Treatment of oral malodor and periodontal disease using an antibiotic rinse

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The purpose of this study was to determine the effectiveness of an antibiotic rinse preparation, containing metronidazole and nystatin, in decreasing oral malodor and periodontal disease for individuals whose chief complaint was halitosis. This topical approach to oral biofilm control, by proactively managing the most pathogenic bacteria, differs from the traditional approach of reactively treating the symptoms by attempting to reduce all oral bacteria. The late Dr. Loesche, University of Michigan, School of Dentistry, had previously described these different paradigms as the *specific plaque hypothesis* and the *non-specific plaque hypothesis,* respectively. Patients in this study were measured before and after treatment for volatile sulphur compounds using a portable sulphide monitor, a digital gas chromatograph, and organoleptic assessment. The presence of periodontal disease was determined by 6-point periodontal probing, to assess pocket depth and bleeding points. Of the 1000 patient charts sent electronically to the University of Michigan for analysis, 649 participants were selected based on complete pre- and post-treatment data, and statistically analyzed by a statistician, who was an expert in case study analysis. The post-treatment reduction of oral malodor was 80% ($P = 0.0001$). The difference in bleeding points pre- and post-treatment was 87% ($P = 0.0001$). There was a decrease in the number of teeth with 6 and 7 mm pockets by 76% and teeth with 5 mm pockets decreased by 84% ($P = 0.0001$). Treatment with the antibiotic rinse had a positive change in the periodontal status and breath odor of these patients. These data indicate that there is considerable advantage to the use of topical antibiotic rinses. A substantial decrease in both halitosis and periodontal disease markers can be achieved without the risk of the systemic effects of an oral antibiotic.

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Periodontal disease is a common affliction of adults, with most forms reflecting a tissue inflammatory response to bacterial accumulations on the teeth.[1] Mild forms of periodontal disease affect 75% of adults in North America, and more severe forms affect 20%-30% of adults.[2] Periodontal disease is a combination of an infection and an inflammatory condition associated with anaerobic Gram-negative bacteria.[3] Whereas gingivitis is an inflammation of the gingival tissue, periodontitis is a biofilm-associated inflammatory disease of the periodontium, and is a major cause of tooth loss.[4] The primary microbial factor contributing to this disease is a shift in the content of oral microflora, while the primary immunological factor is the destructive host's inflammatory response.[4] Periodontal pockets harbor a large assortment of pathogenic species with the most harmful ones being Gram-negative anaerobic rods.[5,6]

In 1999, Loesche described both the old and new approaches to periodontal disease, and proposed a different approach to periodontal disease.[7] Traditionally, periodontal care has been more surgically oriented, based on the *non-specific plaque hypothesis* of reducing all oral bacteria to minimize inflammatory risk and treat periodontal disease.[7] The new paradigm, the *specific plaque hypothesis,* recognizes that only a certain few Gram-negative anaerobic pathogens cause periodontal disease, and that they can be controlled with specific antimicrobial agents.[7] Loesche wrote, *The contrast between the two paradigms can be succinctly stated as follows: The antimicrobial therapy reduces the cause, while the surgical therapy reduced the result of the periodontal infection.*[7] In theory, the specific plaque approach with antimicrobials would decrease risk, make treatment more effective, and be more economical. Furthermore, this new approach would have a beneficial impact on oral links to systemic diseases, such as cardiovascular disease and diabetes.

An ideal opportunity to assess Loesche's specific plaque theory occurred at the *Fresh Breath Clinic* (Toronto, Canada, www.freshbreath.ca). This clinic offered no traditional services, such as prophylaxis, scaling, or surgery. Patients of the clinic were getting those services for some time from their regular dentist, but were dissatisfied enough with the ineffectiveness of the traditional approach to treat their halitosis that they sought an antimicrobial approach in addition to their regular care. Measuring the changes in periodontal reference points, such as bleeding on probing and pocket depths between their initial visit and progressive appointments, would demonstrate the effectiveness or non-effectiveness of the antimicrobial approach. It is important to note that there was no change in the recall or traditional protocol with their regular dentist. In fact, the vast majority of patients did not want their dentist to know they were seeking additional care beyond their dentist's office.

Oral malodor, like periodontal disease, has been linked to the Gram-negative anaerobic pathogens that are implicated in periodontal disease, including *Porphyromonas gingivalis, Prevotella intermedia, and Fusobacterium nucleatum*.[8,9] These bacteria are capable of producing substantial levels of volatile sulfur compounds (VSCs).[10,11] VSCs are able to alter the permeability of gingival tissues, inducing an inflammatory response.[12] In addition, VSCs can penetrate deeply into other tissues and damage the epithelium, basement membrane, and underlying lamina propria.[13] Treatment of oral malodor as a result of VSC production should not be considered esthetic therapy, since these chemicals are toxic to periodontal tissues, even at low concentrations. Decreasing concentrations of VSCs may be a significant adjunct to periodontal therapy and in the prevention of periodontal disease.[14]

Species of oral bacteria are found as plankton (free-floating) bacteria, and in complex polymicrobial associations (biofilms) that exhibit a different structural and functional behavior than planktonic bacteria. In the past, most research was conducted on plankton bacteria, but researchers are now focused on the biofilm properties of dental plaque.[15] The formation of biofilm is a complex structural organization, that includes extracellular matrices of polysaccharides, proteins, lipids, nucleic acids, and other polymers with distinctive architecture, water channels, and available nutrients.[16-18] Biofilm provides a structure whereby different bacterial species are able to share nutrients. Waste matter from one species often becomes another species' food source.[19]

The symbiotic host-microbe relationship changes to a pathogenic one as the microbial community shifts to species that include *red cluster* bacteria, including *Treponema denticola, Porphyromonas gingivalis, Tannerella forsythia,* and others, such as *Prevotella intermedia*.[20] These pathogenic biofilms can avoid an immune system attack, as antibodies are unable to perforate the matrix, and phagocytes have difficulty in engulfing large clumps of biofilm fragments.[21] The inability of many antibiotics to penetrate the matrix offers further protection to the bacteria.[21]

The disease process progresses with few obvious signs. Some of the signs of periodontal disease may be bleeding when flossing, or a bad taste and/or breath odor, but these symptoms are not always recognized as indicators of periodontal infection.[22] These warning signs can sometimes be misinterpreted and assigned to one of the many other etiological factors that contribute to oral malodor.[10,11,22]

The aim of this study was to demonstrate that an oral antibiotic rinse consisting of metronidazole powder combined with nystatin is an effective treatment for both oral malodor and mild to moderate periodontal disease, and that there is a significant positive response by both conditions with this treatment. Prior to his recent passing, Loesche had the opportunity to analyze the results of this study, and witness its implications for a specific plaque approach to periodontal care.

Table 1. Paired t test results showing changes in oral malodor post-treatment.

	Before	After	Difference	DF	*t* value	*P* value
Halimeter	166.0 (639)	74.0 (576)	96.0 (571)	570	15.70	<0.0001
OCH_2S	130.0 (342)	29.0 (421)	102.0 (220)	219	5.89	<0.0001
OCMM	36.0 (342)	8.0 (249)	28.0 (421)	420	5.09	<0.0001
Odor	2.6 (566)	0.5 (577)	2.1 (586)	565	36.56	<0.0001
pH tongue	7.3 (648)	6.8 (562)	0.5 (559)	588	12.92	<0.0001

Measurements are the mean at baseline, and after rinsing with the antibiotic rinse for 2 weeks, 2 times a day. OCH_2S = hydrogen sulfide measured on the OralChroma, OCMM = methyl mercaptan measured on the OralChroma, Odor = organoleptic measurement of malodor (0-5)

Table 2. Pearson correlation analysis of periodontal and malodor measurements.

	Odor	Halimeter	OC-H_2S	OC-MM	OCDMS	BOP
Odor	1.0000	0.40650	0.30455	0.28108	-0.04996	0.24137
		<.0001	<.0001	0.0001	0.4982	<.001
Halimeter	0.40650	1.0000	0.60101	0.48511	0.02457	0.14217
	<.0001		<.0001	<.0001	0.7440	0.0128
OCH_2S	0.30455	0.60101	1.00000	0.54339	-0.02418	0.02527
	<.0001	<.0001		<.0001	0.7426	0.7407
OCMM	0.28108	0.48511	0.54339	1.00000	0.17579	0.01321
	<.0001	<.0001	<.0001		0.0158	0.8626
OCDMS	-0.04996	0.02457	-0.02418	0.17579	1.00000	-0.17338
	0.4982	0.7440	0.7426	0.0158		0.0221
BOP	0.24137	0.14217	0.02527	0.01321	-0.17338	1.00000
	<.0001	0.0128	0.7407	0.8626	0.0221	

Pearson correlation coefficients/prob > IRI under Ho:Rho=0. Data from appointment were analysed. Odor = whole mouth organoleptic scores; Halimeter = halimeter reading; OCH_2S = Hydrogen sulfide reading on OralChroma; OCMM = Methyl mercaptan readings on OralChroma; OCDMS = dimethyldisulfide reading on OralChroma; BOP = bleeding on probing

Materials and methods

Individuals with self-diagnosed halitosis attended the Fresh Breath Clinic. Gender composition of the group was 60% women and 40% men, with an age range of 15 to 85. On the first appointment, patients were interviewed with respect to their health history, and bad breath or taste concerns. VSCs were measured using the Halimeter (Interscan Corporation) and the OralChroma (Abilit Corporation). Organoleptic measurement of the mouth and nose air was determined by experienced dental personnel, and scored according to the standards for this procedure.[23] Tongue base, tongue dorsum, and proximal areas of the dentition were evaluated for odors. Biofilm samples from these areas were taken from each patient. A Gram stain analysis provided morphological information on the microorganisms present in the oral cavity. In addition, the microbiology of the teeth and tongue was tested with a BANA strip for red complex clusters. Six-point periodontal probing was used to assess pocket depth and bleeding points. Scaling and root planing was not available at this clinic, therefore patients

Table 3. Paired t test results showing changes in number of pockets post-treatment.

	Before	After	Difference	DF	*t* value	*P* value
BOP	20.5 (633)	3.2 (422)	18.8 (419)	418	17.05	<0.0001
4 mm pockets	4.9 (641)	1.3 (423)	4.0 (421)	420	9.68	<0.0001
5 mm pockets	1.4 (641)	0.2 (421)	1.2 (422)	421	7.48	<0.0001
6 mm pockets	0.4 (641)	0.1 (421)	0.3 (422)	421	3.98	<0.0001
7 mm pockets	0.2 (641)	0.02 (421)	0.2 (421)	421	3.36	<0.0001

Measurements are the mean at baseline and after rinsing with the antibiotic rinse for 2 weeks, 3 times a day. Difference refers to the change in the number of pockets per patient. Pocket depth and BOP determined by using 6-point probing.

Table 4. Percent change in periodontal parameters and oral malodor measurements (n = 649).

Test	Before	After	Difference
Bleeding on probing	19.98	2.68	87%
No. teeth with 4 mm pockets	4.86	1.24	79%
No. teeth with 5 mm pockets	1.22	0.15	84%
No. teeth with 6 mm pockets	0.38	0.09	76%
No. teeth with 7 mm pockets	0.17	0.04	76%
Odor Score	2.60	0.50	80%

$P = 0.0001$

had no scaling done prior to treatment, although many of them were on a 3-month system of scaling at their dental office.

A sodium fluorescein 0.75% solution was used with a blue filtered mirror to evaluate the amount of biofilm present. Patients were instructed in oral care, with emphasis on techniques such as interdental cleaning and tongue scraping, which were seen as deficient. Patients with calculus and stain were advised to make an appointment with their dentist to have their teeth scaled.

Treatment was based on odor levels, the BANA test, and the results of the microbiology samples. Treatment initially consisted of rinsing with chlorhexidine 0.2% for 2 weeks, twice daily. Patients complained that, although their breath problems had decreased in intensity, some of the odor and bad taste remained, proving that the use of chlorhexidine alone was insufficient to completely reduce oral malodor.[24] To improve treatment response, systemic metronidazole and clindamycin were used to treat the patients, followed by the 0.2% chlorhexidine. However, systemic side effects and the use by patients of other pharmaceutical medications complicated this approach. Thus, another method had to be designed to successfully treat the chief complaint of halitosis.

The treatment chosen was a metronidazole-nystatin mixture that was used as a rinse. Sixteen tablets, each containing 250 mg of metronidazole (APO-metronidazole, Apotex Corp.), were crushed, the larger particles filtered out, and the fine particles mixed with a nystatin suspension and 50 ml of water. Patients dispensed a "capful" (2 ml) of this mixture, swished and gargled for 30 seconds and expectorated the contents. Patients rinsed 3 times a day for 30 seconds each. Once per day, they flossed immediately after rinsing. After each rinse with antibiotic mixture, patients were to abstain from eating or drinking for 30 minutes. Although some patients found the rinse bitter and difficult to use, most were able to comply with the regimen. After 2 weeks of rinsing, patients returned to the clinic for an evaluation of treatment. Breath odor measurements and periodontal measurements were repeated, and compared with those taken at the initial appointment. Microbiology samples of the tongue base, tongue dorsum, and teeth were taken, analyzed, and compared with the pretreatment samples. Patients were then placed on chlorhexidine 0.2% for 2 more weeks, followed by routine rinsing with non-prescription mouthwashes that the patient selected.

To confirm the effectiveness of the antibiotic rinse, 1000 patient charts were sent electronically to the University of Michigan for analysis, of which 649 were selected based on complete pre- and post-treatment data, and then statistically analyzed by an expert in case study analysis.

Results

The clinical results were encouraging, and patients provided positive feedback on the use of this protocol. Differences in baseline and post-treatment measurements of breath odor were compared using a paired t test, and all reductions were significant ($P < 0.0001$) (Table 1). There was significant correlation between the organoleptic measurements, Halimeter readings, and OralChroma measurements of hydrogen sulfide and methyl mercaptan (Table 2). There was no significant correlation between dimethyl sulfide and the other measurements. Bleeding on probing correlated significantly with organoleptic measurements, but all other correlations were weak and insignificant.

The periodontal status of these patients showed significant change (Table 3). A substantial decrease from baseline is shown using a paired t test for bleeding on probing, and for the number of pockets ranging from 4-7 mm. These changes were significant ($P < 0.0001$). The percent decrease was substantial, with reductions in bleeding points at 87%, and a decrease in the number of teeth with 6 and 7 mm pockets by 76% (Table 4). The number of teeth with 5 mm pockets decreased by 84%, and those with 4 mm pockets decreased by 79%. Breath odor decreased by 79%, and bleeding points by 87%. All were highly significant ($P < 0.0001$).

Discussion

The treatment with the antibiotic rinse had a positive change in the periodontal status of these patients, and resulted in substantial reduction in bleeding points and periodontal pockets. Breath odor

decreased dramatically, to the point that most patients felt that their breath had become "normal." Vigorous rinsing, along with flossing to move particles into the sulcus was aided by the phenomenon called the *Venturi effect.* When particles enter the gingival sulcus and float over a pocket, the crevicular fluid drops, pulling the particle deeper into the pocket. The concentrated antibiotic particles can then act on the biofilm found at the base of these pockets. This would explain, in part, the change in pocket depth and the difference in the number of pockets, pre- and post-treatment.

Although scaling and root planing are considered the gold standard in the treatment of periodontal disease and have been used to decrease breath odor, recolonization of pathogens—along with the recurrence of the disease and breath odor—is common after scaling.[25] The use of antimicrobial therapy, along with scaling and root planing, is becoming conventional therapy. Antibiotics can be applied locally or administered systemically. However, since these organisms vary considerably in sensitivity to antibiotics, choosing the appropriate antimicrobial chemotherapy is challenging.[6] As an alternative, treatment aimed at suppressing inflammation or host modulation is also used. Most successful treatments address both the bacterial and inflammatory component of the condition.[4]

When antibiotics are taken orally, the efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and pharmacokinetic characteristics of the drug, and by local environmental factors.[26,27] This treatment is based on the belief that the antibiotic agent taken systemically can provide sufficient concentrations necessary to inhibit the pathogens.

Important considerations when choosing a treatment plan are the protection of pathogens by the extracellular matrix, the total bacterial load relative to maximum achievable antibiotic concentration, and extradental oral sites not affected by the therapy.[28] Several investigators found significant improvement of attachment levels when periodontitis was treated with systemic metronidazole.[29-31] The low minimum inhibitory concentration of metronidazole made it a useful chemotherapeutic agent for treating anaerobic infections, such as *Porphyromonas gingivalis.*[32] Other studies showed improved clinical outcomes with the systemic use of metronidazole/amoxicillin, together with full mouth periodontal debridement.[33,34]

An advantage of systemic antibiotic therapy over topical application of an antimicrobial agent to a specific site is that systemic antibiotics enable the administration of a drug to multiple sites of disease activity, and may reduce pathogens colonizing on oral mucosa, the tongue, and tonsilar areas. The suppression or potential elimination of periodontal pathogens from the oral tissues is an advantage, in that the risk for future translocation of organisms and recolonization is reduced, thereby potentially reducing the risk for recurrent disease.[35,36]

There is, however, a considerable advantage to the use of topical antibiotic rinses. A topical application, in the form of a rinse with tiny particles of antibiotic, will coat all oral tissues, as well as the tonsillar areas, achieving an overall decrease in halitosis and periodontal disease markers without the risk of the systemic effects of an oral antibiotic.

Conclusion

This study of cases from a halitosis clinic shows the potential of using antibiotic rinses to treat periodontal disease and oral malodor caused by oral pathogens. Since these cases were not intended initially to be a component of a study, and were analyzed because of the excellent clinical results that were achieved, a future controlled clinical study would be useful to determine if the results are due to a specific population, or if this can be extrapolated more generally, as a useful adjunct to the treatment of breath odors and periodontal disease.

The results of this study, however, are significant enough to warrant consideration of Loesche's specific plaque approach as an initial therapy, or at least in conjunction with traditional nonspecific approaches, such as scaling and prophylaxis. More economical and effective periodontal care will enhance the chances of success of other restorative, esthetic, and/or implant dental procedures. It will also have a positive impact on oral/systemic disease links.

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