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Letter to the editor

Systemic antibiotics: to use or not to use in the treatment of periodontal infections. That is the question

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Dear Editor,

This letter is in response to a series of publications focusing on the use of systemically administered antibiotics in the treatment of periodontal infections: namely, Guerrero et al. (2005) *Journal of Clinical Periodontology* 32, 1096–1107, the accompanying guest editorial by van Winkelhoff (2005) *Journal of Clinical Periodontology* 32, 1094–1095 and The Letter to the editor from Drs. Needleman and Wilson.

Periodontal diseases are arguably the most common bacterial infections of the human and the most direct route to their control is to control the organisms that cause them. It is clear that systemically administered antibiotics can be of benefit in the treatment of periodontal infections. Two systematic reviews (Herrera et al. 2002, Haffajee et al. 2003) have indicated that systemically administered antibiotics provide a clear clinical benefit in terms of mean periodontal attachment level ''gain'' post-therapy when compared with groups not receiving these agents. Herrera et al. (2002) provided a meta-analysis of the six included papers that indicated an additional benefit of adjunctive antimicrobials over scaling and root planing (SRP) alone in terms of attachment level gain and pocket depth reduction, particularly at initially deep periodontal pockets. Haffajee et al. (2003) compared mean attachment level change in 27 studies comprising over 1000 subjects. Meta-analysis indicated that the antibiotic provided significantly better AL ''gain'' of 0.3–0.4 mm at 6 months post-therapy than the comparison groups not receiving antibiotics. Subjects with aggressive periodontitis showed greater benefit than subjects with chronic periodontitis. The mean ''gain'' in attachment of 0.3–0.4 mm for most studies may appear small, but it was based on change throughout the mouth including sites with shallow probing depths whose post-therapy improvement would be expected to be modest. As a bench mark, periodontitis subjects monitored after treatment and on supportive periodontal therapy for about 12 years only experienced an average annual full-mouth mean attachment loss of 0.042 mm (normal susceptibility subjects) to 0.067 mm (high susceptibility subjects) (Rosling et al. 2001). Thus, attachment level ''gain'' of 0.3 mm would be equivalent to reversing 4–7 years of disease progression in a treated and maintained population.

However, as indicated by Drs. van Winkelhoff, Needleman and Wilson, there are still a number of issues that need to be addressed.

If antibiotics confer therapeutic advantage, should they be given to all individuals? If not, then who should receive these agents and how severe does the periodontal infection have to be in order to justify the use of an antimicrobial agent? There are no ''evidence-based'' guidelines for the use of systemically administered antibiotics. It is recognized that many factors impact on this decision such as the systemic well being of the patient, concomitant medical conditions, the nature of the infecting agent(s), etc. For this reason, guidelines for antibiotic use will always remain that; guidelines. They provide starting points to make complex decisions. In the treatment of periodontal infections, we do not even have this starting point, this guideline. We feel that antibiotics are useful in the treatment of aggressive forms of periodontal diseases, ''refractory'' periodontitis and in smokers. However, in the most common form of the disease, chronic periodontitis, which patients would benefit from systemically administered antibiotics and how would the decision to use antibiotics be made?

There are numerous antibiotics that could be employed to treat periodontal infections, but it is often unclear which antibiotic would provide the greatest benefit to a patient with a specific periodontal infection. Metronidazole, with its narrow spectrum of activity and its effectiveness against many Gram-negative bacteria (including many thought to play an aetiologic role in periodontitis) has been shown to be an effective agent in many studies. This agent coupled

with amoxicillin provides a potent combination in the treatment of aggressive forms of periodontal disease where *Actinobacillus actinomycetemcomitans* may also be prevalent. Nonetheless, as pointed out by Dr. Winkelhoff, not all cases of a ''disease'' may have the same subgingival microbial profile. As a result specific antibiotics or combinations may not work well in all cases of a specific clinical condition. Different absorption rates and delivered levels in the periodontal pocket of the antibiotic may also impact clinical efficacy.

Even if it was established that a subject required an antibiotic and the optimal antibiotic was known, the dosage of the agent(s) is still somewhat arbitrary as well as the timing of the administration of the agent(s) in relation to other mechanical therapies.

Finally, as voiced by Drs. Needleman and Wilson, there are safety issues associated with the use of antibiotics. These include the minor inconveniences to the subject, such as gastrointestinal upsets, more major consequences to the subject of severe allergic reactions and the major concern to both the subject and society of antibiotic resistance. Recently, strains of several bacterial species of significant clinical importance have emerged that defy treatment with nearly all available antibiotics. *Staphylococcus aureus* strains have been reported that are resistant to all antibiotics, except vancomycin. Vancomycin-resistant *Enterococcus* species are on the increase, and there is concern that one of the operons encoding this resistance might be capable of entering *S. aureus* strains. Recently, two *S. aureus* strains were isolated from patients that harboured the *vanA* operon, one of which had clearly obtained the entire operon from an enterococcal strain (Weigel et al. 2003). *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* are capable of causing life-threatening illnesses and are reported to be resistant to every available antibiotic previously shown to be effective in their treatment (Slavkin 1997). Other mechanisms of multiple antibiotic resistance have been demonstrated including the presence of multiple antibiotic resistance genes that are different from genes that confer resistance to individual agents. A major factor in the development of antibiotic resistance is antibiotic usage. The presence of large numbers and types of bacteria within a community, such as the periodontal pocket, some of which might possess antibiotic-resistance genes, might be important in the growth and emergence of antibiotic-resistant bacterial species associated with the progression of periodontal disease or transfer of resistance elements to pathogens associated with other major infectious diseases.

Although these are alarming facts, antibiotic use in the treatment of periodontal infections probably contributed little to this serious situation, particularly given the widespread use of these agents in medicine and husbandry. However, it is important that antibiotics are used judiciously in the treatment of periodontal infections. Previous data from our and other laboratories (Fiehn and Westergaard 1990, Feres et al. 1999, 2002) have indicated that the use of antibiotics to treat periodontal infections increases the proportion of strains in dental plaque that are resistant to a given antibiotic, but that this proportion declines after withdrawal of the agent(s). The major question, however, and one that is extremely difficult to answer, is whether the antibiotic resistant strains were present before the use of the agent or developed as a result of its use. Further, the development of multiple antibiotic resistant strains during the treatment of periodontal infections has received little attention. Such strains could present a significant problem to a patient requiring later treatment for a serious medical infection. Drs. Needleman and Wilson questioned why the data in the periodontal literature addressing this point were very limited. The major reason is that meaningful studies examining changes in antibiotic resistance of specific bacterial species before and after antibiotic therapy are very difficult to perform, extremely time consuming and, thus, extremely expensive. Indeed, our group is anxious to perform such studies, but has been unsuccessful in acquiring funding.

Thus to summarize. One must ask if there is a risk to the subject if periodontal infections are inadequately treated because periodontal diseases have consequences! Apart from the obvious consequence of tooth loss, periodontal diseases are thought to play a role in various systemic conditions including cardiovascular disease, stroke, premature or low birth weight infants, upper respiratory infections and may possibly contribute to other conditions such as diabetes and obesity (Beck & Offenbacher 1998, Scannapieco 1999, Beck et al. 1999, 2000, Champagne et al. 2000, Joshipura et al. 2000, Mealey & Rethman 2003). Whether periodontal therapy is used to prevent tooth loss, or to minimize effects on systemic conditions, it is essential that its performance provides maximum benefit to the patient with minimum cost, risk and pain. For over 100 years, periodontal therapy has relied primarily on mechanical methods to control the infectious component of the diseases. While these methods provide benefit for many patients, they are clearly not adequate for all, and even those that benefit from mechanical forms of therapy might have better therapeutic outcomes with additional or different forms of treatment. Given the infectious nature of periodontal diseases, it is not surprising that antibiotics have been used in some situations for their control. Until recently, the value of such agents has been a subject of some debate. However, the two recent systematic reviews, described above, have indicated that systemically administered antibiotics provide a clear clinical benefit in terms of attachment level ''gain'' when administered alone or in combination with SRP, periodontal surgery, or locally administered antibiotic containing gels (Herrera et al. 2002, Haffajee et al. 2003). While these reviews indicate that, on average, the antibiotics contribute to therapeutic success, they fail to answer a number of critical questions. First, which patient would benefit most from systemic antibiotic administration? Second, which antibiotic or antibiotic combination is most appropriate for which form of periodontal infection? Third, what is the optimum dosage, duration and timing of antibiotic administration (in relation to mechanical debridement)? Fourth, is a poor treatment response due to the use of the wrong agent or failure of the agent to reach the site of action. Fifth, what is the ''downside'' of antibiotic administration; i.e. the negative consequences of side effects and the development of antibiotic resistant species?

Should antibiotics be used in the treatment of periodontal diseases? Absolutely! The data from virtually every controlled study indicate their clinical benefit. Should every periodontal patient get an adjunctive antibiotic? Absolutely not! It is easy to be definitive in answering these questions. Nonetheless, in order to use antibiotics appropriately in the treatment

of periodontal infections definitive answers to a number of specific questions need to be determined.

Sincerely,
Anne Haffajee

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