed in 1999 at the International Workshop for Classification of Periodontal Diseases and Conditions (Table 1). This classification system is separate from the case types recommended by the American Academy of Periodontology (AAP) for third-party insurance payments, which will be discussed later in this course [27; 30].

### USE OF RADIOGRAPHS (X-RAYS)

The two most common means by which periodontal disease is measured are through the use of radiographs (x-rays) and periodontal probing measurements. X-rays are helpful to reveal the presence of alveolar bone loss but have been shown to greatly underestimate the degree of loss [27]. The presence of an interdental crater, for instance, would not been seen on an x-ray. Given a specific time when the disease is actively destroying alveolar bone, it may often take up to six months for the destruction to become evident radiographically. X-rays also do not show the presence of a periodontal pocket [31].
VARIABILITY OF PROBE LOCATION

Periodontal pocket depth measurements are made by carefully placing a periodontal probe into the sulcular area and determining the distance, in millimeters, from the height of the gingiva to where the probe comes to rest at the base of the sulcus or periodontal pocket. Where the probe ends with relation to the tooth surface and to the epithelial attachment is variable. The probe does not, in most instances, stop at the base of the sulcus, even in health, but will penetrate to some extent into the epithelial attachment. What restricts the probe from going further into the epithelial attachment is the health of the supporting, underlying connective tissue. As inflammation increases in the connective tissue, its integrity and ability to support the overlying degenerating epithelium and resist the penetration of the probe lessens and the probe penetrates to reach the connective tissue attachment at the base of the sulcus. When the probe reaches the connective tissue, the clinical sign of bleeding is produced. As there is no blood supply within epithelium, when the clinician produces bleeding upon probing, the connective tissue has been contacted. Depending upon the force used in the placement of the probe and the degree of inflammation present, the probe may penetrate into the underlying connective tissue. Thus, a patient who undergoes a periodontal pocket depth examination when the tissues are inflamed will give a pocket depth reading based on the presence of the periodontal probe within the connective tissue. With reduction in the degree of inflammation in the connective tissue and return to health of the epithelial attachment, the probe, given the same amount of force applied, will not penetrate to the previous depth but will stop somewhere within the newly formed epithelial attachment. The difference between these two levels may be as much as 2 mm. This does not mean that there is a gain of 2 mm in attachment, but rather it is a reflection of the variability of how far the probe penetrates as determined by the relative health of the underlying connective tissue [32; 33].

RESEARCH IN THE DIAGNOSIS OF PERIODONTAL DISEASE

Although periodontal probing and x-rays have been the main tools for diagnosing periodontitis for several decades, new technology is being developed in this area. Realizing the potential of technology using oral fluid-based diagnostics, the National Institute of Dental and Craniofacial Research (NIDCR) announced an initiative for the advancement of these technologies in 2002 [34]. Saliva carries the same diagnostic potential as blood; however, the concentrations of microorganisms are 1,000 to 10,000 times lower. In the past, technology did not have the sensitivity to detect these low concentrations [35]. The NIDCR’s initiative resulted in the development of the Integrated Microfluidic Platform for Oral Diagnostics (IMPOD), a portable device that may be used at the point of care and offers accurate results in 20 minutes or less [35; 36; 37]. Researchers have found the IMPOD can accurately measure concentrations of MMP [38; 39; 87]. This technology also has the ability to measure disease progression. While this technology is still being tested, benefits include [35; 37; 40; 41; 42; 87]:

- Simple collection
- Cost-effectiveness
- Efficiency
- Accuracy
- Future diagnostic potential

Other saliva diagnostic products include My PerioID, which detects type and concentration of specific bacteria that cause periodontal disease; My PerioPath, which tests for genetic susceptibility to periodontal disease; and Electronic Taste Chips, which identifies multiple biomarkers for periodontal disease, including CRP [57].
PHARMACOKINETICS

IRRIGATION
There are a number of pharmacokinetic parameters that should be appreciated and understood before using locally-applied antimicrobials. There are several targets within the periodontal pocket to which antimicrobial agents are directed. These include micro-organisms residing within the soft tissue walls of the pocket; for example, A. actinomyctemcomitans has been shown to invade the connective tissue, and P. gingivalis may invade the epithelium [43]. Experimental evidence has suggested that many forms of local delivery, such as through the use of an antibacterial agent in an oral rinse and applied through an irrigating device, may not reach the intended targets [6]. Irrigants have been shown to reach a maximum of 4–5 mm into the periodontal pocket [44]. Even when a patient is facile enough to employ a cannula and insert it into the sulcular area, thereby accessing the deeper portions of the pocket, merely gaining access to these boundaries does not necessarily mean that the agent has reached the targeted bacteria [24; 45].

BIOFILMS
Subgingival bacterial plaque behaves as a biofilm. Consisting of bacterial communities that exist in a self-produced, hydrated polymeric matrix, biofilm attaches to both living and nonliving surfaces. The bacteria that are present within the biofilm are organized into a community that is resistant to host defenses and antibiotics and may impair the diffusion of or inactivate pharmacologic agents [6; 46]. In order for an agent to have an effective action on the bacteria within the biofilm, it must meet all three pharmacokinetic parameters [47]:

- Delivery: It must reach the target site.
- Concentration: It must be adequate, not only exceeding the minimum inhibitory concentration (MIC) for the targeted pathogens, but sufficient to penetrate the biofilm.
- Duration: It must stay in the area for a sufficient time to affect the target.

The duration of exposure is dependent upon the mechanisms by which the antimicrobial agent inhibits or destroys the target bacteria in addition to the relative potency of the agent. For example, chlorhexidine gluconate kills micro-organisms by compromising the integrity of the cell membranes and requires a shorter exposure time than bacteriostatic agents, such as the members of the tetracycline family, whose action impedes protein synthesis within the bacterial cell.

GINGIVAL CREVICAL FLUID FLOW
Another factor to consider when placing antimicrobial agents within the periodontal pocket is the clearance of the area through the action of the GCF. GCF is an altered serum transudate found in the gingival sulcus and is a result of mechanical irritation or the response to the presence of microorganisms and their products within the pocket. There is an ongoing flow of GCF when the tissue is mechanically irritated or inflamed. It has been estimated that in a 5-mm periodontal pocket, the contents of that pocket are replaced about 40 times each hour [24]. Thus, any antimicrobial agent placed subgingivally has its concentration rapidly reduced by GCF flow [24]. The estimated half-life of any pharmacologic agent placed in the periodontal pocket is about one minute. This very high rate of clearance represents a significant obstacle in producing and maintaining effective concentrations to effectively impact the bacteria within the biofilm. Because of this high rate of GCF clearance, it became evident that to prolong therapeutic duration, the use of a subgingival drug reservoir needed to be developed that could release the agent over a period of time, counteracting its continuous loss due to GCF flow.
A number of local delivery devices have been developed to provide a reservoir of the antimicrobial agent that would limit the release, providing for application over an extended period of time. The goal is to maintain a sufficient concentration of the agent in the site despite GCF clearance [48]. Local delivery devices may be categorized in two classes according to release and duration [24]:

- Sustained release (timing of release)
- Controlled release (duration of the agent)

Sustained release is defined as those formulations within a delivery device that provide for drug delivery in less than a 24-hour period. By contrast, controlled-release delivery systems allow the delivery of the drug for longer than 24 hours [24].

LOCALIZED THERAPY

The American Dental Association (ADA) has defined localized therapy with antimicrobials in the Current Dental Terminology (CDT) update. Section D4381 of the CDT procedure code nomenclature pertains to localized therapy. The CDT definition of localized therapy should be used as a starting point for the development of a practical protocol to incorporate the use of localized, antimicrobial therapy into daily clinical practice [49]:

D4381 – localized delivery of antimicrobial agents via a controlled release vehicle into diseased crevicular tissue, per tooth, by report. FDA-approved subgingival delivery devices containing antimicrobial medication(s) are inserted into periodontal pockets to suppress the pathogenic microbiota. These devices slowly release the pharmacologic agents so they can remain at the intended site of action in a therapeutic concentration for a sufficient length of time.

CONTROLLED-RELEASE ANTIMICROBIAL AGENTS

HISTORICAL DEVELOPMENT

The development of controlled-release antimicrobial agents to be delivered into localized sites was championed by Dr. J. Max Goodson in the late 1970s [50; 51]. Dr. Goodson used tetracycline in a vehicle of hollow fibers of cellulose acetate as the delivery system. In this initial delivery system, 95% of the tetracycline was released in the first few hours. Most of the early work on the drug release kinetics dealt with the delivery system used, how the release could be sustained for at least 24 hours, and how to control release beyond that period of time. Various agents, such as 20% chlorhexidine and 5% metronidazole in a gel preparation, and sanguinarine in 2.5%, 5%, and 10% gel preparations, were studied in the early 1980s. Other vehicles, such as dialysis tubing, were used as delivery systems.

As a result of decades of research and development, a number of products have been developed and marketed for use, including Actisite (no longer available in the United States), PerioChip, Atridox, and Arestin [52; 54].

Locally delivered antimicrobials allow a concentration many times that of systemic therapy [49]. A number of products designed to be locally delivered to specific sites of periodontal involvement are now available for clinical application. These products have been developed to release an antimicrobial agent within a periodontal pocket in a controlled manner for periods exceeding 24 hours. In 2002, an amendment was approved to the California Dental Practice Act (chapter 3: article 5: section 1088[d] [1]) authorizing registered dental hygienists to place these agents [53].
CHLORHEXIDINE GLUCONATE CHIP (PERIOCHIP)

Description
PerioChip is a bioabsorbable local delivery device comprised of 34% chlorhexidine gluconate in a cross-linked hydrolyzed gelatin matrix. Each chip is 5 mm by 4 mm by 0.035 mm and is impregnated with 2.5 mg of chlorhexidine. Chlorhexidine gluconate is a long-chain molecule with a positive charge that is attracted to the negatively charged surface of the biologic membranes of bacterial and epithelial cells. Chlorhexidine has a nonspecific mechanism of action against bacteria. It attaches to the cell walls, disrupting them and entering the cell. This disrupts the cytoplasm, which flows out of the ruptured cell resulting in bacterial death [54; 56].

Pharmacokinetics
In vitro studies of the release of chlorhexidine from its carrier showed that 40% of the chlorhexidine was released within 24 hours, with the remainder being released in the subsequent 7 to 10 days [55; 60]. The mean concentration for the seven-day period was 125 mcg/mL, in contrast to a level of 1,450 mcg/mL at four hours, a second peak of 1,900 mcg/mL at 72 hours, and 480 mcg/mL at three days. Studies have shown suppression of the pocket flora for up to 11 weeks following treatment with PerioChip [10].

Placement
PerioChip is placed in an isolated and dry field. The chips are shipped refrigerated and stored in a like manner. When cool, the chip is firm, but when left at room temperature for any period of time, it softens as it absorbs moisture from the air. A softened chip is more difficult to place. For placement, the chip must be grasped with cotton forceps, with the curved end of the chip directed apically and gently placed into the periodontal pocket, to the depth of the pocket. It is reported to be self-retentive and to biodegrade over the subsequent 7- to 10-day period [55; 56].

As mentioned, PerioChip is biodegradable and, therefore, suitable for placement by hygienists in California. Its design makes placement somewhat difficult in some interdental areas and involved furcation areas. Placing a 5-mm chip into a 5-mm pocket places the outer edge of the chip even with the gingival margin. When multiple sites are employed, multiple chips must be employed. Clinicians have reported some difficulty with the retention of the chip once placed. Patients have reported some minor irritation with the chip’s presence [55].

Clinical Studies
Two large-scale, randomized multicenter trials have assessed the efficacy of PerioChip in combination with SRP procedures versus SRP alone. One investigation employed 118 patients in a split mouth design and utilized pocket depths in the maxillary arch that were greater than or equal to 5 mm [61]. The investigation took place over a six-month period, with baseline application of PerioChip and a repeat application at each three-month visit if pockets in the test group remained greater than or equal to 5 mm. Final results showed pocket depth changes for all sites to be significantly improved for the SRP and PerioChip group at a level of 1.16 mm versus 0.7 mm for SRP alone. Of the improved sites, 35.4% exhibited 2 mm or more improvement with PerioChip versus 21.3% for SRP alone. For pocket depths greater than or equal to 7 mm, the improvement was 1.77 mm for the PerioChip plus SRP versus 1.05 mm for SRP alone. The percentage of sites improving 2 mm or more was 49.5% versus 32.1%.

The second study also pooled data from several centers [58]. It involved 447 patients in an assessment over a nine-month period. Selected pockets were from 5–8 mm. All of the patients were treated with full mouth SRP in a one-hour time frame. PerioChip was applied in the experimental design at baseline and at three- and six-month re-evaluation times if the pocket depth was 5 mm or
greater. The results indicated a significant improvement of pocket depth reduction in the PerioChip plus SRP study group of 0.95 mm versus 0.65 mm for the SRP control and 0.69 mm for the placebo chip plus SRP. Sites with probing depth improvement greater than or equal to 2 mm was 19.1% for the PerioChip group and 8.0% for the SRP only treated sites.

Subsequent studies have indicated that further research should be conducted to validate the benefit of the chlorhexidine chip as an adjunct to SRP [62; 63; 88].

**DOXYCYCLINE PERIODONTAL GEL (ATRIDOX)**

**Description**

Atridox is a biodegradable formulation for subgingival controlled release containing 10% by weight of doxycycline hyclate and a vehicle, each in a separate plastic syringe. One syringe contains 42.5 mg of doxycycline; the other contains 450 mg of the ATRIGEL Delivery System, a flowable polymeric formulation that is a combination of 36.7% poly-DL-lactide (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). The contents of the two syringes are mixed. Upon contact with oral fluids, the product becomes less fluid and eventually solidifies, permitting controlled release of doxycycline for seven days [64].

Doxycycline is a broad-spectrum, semisynthetic tetracycline that is bacteriostatic through inhibition of bacteria protein synthesis due to disruption of transfer ribonucleic acid (RNA) and messenger RNA at ribosomal sites. In vitro testing has indicated that several of the periodontal pathogens, including *P. gingivalis* and *Fusobacterium nucleatum*, are susceptible to doxycycline at concentrations of 6 mcg/mL [64].

**Pharmacokinetics**

In a clinical pharmacokinetic study, doxycycline release characteristics in GCF, saliva, and serum were evaluated for oral dosage and subgingival placement of Atridox [55; 65]. Following placement of Atridox, doxycycline levels in GCF peaked at 1,500 mcg/mL two hours following placement. Levels remained greater than 1,000 mcg through 18 hours. Through day 7, the concentration of doxycycline remained well above the MIC for periodontal pathogens. Serum levels never exceeded 0.1 mcg/mL. In contrast, subjects receiving oral doxycycline had GCF levels peak at 2.5 mcg/mL at 12 hours. There was a high degree of variability reported for both groups.

**Placement**

When preparing Atridox, the two syringes are screwed together and the contents of one syringe are alternately mixed into the opposite syringe for a recommended 100 cycles. At the end of the last cycle, the product is placed into the syringe with the violet band and a blunt cannula is screwed to the tip of the syringe. The constituted product is now a yellow viscous liquid with a concentration of 10% doxycycline hyclate with an equivalence of 42.5 mg. The blunt cannula is directed to the depth of the periodontal pocket and the material is extruded to loosely fill the defect. Upon withdrawal of the cannula, it may be necessary to guide any remaining extruding product back into the periodontal pocket [64].

Atridox can be difficult to administer. Due to its viscosity, it tends to stick to the placement cannula and to instruments. Various methods, including the use of petroleum jelly as a lubricant on the cannula, have been suggested. Another method to employ is to distribute the product at the gingival margin in whatever quantity is desired. By doing this, one can utilize the contents of the syringe for multiple applications and have better control over the amount of agent placed at each site.
Once the agent is present at the gingival margin, it is either allowed to come in contact with oral fluids or water is applied. As it gains viscosity, the product becomes easier to manipulate. A placement instrument, such as a moistened retraction cord plugger or the back side of a curette, may be employed to direct the product into the periodontal pocket. Due to the very high concentrations of antibiotic release, it is not necessary to completely fill the defect. This also assists in the retention of the material. In addition, some clinicians will apply a cyanoacrylate adhesive or utilize a Coe Pak dressing to assist in the retention of the agent for the therapeutic time interval [64]. The product is bioreabsorbable and, therefore, suitable for placement by dental hygienists in the state of California.

Clinical Studies
Several multicenter studies evaluated and compared Atridox to placebo control using the vehicle only, oral hygiene, or SRP alone [66]. Four hundred and eleven patients were evaluated in each study. Each patient demonstrated moderate-to-severe periodontitis with at least two or more quadrants, each with a minimum of four qualifying pockets of 5 mm or greater pocket depth that bled on probing. At least two of the pockets were to be 7 mm or greater. Treatment was provided at baseline and again at four months. Clinical parameters were recorded monthly. Patients received one of the four options in both quadrants. Note that this study evaluated the use of Atridox as a monotherapy (for which it is approved) in contrast to SRP, not in combination with SRP. These clinical trials took place over nine months and involved 19 university dental centers; the data was combined from these centers.

The results indicated that treatment with Atridox and SRP resulted in nearly identical clinical changes over time in both study groups. Mean nine-month clinical attachment gain was 0.8 mm for the Atridox group and 0.7 mm for the SRP group in study 1, and 0.8 mm and 0.9 mm, respectively, in study 2. Mean probing depth reductions were 1.1 mm for the Atridox group and 0.9 mm for the SRP group in study 1. Study 2 showed reductions of 1.3 mm for both groups. In all instances, treatment with Atridox and SRP were shown to be statistically superior to the vehicle control and oral hygiene groups.

Another study investigated the effect of locally-delivered, controlled-release doxycycline on periodontal patients undergoing supportive periodontal therapy or periodontal maintenance procedures and contrasted its use with SRP [67]. One hundred and forty-one patients received Atridox or SRP in all sites that were 5 mm or greater on one-half of their dentition at baseline and at the four-month interval. Clinical results were determined at the nine-month interval. Comparison of baseline measurements for pocket depth recordings versus measurements at the nine-month interval showed similarities between the two groups. Reduction for Atridox was 1.3 mm and for SRP 1.1 mm. Similar results for attachment gain were achieved, with Atridox showing 0.7 mm and SRP 0.8 mm. Equivalency was also noted for those sites, showing 2 mm or greater probing depth reduction. When treated sites were compared to untreated sites with respect to attachment loss during the course of the study, 7.2% of the Atridox group showed a difference in disease activity, 2 mm or more of attachment loss, versus 19.3% of the untreated group. The results for the SRP group were 8.1% for the treated and 14.4% for the untreated.

In one study that evaluated the effect of Atridox on microflora, 45 subjects with adult periodontitis were treated with a single treatment of Atridox [68]. Concentration remained at least 100 times above MIC for periodontal pathogens through day 7, with effective penetration of the biofilm reported. Levels of aerobic and anaerobic bacteria were significantly reduced. All post-treatment samples showed statistically significant differences in the total cultivable anaerobic counts recovered for the Atridox-treated group relative to baseline over the six-month treatment. During these studies no overgrowth of drug-resistant organisms was observed.
MINOCYCLINE HYDROCHLORIDE PERIODONTAL MICROSPHERES (ARESTIN)

Description
Arestin is a controlled-release product containing the antibiotic, minocycline hydrochloride, in a bioresorbable polymer, poly (glycolide-co-D,L-lactide) or PGLA. Minocycline is a member of the tetracycline class of antibiotics and has a broad spectrum of activity. Similar to the other members of the class, it is bacteriostatic and exerts its antibacterial effect by inhibiting protein synthesis. In vitro susceptibility testing yielded results similar to other members of the class, showing activity against organisms such as *P. gingivalis*, *Prevotella intermedia*, *F. nucleatum*, *Eikenella corrodens*, and *A. actinomycetemcomitans* [55].

Each unit dose cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline. The agent is provided in a bioadhesive, bioresorbable polymer (PGLA) produced in a microencapsulation process [55]. Once inserted into the periodontal pocket, these microspheres adhere to the walls of the pocket. GCF hydrolyzes the polymer, causing water-filled channels to form inside the microspheres. These areas provide for the encapsulated antibiotic to be released.

Pharmacokinetics
Over a two-week period, the minocycline diffuses from the microspheres as they are hydrolyzed. At day 14, a level of 340 mcg/mL has still been found in the pocket. Eventually the microspheres themselves are completely fragmented and bioresorbed [69].

Placement
Arestin is a single-site placement agent providing 1 mg of antibiotic per site. The agent is provided in single-use dosages with a syringe. The unit dosage is applied to the syringe, the cannula placed into the periodontal pocket, and the agent dispersed into the site. The manufacturer does not recommend any means of further retention of the product. The product does not have to be refrigerated. A requirement for application in several sites would necessitate several unit dosages [55; 69].

Clinical Studies
Seven hundred and forty-eight patients with moderate-to-advanced periodontitis were studied in a multicenter trial comparing SRP alone, SRP plus the vehicle, and SRP plus Arestin [70]. The primary outcome measure was probing depth reduction, which was determined at nine months. Clinical assessments were performed at baseline and at one, three, six, and nine months. To qualify for the study, patients were required to have four teeth with probing depths of 6–9 mm that bled upon probing. Treatment was administered to all sites of probing depths of 5 mm or greater. Retreatment occurred at three and six months after initial
treatment to sites that continued to exhibit the qualifying criteria of 5 mm or greater depth and also any new site that appeared with a pocket depth of 5 mm or greater.

The results indicated a statistically significant difference from the first month throughout the trial for Arestin plus SRP versus SRP alone. In the first of the two studies, SRP alone produced pocket depth reduction in the nine-month period of 1.04 mm, SRP plus vehicle 0.90 mm, and SPR plus Arestin 1.20 mm. In the second study, the results were 1.32 mm for SRP alone, 1.32 mm for SRP plus vehicle, and 1.63 mm for SPR plus Arestin.

Arestin has the clinical advantage of ease of application. One drawback is that it is a single-use product. In contrast to Atridox, Arestin has 1 mg of antibiotic in its single-use dosage. Atridox contains 42.5 mg of doxycycline and may be used for multiple sites with the same unit provided.

## MAKING A CHOICE

### ADJUNCTIVE THERAPY OR MONOTHERAPY?

There are a number of variables to consider when making a choice of which available product to employ when establishing a protocol for the use of locally-delivered, controlled-release agents. The first of these is U.S. Food and Drug Administration (FDA) approval. Actisite, Arestin, and PerioChip have been approved by the FDA for use in conjunction with SRP, although, as previously mentioned, Actisite is no longer produced by the manufacturer. Atridox has been approved as a monotherapy and has demonstrated improvements in probing depth and attachment loss at nine months that were equivalent to SRP alone [10]. Many studies have additionally shown that the adjunctive use of Atridox in combination with SRP shows significant clinical improvement in pocket depth reduction, clinical attachment gains, and bleeding upon probing [71]. For all of the antimicrobials discussed, adjunctive therapy is recommended over monotherapy for patients with chronic periodontitis [10; 72; 73; 74; 75].

### EFFICACY

An overview of the pharmacokinetics concludes that all of the products available provide concentration of the active antimicrobial agent at levels in excess of the MICs for periodontal pathogens. Their efficacy in the clinical studies also is very similar in terms of pocket depth reduction. Some studies have not addressed gain of clinical attachment [70]. Others have indicated that the gains are small and statistically insignificant [76]. When microbiologic data is present, it reveals that even with high concentrations of agents maintained over a period of time, the agents are not completely capable of eliminating all pathogens from treated sites.

### HANDLING CHARACTERISTICS

Another consideration is the agent’s handling characteristics. The methodology in the application of Arestin makes this product superior to the others. The simplicity of placement of the cannula and a short and swift injecting movement, placing the product into the pocket area, is superior to the less efficient and labor-intensive placement of PerioChip or Atridox.

### CLINICAL CONSIDERATIONS

There are other factors that may impact a clinician’s decision as to which product to use that are more in the line of practice management and cost considerations. These factors will be discussed in the Practice Management section of this course.

Many clinicians developing a rationale and strategy for the use of these agents look at the treatment of multiple sites as being an essential requirement. Their intent is not only to treat sites exhibiting advancing disease but also to reduce and eliminate possible reservoirs of pathogens that may be present in other areas in the mouth. Some clinicians speculate that there is an advantage in disrupting
the biofilm through SRP to permit penetration of the active agent to the micro-organisms. Other clinical considerations may include the time and duration of therapy, ease of use, cost, side effects, and patient acceptability [77].

COMPARING CLINICAL STUDIES
All of the agents described in this course have demonstrated through clinical studies a statistically significant difference when used in conjunction with SRP or, in the case of Atridox, equivalency to SRP when used as monotherapy. However, the use of a given agent may result in a statistically significant result that may or may not have significant clinical impact. Statistical significance only validates a difference between the tested groups to a certain level of probability. It does not indicate the magnitude of clinical change or the importance of the difference in resolving clinical problems [77; 78].

SUMMARY
Making a choice first centers on the clinician’s desire to possibly use the agent as a monotherapy or to only use it in conjunction with SRP. The second consideration is the agent’s handling characteristics and whether the agent is to be applied to multiple sites at one time. In developing the protocol, the recommendation is to select those sites that are resistant to conventional therapy after initial therapy has been accomplished or for those sites that the clinician can anticipate will be less likely to respond to conventional therapy [75; 79].

Though SRP continues to be the standard nonsurgical approach to periodontal therapy, the AAP has recommended that clinicians consider the adjunctive use of locally-delivered antimicrobials in cases of chronic periodontitis [6; 72]. Additionally, two separate trials indicated that the application of minocycline microspheres enhanced the effects of surgery in patients for whom surgery was indicated [84; 90].

PRACTICE MANAGEMENT

PRACTICE PHILOSOPHY
The first subject to consider before structuring treatment protocols is the necessity for a basic change in practice philosophy. That is, the perspective for treatment of any given patient should be altered from restorative to periodontal. Typically, in a practice providing general dentistry, the perspective is for short-term benefit. General dentistry provides restorative solutions that are lasting and require follow-up that is not as critical as that required for periodontal therapy. If the practice is to institute a program of periodontal therapy, incorporating the utilization of site-specific agents, then the entire practice’s attitude toward treatment should shift to the long-term [28]. This requires informing patients of the necessity for more frequent visits and the requirement for monitoring and maintenance of gains achieved through initial therapy. After patients are diagnosed with periodontal disease, the recurrence of the disease process and its multifactorial complexity requires that the patient understands that [79; 80):

- The disease has a bacterial etiology.
- They have demonstrated a susceptibility to the disease.
- The disease is recurrent and requires ongoing care.
- The disease has the potential for significant influence on several aspects of systemic well-being.

PRODUCT COST BASIS
The last consideration before a protocol can be put together is that of cost:

- What will be your fee for D4381?
- Will this fee be for each site or for multiple sites?
- If it is for multiple sites and your fee selected is $100, will you charge $500 for five sites?
The cost of the agents also enters into this consideration. The unit dose packaging of both PerioChip and Arestin is far less expensive than that of Atridox and appears to be the differentiator in the selection of PerioChip or Arestin over Atridox. However, consider that for the smaller cost of Arestin, the clinician will receive 1 mg of antibiotic, and for the larger cost of Atridox, the clinician will receive 42.5 mg of antibiotic. The cost per mg of antibiotic utilized is less for the use of Atridox than for Arestin. If multiple sites are to be treated at one time, or if monotherapy is to be used, then Atridox is the product of choice. Using Atridox also permits the clinician to treat multiple sites with the same syringe, stabilizing the unit cost and regulating the fee based on the unit cost of the material. In contrast, multiple uses of Arestin or PerioChip would necessitate establishing a fixed fee for each site where the agent is applied. Many practices employ a fee schedule for Atridox, based upon a set fee for three or four sites, and then increase that fee by small increments per each additional site until the entire syringe contents have been used. Clinical use of Atridox has shown that the agent may be applied in more than 10 sites per syringe of Atridox.

The bottom line is to consult with the manufacturer’s representatives, conclude whether monotherapy is to be part of the clinical protocol, establish a fee based on single or multiple applications, and conclude what the cost basis would be in the treatment versus single or multiple sites. When multiple sites are present, the clinician should also consider the cost of these agents versus systemic utilization of an antibiotic. If the patient is allergic to the tetracycline family, the choice becomes obvious. Practitioners in California should select an agent that is biodegradable.

**INITIAL THERAPY PROTOCOL**

When establishing or revising a clinical protocol for nonsurgical periodontal therapy, practitioners should start with diagnosis, beginning with the Case Type categorization previously described by the AAP. Case Type categories describe the severity of the disease involvement (Table 2).

Beginning involvement is defined as Case Type I. Established, or cul-de-sac, is defined as Case Type II. Case Type III is considered through-and-through. Once the Case Type of a patient’s involvement is determined, the appropriate treatment may then be decided. Appropriate treatment for Case Type II is SRP as initial therapy [70; 75]. The majority of clinicians are able to accomplish successful therapy for patients with 4–5 mm pocketing and no furcation involvement without the necessity of supplementing their therapy with either controlled-release antimicrobials or agents that modify the host response. An exception to this could be made for those that have systemic circumstances that may adversely impact results. These conditions include smoking and diabetes [75]. There is also a physical limitation to the placement of these agents in pocketing that is 5 mm or less. The size of the PerioChip stands 5 mm when placed. The amount of Atridox that can be

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*Table 2*

<table>
<thead>
<tr>
<th>Type</th>
<th>Classification</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Type I</td>
<td>Gingivitis</td>
<td>—</td>
</tr>
<tr>
<td>Case Type II</td>
<td>Slight periodontitis</td>
<td>4–5 mm pocketing; no furcation involvement</td>
</tr>
<tr>
<td>Case Type III</td>
<td>Moderate periodontitis</td>
<td>6–7 mm pocketing; beginning furcation involvement</td>
</tr>
<tr>
<td>Case Type IV</td>
<td>Severe or advanced periodontitis</td>
<td>&gt;7 mm pocketing; established furcation involvement</td>
</tr>
</tbody>
</table>

*Source: [27]*
incorporated and maintained within a 5-mm defect is small, as is the retention of Arestin in the same area [54; 56; 64]. Recommended therapy for Class II patients without systemic influences is to perform initial therapy of SRP procedures and, at the 30-day re-evaluation time, consider retreatment with the addition of site-specific agents in combination with SRP or as monotherapy [28; 75].

For Case Type III patients, the judgment is less clear. Defined as 6–7 mm pocketing, the initial treatment for Class III patients is SRP procedures, a re-assessment, and surgical therapy where appropriate [75]. These patients would benefit greatly from the adjunctive use of localized antibiotic therapy and host modulation therapy using Periostat. Depending on the number of sites involved and the working relationship with the periodontist, a decision may be made whether to utilize controlled-release antimicrobials in conjunction with initial therapy [28; 75].

There are some circumstances in which a patient either refuses the specialty referral or is not a good surgical candidate (e.g., advanced age, chronic illness) [79]. The clinician should attempt to do everything possible within the initial therapeutic regimen to achieve the best possible result, knowing that this is the level of health to be maintained in subsequent visits. Perhaps there are defects in the maxillary anterior region, which do not lend themselves to a surgical approach. Appropriately, these would be treated with site-specific therapy at the time of initial therapy. It is also advisable that the patient be told of the likely necessity of the repeat applications of the site-specific agent in light of the recurrent nature of the disease [81].

For Case Type IV patients, the recommended initial step is referral for specialty evaluation and care [28; 74]. Case Type determinations are also useful in planning a schedule of periodontal maintenance. Case Type II patients may be cared for on a three-month basis in the general dentist’s office. Case Type IV may be likewise more appropriately cared for with a greater frequency than alternating in the periodontist’s practice, in some cases with the regimen exclusively with the periodontal staff, and a return to the general dentist for annual exams. Case Type III patients are appropriately alternated between the general dentist’s and the specialist’s offices on a three-month basis [28; 82].

In addition to the Case Type determinations that define the severity of disease involvement, recommendations by the AAP advise diagnostic conclusions in the following categories [83]. The clinician is asked to determine whether the disease is localized or generalized and whether it is aggressive or chronic. Determination is based on whether the disease is resistant to therapy. However, that determination can only be made following therapy; so, it is inappropriate to conclude at the initial examination. Diagnosis may therefore be concluded with the following: Case Type, chronic or aggressive, localized or generalized. Thus, the diagnosis might be “localized aggressive advanced periodontitis” or “generalized slight chronic periodontitis” or “generalized advanced chronic periodontitis.” This conclusion may be indicated with a simple recording system in the patient’s periodontal record (Figure 1).
MAINTENANCE PROTOCOL

It is important to develop a second protocol with regard to how to deal with individual isolated sites presenting either at initial treatment or at subsequent maintenance times. Before concluding initial treatment of an isolated site of involvement, the clinician should determine the cause of the isolated defect. Isolated defects are not only attributable to periodontal disease but also to endodontic lesions that manifest themselves through the sulcular area, fractured teeth, and developmental defects on teeth such as distal lingual grooves commonly associated with maxillary lateral incisors.

There are many individual circumstances that may require ongoing consideration for controlled-release antimicrobials during the course of the maintenance period. These include: inoperable sites distal to the lower second molars, furcation involvement where further surgical or definitive therapy is not possible, maxillary incisors where esthetics is a consideration, and areas showing advancing disease. It is absolutely essential that clinicians are very conscientious about monitoring the disease presence and activity through pocket depth readings and evaluations at each maintenance visit. The patient should be forewarned of the possible necessity for the utilization of localized agents when the need presents itself.

It is appropriate to treat the patient immediately rather than delay another three months to see if further progression occurs [28; 81]. This means that the patient must be prepared for the fee associated with periodontal maintenance procedures, which should be greater than that for a prophylaxis, and also be prepared for the additional fee of the localized therapy. If this is communicated from the initial exam through the initial therapy and at each maintenance visit, the patient is much more likely to accept and go forward with the recommended treatment.

CONCLUSION

Decades have passed since the pioneering work of Dr. J. Max Goodson in the development of controlled-release antimicrobials used in periodontal therapy. Actisite was the first and only product available for some time. Clinicians now have more than one choice of agents to employ, with possible additional choices forthcoming. Clinical studies have demonstrated that site-specific therapy does have a place in periodontal treatment. Changes to the dental practice law in the state of California have also provided an opportunity for dental hygienists to expand their scope of practice.
RESOURCES

American Academy of Periodontology
737 North Michigan Avenue, Suite 800
Chicago, IL 60611
(312) 787-5518
http://www.perio.org

American Dental Association
211 East Chicago Avenue
Chicago, IL 60611
(312) 440-2500
http://www.ada.org

Arestin
Manufactured for OraPharma, Inc.
(866) 273-7846
http://arestinprofessional.com

Atridox
Manufactured by TOLMAR, Inc.
https://www.denmat.com/Oral%20Hygiene/Antibiotic/Atridox

Dental Board of California
2005 Evergreen Street, Suite 1550
Sacramento, CA 95815
(916) 263-2300
http://www.dbc.ca.gov

National Institute of Dental
and Craniofacial Research
9000 Rockville Pike
Bethesda, MD 20892
(866) 232-4528
http://www.nidcr.nih.gov

PerioChip
Manufactured by Dexcel Pharma
(800) 737-4624
http://us.periochip.com
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