Risk of Bacterial Resistance Associated with Systemic Antibiotic Therapy in Periodontology

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ABSTRACT

Given the infectious nature of most periodontal diseases and the limited results that are sometimes achieved with conventional mechanical therapies, the use of antibiotics is warranted in certain cases. However, systemic antibiotic therapy is associated with certain risks, notably the development of antibiotic resistance in various bacterial species. In the past 20 years, reports of the existence of antibiotic-resistant, and even multiresistant, oral bacteria have been increasing. This article provides an update on the problem of antibiotic resistance among oral bacteria.

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Gingival health is associated with the presence of a thin biofilm composed principally of gram-positive bacteria of the genera *Streptococcus* and *Actinomyces*.[1] However, as discussed in an earlier article,[2] the accumulation and proliferation of certain bacterial species in subgingival sites are the initiating steps in the onset and progression of periodontal lesions. According to the currently accepted theory of the development of periodontal disease, known as the specific plaque hypothesis, only a limited group of bacteria have the capacity to cause periodontitis. The occurrence of infection depends on there being a sufficient concentration of periodontal pathogens, and these pathogens must express virulence factors. A person could therefore be infected by these pathogens without presenting any clinical symptoms. Symptoms appear only if the host's defence mechanisms are no longer able to maintain homeostasis, and the host's immune response modulates disease progression toward destruction.[3]

Systemic Antibiotic Therapy in the Treatment of Periodontitis

Mechanical debridement of the dental biofilm and elimination of local irritating factors are the basis of periodontal therapies, but are not effective for all sites and forms of periodontal disease. Given the infectious nature of periodontitis and the limited results that are sometimes achieved with conventional mechanical therapies, the use of antibiotics is warranted for certain forms of the disease or for certain patients.[2] Systemically administered antibiotics can reach microorganisms that are inaccessible to scaling instruments or that are colonizing the deep crevices of the tongue, as well as clinically nondiseased sites that could potentially cause chronic re-infection. However, in deciding whether to use curative systemic antibiotic therapy, it is important to consider the potential benefits and adverse effects, including the development of resistant bacterial species.

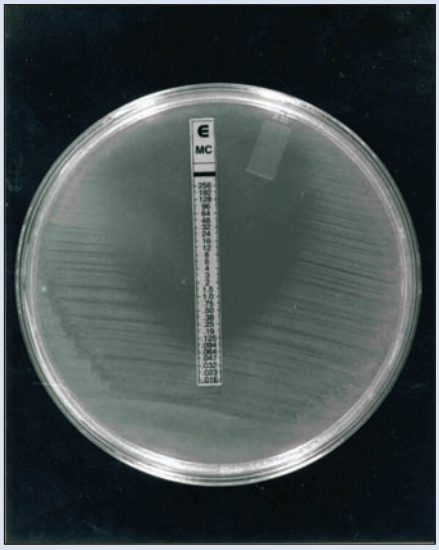

Figure 1: An agar-based concentration gradient diffusion assay (E-test) can be used to determine the minimum inhibitory concentration of minocycline on *Aggregatibacter actinomycetemcomitans*.

Bacterial Resistance to Antibiotics

The introduction of new antibiotics has always been associated with the appearance of resistant bacterial strains, and constant discovery and development of new antimicrobial molecules is required to circumvent this response. Unfortunately, blind confidence in the potential benefits of antibiotics has led to their widespread but often inappropriate use, and bacteria with resistance to one or more antibiotics are now widely observed. All bacterial species, all antibiotics and both veterinary and human medicine are implicated. Antibiotic resistance constitutes a truly global phenomenon, the resolution of which must be conceived from a world ecological perspective.

Resistance Mechanisms

The occurrence of bacterial resistance corresponds to an increase in an antibiotic's minimum inhibitory concentration (the lowest concentration of the antibiotic capable of inhibiting bacterial growth) for a particular bacterial strain, relative to the minimum inhibitory concentration of the same antibiotic for the wild population of the same bacterial species (**Fig. 1**). A strain is considered resistant when it is no longer affected by a normally effective concentration of antibiotic.

Bacteria have a wide variety of mechanisms for resisting antibiotics. A particular type of resistance is not exclusive to a single family of antibiotics, and, conversely, different bacterial species may use different mechanisms to resist the same antibiotic agent. The principal mechanisms of antibiotic resistance in periodontology are summarized in **Table 1**. Resistance to an antibiotic may arise if the bacterium synthesizes an enzyme that can hydrolyze the antimicrobial. The most well-known example of this mechanism is penicillin-resistant *Staphylococcus*.[4] Resistant strains of this bacterial genus produce a β-lactamase that hydrolyses the constitutive β-lactam ring of penicillins and cephalosporins. In some formulations, such as Augmentin (GlaxoSmithKline, Mississauga, Ont.), this mechanism of resistance is circumvented by a combination of penicillin with clavulanic acid. The latter acts as a "decoy," serving as the prime target for the β-lactamase and thereby protecting the penicillin's β-lactam core.

A second mechanism of resistance involves the alteration of the antibacterial properties by adding chemical groups to the molecule.[5] For example, microorganisms may phosphorylate aminoglycosides or acetylate chloramphenicol. Bacteria may also eject an antibiotic from cells that it has just entered.[6] This mechanism depends on the presence of intramembranal pumps, which expel the drug before it can act. Such transport proteins are relatively nonspecific and are often associated with resistance to multiple agents. Finally, the target of the antibiotic may be modified by genetic modification (mutation), which reduces the drug's affinity for its substrate. This mechanism is often associated with resistance to erythromycin and vancomycin.[7]

Resistance to antibiotics can be divided into 2 categories: intrinsic and acquired. Intrinsic resistance implies a natural resistance to the antibiotic, without any previous exposure. For example, strict anaerobic bacteria, including numerous periodontal pathogens, lack the oxygen-dependent transport mechanism required for aminoglycosides to penetrate bacterial cells; these bacteria are therefore constitutively resistant to aminoglycosides. Similarly, the resistance of many gram-negative bacteria to penicillin is intrinsic, since this drug cannot cross the external membrane of the bacterial envelope. Acquired resistance corresponds to the acquisition of a resistant gene by a bacterial population that is not naturally resistant. Acquired resistance can arise following random genetic mutation, or it can be the result of a genetic material transfer between bacteria. There are 3 principal mechanisms for an exchange of genetic material between bacteria leading to the acquisition of resistance: transformation, conjugation and transduction. Transformation involves the capture of fragments of naked DNA present in the environment and their incorporation into the receiving chromosome. Transduction and conjugation refer to the transfer of genetic material between 2 bacteria through specific vectors: bacteriophages (bacterial viruses) for transduction and plasmids (molecules of extrachromosomal circular DNA) for conjugation. Conjugation is the most common mode of genetic transfer in the propagation of bacterial resistance.

Table 1 Mechanisms of resistance to the principal antibiotics used in periodontology

Antibiotic	Mode of action of antibiotic	Bacterial response
Penicillins and cephalosporins	Inhibition of synthesis of the cell wall	• Destruction of the β-lactam ring by β-lactamases • Conformational modification of the target • Reduction in autolysis
Erythromycin	Inhibition of protein synthesis	• Immediate excretion by intramembranal pumps • Conformational modification of the antibiotic target
Tetracycline and derivatives	Inhibition of protein synthesis	• Immediate excretion by intramembranal pumps • Conformational modification of the antibiotic target • Enzymatic modification of the antibiotic
Metronidazole	Inhibition of DNA replication	• Lack of metronidazole activation through modification of bacterial nitroreductases • Reduction in uptake

Regardless of the mechanism, resistance is induced not by the antibiotic itself, but rather by its use, which exerts a selective pressure on a bacterial species, giving resistant organisms a competitive advantage over susceptible ones. The prevalence of bacterial resistance is therefore directly related to the use of antibiotics.

Acquisition of Resistance by Oral Bacteria

The oral cavity is not exempt from the phenomenon of bacterial resistance to antibiotics. Given that approximately 10% of common antibiotics, including penicillins, cephalosporins, macrolides and tetracyclines, are prescribed in dental medicine, dentistry's contribution to the problem may well be substantial.[8] In the past 20 years, numerous studies have reported the existence of antibiotic-resistant and even multiresistant oral bacteria.[9,10] This emergence of resistance in the oral microflora is almost certainly linked in large part to the improper use of antibiotics, in terms of either dosage (duration of treatment too long or dose too weak) or indication. The association between the prevalence of resistant bacterial strains at subgingival sites and the consumption of antibiotics has already been demonstrated.[11] In most cases, antibiotics for the treatment of periodontitis are prescribed empirically, which may mean inappropriate treatment and the development of bacteria that are resistant to one or more antibiotics.

The specific organization of pathogenic periodontal bacteria in the biofilm affects their resistance to antibiotics.[12,13] Bacteria within the biofilm may be up to 1,000 times more resistant than those in planktonic form (not attached to one another or to a solid surface).[14] The mechanisms conferring this greater bacterial resistance are now better understood.[15] One important mechanism appears to be the low bacterial metabolic activity within the biofilm, which limits the assimilation of antibiotics. In addition, the extracellular matrix of the biofilm limits the diffusion of antimicrobial agents. Finally, the extracellular bacterial enzymes involved in deactivating antibiotics are trapped and concentrated in the biofilm, which increases their ability to neutralize antimicrobial agents. Therefore, despite the limitations of mechanical debridement of the biofilm mentioned above, such mechanical therapy is an essential prerequisite for eventual antibiotic treatment. Moreover, antibiograms indicating the antibiotic sensitivity of bacteria present at diseased periodontal sites may be of limited use, given that the behaviour of bacteria inside the biofilm is completely different from that observed for the same bacteria in planktonic form.

Resistance to penicillin in the oral flora was documented for the first time in 1983 with viridans streptococci.[16] This observation was later confirmed in the United States[17] and Europe.[18] More specifically, in the United States, 40% to 50% of strains of α-hemolytic streptococci are resistant to penicillins.[19] Some streptococcal strains are also resistant to tetracyclines and clindamycin.[19,20] Production of β-lactamases is frequently observed among gram-negative species belonging to the genera *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Veillonella* and *Capnocytophaga*.[21–24] In a study of 406 samples of gingival fluid taken from 52 adults with periodontitis, β-lactamase activity was demonstrated in 64% of subjects and 24% of sites.[25] This enzyme is most frequently found in periodontal pockets deeper than 3 mm. In one study, it was present in 76% of patients who had previously been exposed to penicillin but only 48% of those who had no previous exposure.[26] Feres and others[27] demonstrated that a large number of bacterial strains of subgingival plaque belonging to various species were resistant to amoxicillin and metronidazole. Systemic administration of these antibiotics resulted in a temporary (90-day) increase in the percentage of resistant species, even though a large proportion of the subgingival plaque remained susceptible to the antibiotics during this period.

Resistance to tetracycline is encoded by *tet* genes, of which 27 have been described to date, most from

bacterial species of oral origin, including *Porphyromonas gingivalis* and *Fusobacterium nucleatum*.[10] The *tet*M gene is the most frequently reported. Ready and others[28] studied the prevalence of tetracycline-resistant strains in the dental plaque of children from different ethnic groups and found that children from Japan and South Asia had a significantly higher percentage of tetracycline-resistant isolates than white children. Strains of tetracycline-resistant *Treponema denticola* have already been isolated.[29] Resistance to tetracycline is often a comarker among penicillin-resistant species of oral origin.[30]

Resistance to erythromycin is generally the result of acquisition of 1 of the 21 *erm* genes, *erm*F being the most frequent.[31] Bacterial strains of *P. gingivalis* and *Tannerella forsythia* carrying the *tet* and *erm* resistance genes are commonly isolated.[32]

Generally speaking, most anaerobic bacteria, including periodontal pathogens, are susceptible to metronidazole. Four genes that can confer resistance to this antibiotic (*nim*A, *nim*B, *nim*C and *nim*D) have already been identified among species of extraoral origin in the genus *Bacteroides*.[33] However, the presence of these genes in oral bacteria has not yet been fully elucidated.

The use of doxycycline at subantimicrobial concentrations as an adjunct to scraping and root planing has raised questions with regard to the development of antibiotic-resistant bacterial flora. However, Thomas and others[34] reported that long-term use of subinhibitory concentrations of doxycycline did not contribute to a change in the antibiotic susceptibility of the subgingival microflora. Additional studies will be required to confirm that oral bacteria do not develop bacterial resistance in the presence of subinhibitory concentrations of doxycycline for long periods.

Wang and others[35] clearly demonstrated that 2 species of oral bacteria present within an experimental biofilm, specifically *Streptococcus gordonii* and *T. denticola*, can exchange genetic material, including genes encoding antibiotic resistance. This phenomenon of genetic exchange is particularly favoured in the biofilm and could, if it occurs more generally, greatly contribute to an increase in resistant bacterial strains in the mouth.

Finally, some methicillin-resistant strains of *Staphylococcus aureus*, the source of nosocomial infections in hospitals, can colonize the oral cavity over several years.[36] As such, the oral cavity can be considered a reservoir for extraoral pathogens.

Conclusions

In certain cases, the infectious nature of periodontal disease justifies the use of antibiotics as a therapeutic strategy. When deciding whether to use curative systemic antibiotic therapy, it is important to consider both the benefits and the undesirable effects. The potential risks associated with systemic antibiotic therapy include the selection of resistant bacterial strains, and the development of antibiotic resistance has now been illustrated among oral bacteria. Appropriate use of antibiotics in conjunction with education for both practitioners and patients should lead to decreased rates of resistance. Periodontists must therefore have a good understanding of the antibiotic therapy and limit the use of antibiotics to cases where indications for use have been fully validated.

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