

## Position Paper

# Systemic Antibiotics in Periodontics\*

This position paper addresses the role of systemic antibiotics in the treatment of periodontal disease. Topical antibiotic therapy is not discussed here. The paper was prepared by the Research, Science and Therapy Committee of the American Academy of Periodontology. The document consists of three sections: 1) concept of antibiotic periodontal therapy; 2) efficacy of antibiotic periodontal therapy; and 3) practical aspects of antibiotic periodontal therapy. The conclusions drawn in this paper represent the position of the American Academy of Periodontology and are intended for the information of the dental profession. *J Periodontol* 2004;75:1553-1565.

The microbial etiology of inflammatory periodontal diseases provides the rationale for the use of antimicrobial medication in periodontal therapy. As evidence for bacterial specificity in periodontitis has accumulated and strengthened over the past three decades, dentists have increased their use of systemic antibiotics in periodontal therapy. This concept is based on the premise that specific microorganisms cause destructive periodontal disease and that the antibiotic agent *in vivo* can exceed concentrations necessary to kill or inhibit the pathogen(s). Antibiotics are defined in this report as naturally occurring or synthetic organic substances that in low concentrations can inhibit or kill selective microorganisms.

Antibiotics may be prescribed for periodontal patients who do not respond to conventional mechanical therapy, for patients with acute periodontal infections associated with systemic manifestations, for prophylaxis in medically compromised patients, and as an adjunct to surgical and non-surgical periodontal therapy. Antibiotic therapy for medical indications has been discussed elsewhere and will not be considered here.<sup>1,2</sup> This position paper is concerned with the use of antibiotics in the treatment of periodontitis lesions.

The concept of antibiotic periodontal therapy centers upon the pathogenic microbiota, the patient, and the drug. These issues are each addressed separately.

### PERIODONTAL PATHOGENS

The most effective use of antibiotics for the treatment of periodontitis presupposes knowledge of the pathogenic microbiota. At least 500 bacterial taxa have

been identified within periodontal pockets.<sup>3</sup> However, relatively few species have been clearly associated with progressive periodontitis (Table 1). Most putative pathogens are indigenous to the human oral cavity, but possible superinfecting organisms (enteric Gram-negative rods, pseudomonas, staphylococci, yeasts) may also inhabit periodontal pockets. Periodontitis lesions usually harbor a constellation of putative pathogens rather than a single pathogenic species.

Most putative periodontal pathogens are Gram-negative anaerobic rods. However, some pathogens are Gram-positive facultative and anaerobic cocci and rods and others are Gram-negative facultative rods. Putative periodontal pathogens vary considerably in sensitivity to several antibiotics making simplistic approaches to antimicrobial chemotherapy problematic.<sup>6</sup>

### PATIENTS

Prime candidates for systemic antibiotic therapy are patients who exhibit continuing loss of periodontal attachment despite diligent conventional mechanical periodontal therapy. Recurrent or refractory periodontitis is often related to persistent subgingival pathogens and perhaps to impaired host resistance.<sup>7</sup> Patients with aggressive types of periodontitis,<sup>8</sup> or with medical conditions predisposing to periodontitis<sup>9</sup> may benefit from antibiotic therapy. Patients with acute or severe periodontal infections (periodontal abscess, acute necrotizing gingivitis/periodontitis) may also need antibiotic therapy.<sup>10</sup> Patients with gingivitis or chronic periodontitis usually respond well to mechanical debridement and topical antiseptics and may not derive clinically significant additional benefit from antibiotic therapy.<sup>11</sup> However, evidence exists suggesting that antibiotic use in chronic periodontitis may result in improvement in clinical attachment level, although many questions regarding the indications for this therapy remain unanswered.<sup>12</sup>

\* This paper was prepared by the Research, Science and Therapy Committee and approved by the Board of Trustees of the American Academy of Periodontology in August 2004.

## DRUGS

The pharmacological characteristics of antibiotics are critical in deciding their use, dosage and routes, and frequency of administration. Important pharmacological determinants include body weight, degree of absorption, rate of metabolism, and duration of effective antimicrobial levels at the site of infection.

To maintain effective antimicrobial levels after oral administration, penicillins and clindamycin must be taken three times a day, metronidazole and ciprofloxacin twice a day, and doxycycline and azithromycin once a day (Table 2).

**Table 1.**

### Association Between Putative Periodontal Pathogens and Periodontitis\*

Very Strong	Strong	Moderate	Early Stage of Investigation
<i>Porphyromonas gingivalis</i> <i>Actinobacillus actinomycetemcomitans</i> <i>Tannerella forsythensis</i> † Spirochetes of acute necrotizing gingivitis	<i>Prevotella intermedia</i> <i>Dialister pneumosintes</i> / <i>Dialister invisus</i> <i>Eubacterium nodatum</i> <i>Treponema denticola</i>	<i>Campylobacter rectus</i> <i>Peptostreptococcus micros</i> <i>Fusobacterium nucleatum</i> <i>Selenomonas noxia</i> <i>Eikenella corrodens</i> Beta-hemolytic streptococci	Gram-negative enteric rods <i>Pseudomonas</i> species <i>Staphylococcus</i> species <i>Enterococcus faecalis</i> <i>Candida albicans</i>

\* Modified from Haffajee and Socransky<sup>4</sup> and Slots and Chen.<sup>5</sup> The list is not all-inclusive.

† Previously, *Bacteroides forsythus*.

The efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and the pharmacokinetic characteristics of the drug<sup>13</sup> and by local environmental factors<sup>14</sup> including 1) drug binding to tissues; 2) protection of pathogens through binding, consumption, or degradation of the drug by non-target microorganisms; 3) subgingival plaque biofilm protecting the pathogens; 4) total bacterial load relative to the maximum achievable antibiotic concentration; 5) effectiveness of the host defenses; and 6) pathogens

**Table 2.**

### Selected Pharmacological Features and Common Adverse Reactions of Antibiotics\*

Antibiotic	% Absorption After Oral Administration	Peak Serum Level (µg/ml)	Serum Half-Life (Hours)	Most Common Adverse Reactions (% occurrence)	Usual Daily Adult Oral Dosage (average) in Periodontics
Metronidazole	90	20-25	6-14	Nausea/vomiting: 12%	500 mg b.i.d. or t.i.d.
Clindamycin	90	5	2.4	Diarrhea: 7%	300 mg t.i.d. or q.i.d.
Penicillins (amoxicillin)	75	5-8	1.2	Hypersensitivity (rash): 5% Diarrhea: 5%	250-500 mg t.i.d.
Tetracyclines (doxycycline)	93	2-4	18	Photosensitivity (sunscreen advised)	200 mg q.d.
Azithromycin	37	0.4	12	Diarrhea: 5%	250-500 mg q.d.
Clarithromycin	50	2-3	5-7	Diarrhea: 3% Photosensitivity	500 mg b.i.d.
Fluoroquinolones (ciprofloxacin)	70	1.5	4	Nausea/vomiting: 5% Photosensitivity Risk of Achilles tendon disorders with exercise	500 mg b.i.d.

in periodontal tissues, root surfaces, and extra-dental oral sites not affected by the therapy. The unique therapeutic difficulties imposed by dental biofilms are highlighted elsewhere.<sup>15</sup>

Systemic antibiotic therapy has certain advantages over topical application of antimicrobial agents. Systemic antibiotics may enable the simple, easy administration of the drug to multiple sites of disease activity. They may also eliminate or reduce pathogens colonizing on oral mucosa and on other extra-dental sites including the tongue and tonsillar areas.<sup>16-18</sup> The possibility of markedly suppressing or eliminating periodontal pathogens from virtually the entire mouth may reduce the risk for future translocation of organisms and recolonization of the periodontal pocket, thereby potentially reducing the risk for recurrent disease progression.

Disadvantages of systemic antibiotic therapy as compared to locally applied antimicrobial agents include inability of systemic drugs to achieve high gingival crevice fluid concentration,<sup>19</sup> an increased risk of adverse drug reactions,<sup>20</sup> increased selection of multiple antibiotic resistant microorganisms,<sup>6</sup> and uncertain patient compliance.<sup>21</sup>

Combination drug therapy may be useful in periodontitis that involves a variety of periodontopathic species with differing antimicrobial susceptibilities or to overcome the drug-protective effects of the biofilm. Also, therapeutic failure with some antibiotic regimens due to the presence or development of resistant strains may be an emerging problem in periodontal treatment.<sup>6,22</sup> One strategy aimed at combating resistant subgingival bacteria is the use of treatment regimens that incorporate agents with complementary but different mechanisms of action. Combination therapy should include drugs that exhibit synergy or additive effects in vitro. Metronidazole-amoxicillin and metronidazole-ciprofloxacin act synergistically against *Actinobacillus actinomycetemcomitans* and other major periodontal pathogens.<sup>23</sup> Some antibiotics, through combination antagonism, can lead to a reduction, rather than an increase, in antimicrobial activity. Antagonism occurs, for example, between bacteriostatic tetracyclines and bactericidal  $\beta$ -lactam antibiotics.<sup>24</sup>

Table 2 lists the most common adverse reactions of antibiotics frequently used in periodontal treatment. The possibility of unique age- or physical condition-related adverse effects is an important consideration in prescribing antibiotics (Table 3). Administration of antibiotics to pregnant women is a cause for particular concern. Serious adverse reactions are fortunately rare and are described elsewhere.<sup>20</sup>

Many antibiotics may interact with other drugs and cause clinically significant effects (Table 4). Interaction occurs when one drug alters the other drug's pharmacokinetics with respect to absorption, distribution, metabolism, or excretion. Patients on long-term medication for cardiovascular disease, asthma, seizures, or diabetes are at particularly high risk for drug interactions.

### CLINICAL STUDIES

Controlled clinical trials will add to current knowledge about the effectiveness of antibiotic therapy in periodontics.<sup>26</sup> Many existing studies are difficult to interpret because of open-study designs, small sample size, short-term evaluation periods, clinically different patient groups, undetermined periodontitis disease activity, unknown baseline microbiota, varying antimicrobial regimens, and insufficient supragingival plaque control.<sup>11</sup> Since many clinical trials on antibiotic periodontal therapy have been performed in patients with little or unknown disease activity, they may have underestimated the potential value of systemic antibiotics in the treatment of progressive periodontitis.

Studies of several types of periodontitis have evaluated systemic antibiotics as an adjunct to periodontal scaling and root planing. This is in agreement with good medical practice that dictates that the bacterial load should be reduced as much as possible prior to administration of antibiotic therapy. Most study designs aim to investigate possible additional clinical and/or microbiological effects of antibiotics in comparison to a placebo medication or no medication.

Table 5 lists investigations that have evaluated the effect of antibiotic therapy in periodontitis patients. Most studies concerned with patients with disease progression suggest that properly selected systemic antibiotics may provide significant additional clinical benefit to conventional mechanical periodontal therapy, particularly in patients with recurrent or refractory periodontitis. Systemic antibiotics are particularly valuable in the treatment of aggressive periodontitis in adolescents, especially cases predominated by *Actinobacillus actinomycetemcomitans* (previously termed "localized juvenile periodontitis").<sup>48</sup>

### PRACTICAL ASPECTS OF PERIODONTAL ANTIBIOTIC THERAPY

A conservative and selective approach is recommended for periodontal antibiotic therapy. Indiscriminate antibiotic administration is contrary to sound clinical practice and may cause overgrowth of intrinsically resistant pathogens<sup>49,50</sup> or may unnecessarily

**Table 3.**

## Adverse Antibiotic Reactions in Relation to Patient Age or Condition\*

Age/ Condition	Antibiotic	Reactions	Comments
Pregnancy	Metronidazole (Pregnancy Category B)	Possible risk of teratogenicity	Avoid in first trimester
	Clindamycin (Pregnancy Category B)	None known	Probably safe
	Penicillins (Pregnancy Category B)	None known, although ampicillin/amoxicillin has been associated with increased risk of <i>Streptococcus</i> group B neonatal infection	Probably safe
	Tetracyclines (Pregnancy Category D)	Discoloration and hypoplasia of teeth and depressed skeletal growth	Contraindicated
	Erythromycins (Pregnancy Category B)	Clarithromycin (Pregnancy Category C) may cause fetal toxicity in primates	Avoid
	Fluoroquinolones (Pregnancy Category C)	Arthropathy in animals	Contraindicated
Children	All antibiotics		Dosage adjustment to avoid excessive concentrations
	Tetracyclines	Discoloration and hyperplasia of teeth and depressed skeletal growth	Contraindicated
	Fluoroquinolones	Cartilage toxicity in young animals	Contraindicated
Elderly adults	All antibiotics	Advanced age may be associated with altered pharmacokinetics of antibiotics	
	Clindamycin	Increased frequency of pseudomembranous colitis; other antibiotics can also give rise to the disease	
	Penicillins	Increased frequency of anaphylaxis due to prior exposure	

\* Modified from Root.<sup>25</sup>

**U.S. Food & Drug Administration Pregnancy Categories for guiding antimicrobial therapy:**

A: [Generally considered safe]. Controlled studies show no risk in first trimester; no evidence of second or third trimester risk; risk of fetal harm remote.

B: [Caution advised]. Animal studies show no risk, but controlled human first trimester studies not available; no evidence of second or third trimester risk; fetal harm possible but unlikely.

C: [Weigh risk/benefit]. Animal studies show adverse fetal effect(s) but no controlled human studies; weigh possible fetal risk versus maternal benefit.

D: [Weigh risk/benefit]. Positive evidence of human fetal risk; maternal benefit may outweigh fetal risk in serious or life-threatening situation.

X: [Contraindicated]. Positive evidence of serious fetal abnormalities in humans, animals, or both; fetal risks clearly outweigh maternal benefit.

increase in vivo resistance to antibiotics that are valuable in potentially fatal medical infections.<sup>51,52</sup>

Antibiotics should target offending periodontal pathogens, and bactericidal agents are preferred. Empirical antibiotic therapy may be employed for periodontal diseases with known microbial etiologies, such as acute necrotizing ulcerative gingivitis that is caused by anaerobic organisms and can be cured by metronidazole,<sup>53</sup> and early stages of aggressive adolescent periodontitis that mostly involve *Actinobacillus actinomycetemcomitans*, which can be controlled or eradicated by systemic metronidazole-amoxicillin combination therapy.<sup>54,55</sup> However, since even the most careful clinical examination cannot delineate the likely microbial pathogens in most cases of periodontitis, a microbiological analysis is sometimes necessary to identify the antibiotic therapy that covers resident periodontal pathogens. There is some

limited evidence to support microbial culture and sensitivity testing in cases that do not respond to conventional therapy.<sup>56</sup>

### Patient Selection

Antibiotic therapy is usually reserved for patients having continued periodontal breakdown after conventional mechanical treatment. However, some patient categories with recognized increased risk for periodontal breakdown, such as progressive adolescent periodontitis and other types of early-onset periodontitis, may be treated with systemic antibiotics as an adjunct to initial mechanical therapy. It is especially important to consider antibiotic therapy in the treatment of aggressive periodontitis, which often involves several specific pathogens having the potential to invade pocket epithelium and connective tissue. In patients with chronic periodontitis, the utility of systemic

**Table 4.**  
**Important Antibiotic Drug Interactions\***

Antibiotic	Interacting Drug	Effect	Clinical Significance
Metronidazole	Barbiturates and hydantoins	Decreased effectiveness of metronidazole	Probable
	Oral anticoagulants (warfarin)	Increased anticoagulant effect	Definite
	Ethanol	Disulfiram-like (antabuse) reaction	Probable
Clindamycin	Anti-diarrheals (kaolin)	Decreased absorption of clindamycin	Probable
	Muscle relaxants (diazepam)	Increased frequency and duration of respiratory paralysis	Probable
	Erythromycin	Mutual antagonism	Probable
Penicillins (amoxicillin)	Probenecid	Increased levels of penicillins	Probable
Tetracyclines (doxycycline)	Antacids, aluminum, bismuth, iron, Mg <sup>++</sup>	Decreased absorption of tetracyclines due to chelation	Probable
	Barbiturates and hydantoins	Decreased serum half-life of doxycycline	Probable
	Carbamazepine (Tegretol)	Decreased serum half-life of doxycycline	Probable
	Digoxin	Increased serum levels of digoxin	Probable
Erythromycins (azithromycin, clarithromycin)	Carbamazepine	Increased serum levels of carbamazepine, with nystagmus, nausea, vomiting, and ataxia	Definite
	Cisapride	Increased cisapride concentration, with risk of life-threatening arrhythmias	Definite
	Cyclosporin	Increased serum levels of cyclosporin with toxicity	Probable
	Methylprednisolone	Increased steroid concentration	Definite
	Non-sedating antihistamines (terfenadine, astemizole)	Increased antihistamine concentration, with risk of life-threatening arrhythmias	Definite
	Theophylline	Increased serum levels of theophylline, with nausea, vomiting, seizures, and apnea	Definite
	Oral anticoagulants (warfarin)	Increased anticoagulant effect	Probable
Fluoroquinolones (ciprofloxacin)	Cations (Al <sup>+++</sup> , Ca <sup>++</sup> , Fe <sup>++</sup> , Mg <sup>++</sup> , Zn <sup>++</sup> ) in antacids, vitamins, and dairy products	Decreased absorption of fluoroquinolones due to chelation	Definite
	Caffeine	Increased caffeine concentration	Probable
	Cimetidine	Increased serum levels of fluoroquinolones	Probable
	Cyclosporin	Increased serum levels of cyclosporin	Probable
	Non-steroidal anti-inflammatory drugs	Increased risk of stimulation of the central nervous system	Definite
	Probenecid	Decreased ciprofloxacin clearance	Probable
	Sucralfate	Decreased absorption of fluoroquinolones	Definite
	Theophylline	Increased serum levels of theophylline	Definite
	Oral anticoagulants (warfarin)	Increased anticoagulant effect	Probable

\* Modified from Root.<sup>25</sup>

antibiotics is not as clear. Since most clinical studies of antibiotic efficacy have been conducted in patients with chronic periodontitis, who respond well to scaling and root planing, they may have underestimated the value of adjunctive systemic antibiotics in aggressive types of periodontitis.

### **Microbiological Analysis**

With the use of antibiotics for treatment of periodontal disease, the dentist is encouraged to know the pathogenic microbial content of the subgingival microbiota and the specific antimicrobial susceptibility pattern of suspected pathogens in order to avoid

**Table 5.**  
**Clinical Studies of Systemic Antibiotic Therapy in Patients With Severe Periodontitis**

Reference	N Patients/ Disease	Antibiotic/ Dose, Time	Concurrent Treatment	Control	Follow-Up Time (months)	Outcomes
<b>Metronidazole</b>						
Loesche et al. <sup>27</sup>	15 test; 18 placebo/PPA	MET 250 mg t.i.d., 7 d	Scaling	Placebo medication	1-1.5	Test showed more reduction in PD, more gain in CAL, reduced level of pathogens, and less need for surgery
Saxén & Asikainen <sup>28</sup>	27/LAgP	MET 200 mg t.i.d., 10 d or TET 250 mg q.i.d., 12 d	Scaling	Scaling	18	Best clinical results with MET. <i>Aa</i> eliminated in 100% of MET group, in 44% of TET group, and in 67% of scaling group
Nieminen et al. <sup>29</sup>	18 test; 15 control/PPA	MET 250 mg t.i.d., 10 d	Scaling	Modified Widman flap surgery	18	Test showed less BOP and more reduction in PD
Palmer et al. <sup>30</sup>	31 test; 27 control/PPA	MET 200 mg t.i.d., 7 d	Ultrasonic scaling	Ultrasonic scaling	6	Test and control groups showed no statistically significant differences
Söder et al. <sup>31</sup>	32 test; 32 placebo/PPA	MET 400 mg t.i.d., 7 d	Scaling/surgery or no surgery	Placebo medication	60	PD significantly reduced in test but not in placebo group
<b>Clindamycin</b>						
Gordon et al. <sup>32,33</sup>	13/PPA	CLIN 150 mg q.i.d., 7 d	Scaling	None	12	CLIN + scaling improved clinical variables, reduced motile organisms, and decreased annual rate of sites with disease activity from 1.0% to 0.5%
Walker & Gordon <sup>34</sup>	24/PPA	CLIN 150 mg q.i.d., 7 d	Scaling	None	24	CLIN + scaling improved clinical variables and reduced annual rate of sites with disease activity from 8.0% to 0.5%. <i>Pg</i> , <i>Pi</i> , and <i>Pm</i> were reduced or absent from 12 months
<b>Penicillins/Amoxicillin</b>						
Kunihira et al. <sup>35</sup>	16/LAgP	PEN 250 mg q.i.d., 10 d every 3 mo for 9 mo	Surgery	Placebo medication	9	No advantage to adjunctive PEN; double-blind study
Haffajee et al. <sup>36</sup>	40/PPA	AMOX/CLA 250 mg t.i.d., 30 d	Surgery	Placebo medication	10	AMOX/CLA improved PD and CAL compared to placebo or ibuprofen. More decrease in <i>Aa</i> , <i>Pg</i> , <i>Pi</i> , and <i>Cr</i> with AMOX/CLA than with placebo
Winkel et al. <sup>37</sup>	10 test; 11 control/PPA	AMOX/CLA 500 mg t.i.d., 10 d	Scaling	Placebo medication	12	No clinical or microbiological difference between test and control; double-blind study

**Table 5. (continued)**

## Clinical Studies of Systemic Antibiotic Therapy in Patients With Severe Periodontitis

Reference	N Patients/ Disease	Antibiotic/ Dose, Time	Concurrent Treatment	Control	Follow-Up Time (months)	Outcomes
<b>Tetracycline/Doxycycline</b>						
Rams & Keyes <sup>38</sup>	21/PPA	TET 250 mg q.i.d., 14 d	None	Placebo medication	11	TET reduced PD, motile organisms, and crevicular leukocytes recalcitrant sites; double-blind study
Novak et al. <sup>39</sup>	4 LAgP	TET 250 mg q.i.d., 42 d	None	None	2-48	TET without scaling reduced PD, CAL, and BOP for up to 4 years
Saxén et al. <sup>40</sup>	7 test; 7 control/LAgP	DOX 100 mg q.d., 13 d	Scaling	Placebo medication	20	DOX reduced <i>Aa</i> better than placebo; double-blind study
Haffajee et al. <sup>41</sup>	40/PPA	TET 250 mg q.i.d., 30 d	Surgery	Placebo medication	10	TET improved PD and CAL compared to placebo or ibuprofen. More decrease in <i>Aa</i> , <i>Pg</i> , <i>Pi</i> , and <i>Cr</i> with TET than with placebo
Ramberg et al. <sup>42</sup>	35 test; 80 control/PPA	TET 250 mg q.i.d., 21 d	Scaling	Scaling	12	TET improved CAL but not PD or BOP; TET had no beneficial effect beyond 1 year post-treatment
<b>Azithromycin</b>						
Smith et al. <sup>43</sup>	23 test; 21 control/PPA	AZI 500 mg q.d., 3 d	Scaling	Placebo medication	5	AZI reduced BOP and PD better than placebo; double- blind study
<b>Combination Therapy</b>						
van Winkelhoff et al. <sup>44</sup>	22/LAP; 90/PPA	MET 250 mg + AMOX 375 mg t.i.d., 7 d	Scaling	None	3-9	Improved clinical status. <i>Aa</i> was eliminated in 97% and <i>Pg</i> in 88% of patients
Berglundh et al. <sup>45</sup>	8 test; 8 control/PPA	MET 250 mg + AMOX 375 mg b.i.d., 14 d	With and without scaling	Placebo	12-24	Improved clinical status. <i>Aa</i> and <i>Pg</i> were markedly suppressed or eliminated 2 months post-antibiotic. Combined mechanical and antibiotic therapy was most effective
Flemmig et al. <sup>46</sup>	18 test; 20 control/PPA	MET 250 mg + AMOX 375 mg t.i.d., 8 d	Scaling	Scaling	12	Patients harboring <i>Aa</i> benefited clinically and microbiologically from the antibiotic therapy
Winkel et al. <sup>47</sup>	23 test; 26 control/PPA	MET 250 mg + AMOX 375 mg t.i.d., 7 d	Scaling	Placebo	6	More improvement in PD, CAL, and BOP and more suppression of <i>Pg</i> , <i>Tf</i> , and <i>Pi</i> in the antibiotic group than in the placebo group

PPA = progressive periodontitis in adults; LAgP = localized aggressive periodontitis; AZI = azithromycin; MET = metronidazole; CLIN = clindamycin; PEN = penicillin; AMOX = amoxicillin; AMOX/CLA = amoxicillin/clavulanic acid; TET = tetracycline; PD = probing depth; CAL = clinical attachment level; BOP = bleeding on probing; *Aa* = *Actinobacillus actinomycetemcomitans*; *Pg* = *Porphyromonas gingivalis*; *Pi* = *Prevotella intermedia*; *Cr* = *Campylobacter rectus*; *Tf* = *Tannerella forsythensis*.

prescribing antibiotics against pathogens that are resistant to treatment. Prescription of inappropriate antimicrobial agents may lead to overgrowth of pathogens and poor clinical response.<sup>57</sup>

Microbiological analysis may be carried out after completion of conventional mechanical therapy to help assess the need for additional therapy, such as antibiotic treatment. Reevaluation with microbiological testing at 1 to 3 months after antimicrobial therapy may be desirable to verify the elimination or marked suppression of the putative pathogen(s) and to screen for possible superinfecting organisms, including Gram-negative enteric rods, pseudomonads, and yeasts. Microbiological analysis is best performed in periodontal sites that have not received instrumentation in the immediate past as repopulation of most pathogens to pretreatment levels usually requires 4 to 8 weeks following instrumentation.

**Sampling procedure.** Microbial samples may be obtained from individual pockets with recent disease activity or from pooled subgingival sites. A pooled subgingival sample may provide a good representation of the range of periodontal pathogens to be targeted for antibiotic therapy.<sup>58</sup> A representative subgingival sample can be obtained from pooling three or four progressing or deep periodontal pockets in a patient. Subgingival samples can be collected with sterile paper points or a curet. For culturing, the specimens must be placed in a transport medium that has been formulated with reducing conditions to sustain viability of sampled microorganisms.

**Culture methods.** Microbial anaerobic culturing presently provides the most comprehensive assessment of the periodontal microbiota. Total viable cell counts, the relative proportions of putative periodontal pathogens, and the occurrence of unusual subgingival organisms can be determined. Culturing remains a prerequisite for in vitro antimicrobial sensitivity testing. Disadvantages with culturing are a time-consuming analysis, requirement of skilled technical personnel, relatively high financial costs, inability to grow some organisms, and limited survival time of sampled bacteria. Also, microbial culture identification relies on the quality of the specimen provided and the assiduity with which microbial isolates are studied. Studies report both high<sup>59</sup> and low<sup>60</sup> agreement between results from different microbiology testing laboratories. Occasionally, a microbiological culture has to be repeated to confirm or reject an odd result.

**Non-culture techniques.** Molecular genetic techniques to detect periodontal bacteria include species-specific DNA probes and polymerase chain reaction-

based assays.<sup>61,62</sup> These techniques do not require viable cells and can show high sensitivity and specificity. They also have the potential to discriminate between high and low virulent strains of a given species. Molecular genetic detection techniques are relatively easy, fast, and inexpensive to perform. Disadvantages are the limited number of species that can presently be routinely detected, the difficulty of quantifying target organisms, and the inability to perform antimicrobial sensitivity testing of target microorganisms. However, rapid progress in molecular genetic techniques may soon overcome existing obstacles. One study suggests that only about 40% of the oral flora can be grown in the laboratory by current techniques when compared to those identifiable by culture-independent molecular methods.<sup>3</sup>

Polyclonal or monoclonal antibodies can be used to detect putative periodontal pathogens in direct plaque smears.<sup>61,62</sup> Most immuno-serodiagnostic assays are based on immunofluorescent or enzyme-linked immunosorbent detection. Disadvantages of immuno-serodiagnostic techniques are the limited number of species that can be detected and the inability to determine antimicrobial sensitivity of suspected pathogens.

**Antimicrobial sensitivity testing.** Resistance of putative periodontal pathogens to antimicrobial agents has increased.<sup>6</sup> Therefore, antimicrobial sensitivity testing can be important if the clinician contemplates using antibiotics in the management of patients with refractory periodontitis. The American Academy of Periodontology's "Parameter on 'Refractory' Periodontitis"<sup>63</sup> states:

Once the diagnosis of refractory periodontitis has been made, the following steps may be taken:

1. Collection of subgingival microbial samples from selected sites for analyses, possibly including antibiotic-sensitivity testing.
2. Selection and administration of an appropriate antibiotic regimen.
3. In conjunction with the administration of an antimicrobial regimen, conventional periodontal therapies may be used.
4. Reevaluation with microbiological testing as indicated.

There are clinical situations in which sensitivity testing may not add information that significantly alters the way the disease is treated. For example, some periodontal putative pathogens (i.e., *Porphyromonas gingivalis* and *Campylobacter rectus*) are usually susceptible to a wide range of antimicrobial agents and the antimicrobial profiles are quite predictable.<sup>20</sup>

### Selection of Antibiotics

Relatively few studies have been performed regarding which antibiotics should be selected for aggressive periodontitis patients in whom the subgingival microbiota have been characterized through microbiological testing. In addition, the optimal dose of antibiotics remains unclear<sup>13</sup> since most current antibiotic regimens are empirically developed rather than through systematic research.<sup>26</sup> Tables 5 and 6 and a recent review<sup>64</sup> may be of value in making decisions on appropriate prescription regimens. Table 6 lists frequently prescribed antibiotic regimens for treatment of periodontitis.<sup>65</sup>

Metronidazole may arrest disease progression in recalcitrant periodontitis patients with *Porphyromonas gingivalis* and/or *Prevotella intermedia* infections with few or no other potential pathogens.<sup>27</sup> Metronidazole can readily attain effective antibacterial concentrations in gingival tissue and crevicular fluid.<sup>66,67</sup> Metronidazole therapy in conjunction with scaling and root planing may result in slight but statistically significant improvement in clinical attachment levels.<sup>12</sup> Metronidazole is cleared by hepatic metabolism with a half-life of about 6 to 14 hours in most patients. The half-life is unchanged with renal dysfunction but is prolonged in patients with hepatic function impairment. Although adverse effects are relatively minor, there is an important interaction of metronidazole with warfarin.

Clindamycin has demonstrated efficacy in recurrent periodontitis and may be considered with periodontal infections of *Peptostreptococcus*,  $\beta$ -hemolytic

streptococci, and various oral Gram-negative anaerobic rods.<sup>34</sup> *Eikenella corrodens* is resistant to clindamycin. Clindamycin should be prescribed with caution because of the potential for pseudomembranous colitis as a result of intestinal overgrowth with *Clostridium difficile*. Other antibiotics can occasionally also cause pseudomembranous colitis.

Tetracyclines (tetracycline-HCl, doxycycline, minocycline) may be indicated in periodontal infections in which *Actinobacillus actinomycetemcomitans* is the prominent pathogen; however, in mixed infections tetracycline antibiotics may not provide sufficient suppression of subgingival pathogens to arrest disease progression.<sup>14</sup> Contrary to earlier concepts, the average gingival crevicular fluid concentration of tetracycline after systemic administration seems to be less than the that of plasma concentration and varies widely among individuals (between 0 and 8  $\mu\text{g/ml}$ ) with approximately 50% of samples not achieving levels of 1  $\mu\text{g/ml}$ , possibly explaining much of the variability in clinical response to systemic tetracyclines observed in practice.<sup>68</sup> The tetracyclines also have the possible benefit of inhibiting gingival collagenases.<sup>69</sup> Doxycycline has the highest protein binding capacity and the longest half-life, and minocycline has the best absorption and tissue penetration of tetracyclines. All tetracyclines have important adverse reactions with respect to teeth and bones, and they are contraindicated during pregnancy and for children below 8 years of age.

Fluoroquinolones (ciprofloxacin) are effective against enteric rods, pseudomonads, staphylococci, *Actinobacillus actinomycetemcomitans*, and other periodontal microorganisms.<sup>70</sup> Fluoroquinolones penetrate readily into diseased periodontal tissue and gingival crevice fluid and may even reach higher concentrations than that of serum.<sup>71</sup> Fluoroquinolones may induce tendinopathy and strenuous exercise should be avoided during therapy.

Azithromycin exhibits an excellent ability to penetrate into both normal and pathological periodontal tissues.<sup>72</sup> It is also highly active against many periodontal pathogens<sup>73</sup> although some *Enterococcus*, *Staphylococcus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, and *Peptostreptococcus* strains may exhibit resistance.<sup>74,75</sup>

Metronidazole plus amoxicillin provides a relatively predictable eradication of *Actinobacillus actinomycetemcomitans* and marked suppression of *Porphyromonas gingivalis* in aggressive forms of adolescent periodontitis and in recalcitrant adult periodontitis.<sup>23,44,76</sup>

Metronidazole plus ciprofloxacin may substitute for metronidazole plus amoxicillin in individuals who are

**Table 6.**

### Common Antibiotic Therapies in the Treatment of Periodontitis\*

Antibiotic	Adult Dosage
Metronidazole	500 mg/t.i.d./8 days
Clindamycin	300 mg/t.i.d./8 days
Doxycycline or minocycline	100-200 mg/q.d./21 days
Ciprofloxacin	500 mg/b.i.d./8 days
Azithromycin	500 mg/q.d./4-7 days
Metronidazole + amoxicillin	250 mg/t.i.d./8 days of each drug
Metronidazole + ciprofloxacin	500 mg/b.i.d./8 days of each drug

\* The antibiotic regimens listed do not represent recommendations of the American Academy of Periodontology.

allergic to  $\beta$ -lactam drugs and are at least 18 years of age. Metronidazole plus ciprofloxacin is also a valuable drug combination in periodontitis patients having mixed anaerobic-enteric rod infections.<sup>65</sup> Non-periodontopathic viridans streptococcal species that have the potential to inhibit several pathogenic species (beneficial organisms) are resistant to the metronidazole-ciprofloxacin drug combination and may recolonize in treated subgingival sites.

In addition to reducing levels of periodontopathic bacteria, systemic antibiotic therapy may lead to increased levels of antibiotic-resistant, innocent or beneficial bacteria like streptococci or actinomyces.<sup>77-79</sup> Subgingival overgrowth of periodontally harmless bacteria may occupy niches previously inhabited by periodontal pathogens and, because of antagonistic bacterial interactions,<sup>80</sup> delay or prevent major Gram-negative pathogens from re-colonizing subgingival sites. However, overgrowth of mutans streptococci on exposed root surfaces may increase the risk of dental caries and argue for prophylactic application of topical fluoride concomitant with antibiotic periodontal therapy.<sup>81</sup>

Antibiotic therapy is indicated for periodontal abscesses with systemic manifestations (fever, malaise, lymphadenopathy). Antibiotics for the treatment of abscesses should be prescribed in conjunction with surgical incision and drainage.<sup>82</sup> Table 7 describes adult regimens that may be used with acute periodontal abscesses.

Food does not influence the bioavailability of most oral antibiotics, with the exception of tetracyclines, fluoroquinolones, and azithromycin. These three groups of antibiotics should be taken 1 hour before or 2 hours after food intake.

**Table 7.**  
**Antibiotic Regimens for Adult Patients With Acute Periodontal Abscesses\***

**Amoxicillin:** Loading dose of 1.0 g followed by a maintenance dose of 500 mg/t.i.d. for 3 days, followed by a patient evaluation to determine whether further antibiotic therapy or dosage adjustment is required.

**With Allergy to  $\beta$ -lactam drugs:**

Azithromycin: loading dose of 1.0 g on day 1, followed by 500 mg/q.d. for days 2 and 3;

or

Clindamycin: loading dose of 600 mg on day 1, followed by 300 mg/q.i.d. for 3 days.

\* Reprinted with permission from Blackwell Munksgaard.<sup>13</sup>

Cost can be a determinant in selecting antimicrobial periodontal therapy. Antibiotics in the lower cost group include tetracyclines, amoxicillin, and metronidazole. More expensive antibiotics include azithromycin, clarithromycin, ciprofloxacin, amoxicillin/clavulanic acid, and clindamycin.

### **Sequencing of Antibiotic Therapy**

Antibiotics should be considered as an adjunct to mechanical periodontal debridement. Use of potent antibiotics presupposes adequate clinical diagnosis, thorough mechanical debridement, and microbiological analysis where indicated. The following schedule represents a practical approach to periodontal antibiotic therapy.

1. Initial periodontal therapy should include thorough mechanical root debridement followed by surgical access if needed.
2. Antibiotics may be prescribed on the basis of the clinical need for further treatment, the findings of microbiological testing, and the medical status and current medications of the patient.
3. The clinical response should be evaluated 1 to 3 months after completion of the mechanical therapy. If periodontal disease appears to progress or if inflammation does not resolve, a microbiological examination of the subgingival microbiota may help determine the presence and amount of remaining putative periodontal pathogens.
4. If the clinical examination warrants it, 1 to 3 months after systemic antimicrobial therapy, another microbiological test may be needed to verify the subgingival elimination of target pathogen(s) and screen for possible superinfecting organisms. High levels of subgingival viridans *Streptococcus*, *Actinomyces*, and *Veillonella* species are suggestive of periodontal health or minimal disease.<sup>83</sup>
5. After resolution of the periodontal infection, the patient should be placed on an individually tailored maintenance program. Supragingival plaque control in the supportive periodontal therapy phase may help prevent recolonization by putative periodontal pathogens.<sup>84</sup> Recurrence of progressive disease may prompt repeated microbiological testing and subsequent antibiotic therapy targeted against the specific microorganisms detected.

### **SUMMARY**

Severe periodontal infections represent such a great threat to oral and possibly systemic health that the prudent use of effective antibiotics is ethically acceptable in appropriately selected patients. However, the

emerging antibiotic resistance among human pathogens dictates a restrictive and conservative use of systemic antibiotics.

Systemic antibiotic therapy in periodontics aims to reinforce mechanical treatment and to support host defenses in overcoming periodontal infections by killing subgingival pathogens that remain after periodontal instrumentation. Pathogens may escape the effect of mechanical debridement because of their ability to invade periodontal tissues, to reside in anatomical tooth structures inaccessible to periodontal instrumentation, or as a result of poor host defense.

Systemic antibiotic therapy can provide greatest benefit to periodontitis patients who do not respond well to mechanical periodontal therapy or who are experiencing fever or lymphadenopathy. Single antimicrobial drug therapies may be able to suppress various periodontal pathogens for a prolonged period of time depending on the effectiveness of the host defense and the oral hygiene efforts. Combination drug therapies, which aim at enlarging the antimicrobial spectrum and exploiting synergy between antibiotics, are often indicated with complex mixed periodontal infections. Prescription of any systemic antibiotic therapy requires a careful analysis of patients' medical status and current medications. In severe infections, it may include antimicrobial sensitivity testing.

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