Periodontitis as a Contagious Infection: Contemporary Use of Antimicrobial Agents. Part I: Bisbiguanides

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Bacteremia is a common occurrence in patients with periodontal diseases, even simple gingivitis. Tooth brushing, especially improper and/or overzealous tooth brushing, routinely occasions a significantly perceptible elevation in the quantity of oral-origin microorganisms in the circulating blood. Initial therapy, whether a routine prophylaxis in a gingivitis case, or scaling and root planing in a periodontitis patient, always leads to bacteremia, often massive; hitherto, most such bacteremias have been assumed to be both transient and inconsequential for the patient's systemic health. This assumption is no longer tenable in the light of new clinical and scientific knowledge. The purposes of the present article are: 1) to critically review the contemporary use of antimicrobial agents in dental and dental hygiene practice in the USA and internationally; 2) to revisit and review the peculiarities that characterize inflammatory gingival/periodontal disorders which may demand more aggressive use of antimicrobial agents now and in the future; and 3) to conceptualize the emerging treatment concepts that are targeted towards treatment of gingival/periodontal diseases as acutely contagious clinical entities.

Key words: periodontitis, contagion, full mouth disinfection, chlorhexine, medicinal treatment

INTRODUCTION

Numerous clinical studies over the past decade have demonstrated the potentially serious systemic health consequences of penetration into the bloodstream by putatively pathogenic microorganisms from the oral cavity, or the toxic products of such microorganisms. The positive correlations between and among periodontitis, cardiovascular diseases, pulmonary disorders, premature and low birth weight infants, stroke and other systemic problems have provided the impetus for a renaissance to the ages old concept of "focal infection" as an etiologic factor in systemic diseases (DeRiso et al, 1996; Beck and Offenbacher, 1998).

It is now acknowledged that rinsing with an antiseptic solution before dental treatment reduces the absolute number of bacteria in the oral aerosol emanating from a patient's mouth (Micik et al, 1969; Wyler et al, 1971; Worall et al, 1998); this leads to a reduction in the potential danger of pulmonary bacterial aspiration by the patient, and reduces the severity of subsequent bacteremia (Logothetis and Matinetz-Welle, 1995; Ellworthy et al, 1996).

It was recently shown that successfully incorporated dental implants in periodontitis patients are rapidly infected by microorganisms that derive from infected sites elsewhere in the mouth, or even via salivary transmission of pathogenic bacteria from kissing a periodontally diseased spouse (Asikainen and Chen, 2000).

Conceptually, it is therefore not difficult to understand that the traditional approach to the conservative initial therapy for periodontal disease, specifically the quadrant-by-quadrant approach to debridement, and neglecting entirely any evaluation of the patient's life partner, foster a circumstance that encourages rapid periodontal re-infection.

For these reasons, enhanced antibacterial measures in the dental and dental hygiene operatories, and at-home by patients, appear to have become necessary in the face of such new scientific knowledge (Dajani et al, 1997).

In choosing an appropriate agent for intra-oral disinfection, it will be incumbent upon the clinician to consider only those products whose efficacy has been scientifically proven. In this article we will provide a comprehensive appraisal of contemporary oral antimicrobial agents, and point out new possibilities and new indications for the use of such agents by the dental team. The questions that remain include: Is the target to be supra-gingival or sub-gingival plaque microorganisms? And, perhaps more importantly, what is the end-goal of any antimicrobial application: Oral health? Systemic health? A supportive effect? A true therapeutic effect?

HISTORICAL PERSPECTIVE

Local (topical) antiseptic agents have been used in clinical medicine for more than 140 years. Lister (1860) successfully prevented wound infections by use of a topical 5% carbolic acid solution. As early as 1940, attempts were made to inhibit dental plaque formation through use of rinsing solutions containing heavy metals such as copper, zinc and silver; however, none was particularly effective and the adverse effects were unacceptable (Slanetz and Brown, 1949; Saxer, 1980). It was not until 1962 that the plaque-inhibiting properties of chlorhexidine digluconate (CHX) were described (Schroeder et al, 1962). Subsequently, other agents were tested and employed for oral disinfection, with greater and lesser success (see below). The therapeutically fostered intent was to reduce gingivitis, on the assumption (at that time) that gingivitis was an obligate precursor to destructive periodontitis. Then, the goals for prevention and treatment of periodontitis included reduction of the growth of bacteria, their pathogenicity and their by-products, in order to maintain periodontal tissue integrity. Earlier studies in the discipline of cariology had shown that antiseptic agents could significantly inhibit acid production by plaque microorganisms (Skjörland et al, 1978); the extrapolation was that a similar beneficial effect could be attained in the soft tissues by the application of antimicrobial solutions, to reduce destructive enzymatic substances (Roella et al, 1997).

PECULIARITIES OF THE PERIODONTAL INFECTION

Topical application of antimicrobial agents in instances of skin abrasions, lacerations, burn wounds etc. is generally effective because the offending microorganisms are accessible to the solutions or salves employed. The situation in the oral cavity of a periodontitis patient, however, presents several significant obstacles to traditional topical antibacterial treatment. First, the periodontal pocket (or even the gingival sulcus) is only a "potential" space, i.e., the soft tissue of the lateral pocket wall is closely apposed, though not integrally attached, to the tooth surface, held there effectively by fluid surface tension forces. While a pocket can be mechanically probed to its true depth, the pocket is not "open" to the oral cavity. Therefore, while rinsing with an effective antimicrobial solution will reduce bacterial levels in the mouth, such rinsing will in no case have any effect on microorganisms within periodontal pockets, or even within gingival sulci (Slots, 2000).

Secondly, dental plaque is a true "biofilm," consisting of thick layers of microorganisms within a polymeric matrix which is produced by the microorganisms themselves. Within this biofilm, microorganisms become organized into colonies that attach tenaciously to the tooth surface, and which are protected by a surface glycocalyx layer. For example, bacteria within an organized biofilm are 500–200,000 times more resistant to various antimicrobial agents than individual bacteria in culture (Tonetti, 1997; Dreeszen, 2000; Slots, 2000). Therefore, if traditional antimicrobial agents are to be effective, the biofilm's architectural structure must first be disrupted. This can be accomplished by sonic or ultrasonic subgingival instrumentation (Baehni et al, 1992), and improved gingival conditions after this type of treatment have been reported (Walsh et al, 1992; Walsh et al, 1995; Cutler et al, 2000). In addition, bacteria that are normally killed or suppressed by, for example, chlorhexidine often develop resistant strains (Marrie and Costerton, 1981), a phenomenon that has also been demon-

strated for povidone iodine (Anderson et al, 1990). The possible effects of targeted and combined use of antiseptics in clinical situations has not yet been sufficiently researched, but there is accumulating evidence that traditional debridement may need to be followed-up by effective irrigation with antimicrobial solutions in order to sufficiently suppress bacteria over the long term (Pallasch and Slots, 1996; Socransky et al, 1999).

INFECTION AND TRANSMISSION OF BACTERIA

The past decade has seen reports from numerous research centers demonstrating that periodontopathic bacteria within a patient can be transmitted from an untreated quadrant to previously treated quadrants, for example via interdental hygiene products, and also from person to person via saliva (Alahuusua et al, 1991; Quirynen et al, 1996; von Troil-Linden et al, 1996). Oral hygiene devices (e.g., tooth brushes, interdental aids) routinely test positive for both aerobic as well as anaerobic bacteria after intraoral use (Quirynen et al, 2001). In addition, pathogenic microorganisms from periodontal pockets, intraoral niches, tongue, tonsils and partially-erupted third molars can transfer to, and subsequently infect, recently-treated periodontal sites. It is for these reasons that the concept of "full mouth disinfection" has recently come under scrutiny in periodontics and periodontal therapy. While the concept is well-established in cariology, it is relatively new in periodontics and dental hygiene. For example, Axelsson et al (1987) demonstrated that professional plaque removal in combination with chlorhexidine rinses in children with initially high *Streptococcus mutans* levels led to significant caries reduction. Recent advanced technology in microbiology has proven that most oral bacteria can be transmitted via oral fluids (Asikainen and Chen, 1999). Such knowledge leads to the conclusion that periodontitis is, in fact, a contagious infection, which must be treated by means of antibacterial strategies, and not solely by mechanical debridement. A combined therapeutic approach should lead to protection and enhancement of periodontal tissue homeostasis and integrity (Slots, 2000).

ANTIMICROBIAL AGENTS FOR INTRAORAL USE

Bisbiguanides

Chlorhexidine (CHX): Following the pioneering work of Schroeder et al (1962), Renggli (1966) confirmed the favorable intra-oral antimicrobial properties of chlorhexidine digluconate, which is chemically a bisbiguanide. Numerous investigators worldwide corroborated the early research (Löe and Schiött, 1970; Lang et al, 1982; Mühlemann, 1984; Gjermo, 1989; Addy and Moran, 2000). Even in the absence of routine mechanical oral hygiene practices, rinsing daily with CHX can almost completely prevent plaque formation and subsequent gingivitis. Numerous comparative clinical studies have repeatedly demonstrated that, in comparison to all other antiseptic solutions (see below), CHX is the most effective antimicrobial agent for use in the oral cavity to inhibit plaque formation (Siegrist et al, 1986; Grossman et al, 1989; Mankodi et al, 1989; Overholser et al 1990; Roella et al, 1997). Chlorhexidine possesses a very broad spectrum of antibacterial efficacy (Addy and Renton-Harper, 1997), and it binds tenaciously to both dental and mucosal surfaces, a characteristic known as "substantivity." Active CHX is thus released slowly over time, making a single oral rinse effective for up to 24 hours post-rinsing (Table 1). Lander et al (1996) reported that a single rinse with a 0.2% CHX solution (or a 0.2% CHX **gel**, see below) resulted in a significant reduction of intraoral spirochetes and motile rod-shaped bacteria. Using a 0.2% rinsing solution, CHX effectiveness against *Candida albicans* was also observed (Budtz-Jörgensen and Lombardi, 1996). Numerous subsequent clinical studies in recent years have again confirmed these multispecies results (Hull, 1980; Addy, 1986; Korman, 1986; Lang and Brecx, 1986; Mandel, 1988; Lang et al, 1997; Schiffner, 2000). Because of its efficacy, CHX has also been advocated for physically and/or mentally handicapped individuals whose oral care has to be administered by non-dental professional care-givers (Addy and Renton-Harper, 1997; Hassel et al, 2000).

The **adverse side effects** of oral CHX use are well known, including dental staining and a reversible disturbance of taste perception, both of which have been reported to occur relatively infrequently (Plüss et al, 1975; Gargari and Kabani, 1995),

Table 1 Concentration of chlorhexidine in saliva 0.5–24 hours after rinsing with 0.2% chlorhexidine solution, expressed in nmol (nanomoles) and in ppm (parts per million), by three subject volunteers*

Nmol conc	0.5	1	2	4	8	12	24 hr
Subject A	89	44	23	13	5	0.6	0.33
Subject B	89	71	45	28	2.2	1.1	1.1
Subject C	336	140	52	51	11	5.6	5.6
PPM conc							
Subject A	0.05	0.02	0.01	0.01	♦	♦	♦
Subject B	0.05	0.04	0.02	0.015	♦	♦	♦
Subject C	0.17	0.07	0.03	0.03	♦	♦	♦

* adapted from Bonesvoll and Gjermo, 1978
♦ negligible

but which effectively limit the routine and prolonged use of this agent. In contemporary dental practice, CHX is mainly employed as a secondary preventive agent following periodontal or oral surgical procedures (Westfelt et al, 1983), as well as before and after the placement of dental implants (Ivanove et al, 2000), and following surgery for the placement of membranes ("GTR" technique; Zucchelli et al, 2000). Jenkins et al (1988) demonstrated that "targeted" topical CHX application onto individual tooth surfaces provides effects equal to those achieved with oral rinsing, but side effects were less often observed. Other studies corroborated this finding (Jones, 1997; Francetti et al, 2000; Slots, 2000). A few reports showed that CHX is mildly toxic to gingival fibroblasts (Bassetti and Kallenberger, 1980) and may therefore impair wound healing, but this potential effect is generally regarded as not clinically relevant.

When considering the use of CHX, the clinician must always ask: "What is the goal?" Ellworthy et al (1996) were able to show that approx. 2–3 hours after an oral CHX rinse, the maximum bacterial reduction (approx. 90%) is achieved. Therefore, in cases where the goal is to prevent a bacteremia, CHX rinsing should be performed 2–3 hours before and immediately before the dental procedure, as recommended by the American Heart Association (Cohen and Rose; 1998). As another example, rinsing with CHX reduced by 65% the frequency of hospital-acquired respiratory infections in patients who had undergone cardiac surgery (DeRiso et al, 1996). A recent report described a positive correlation between periodontitis and chronic obstructive pulmonary disease (Scannapieco, 1999).

In the United States, chlorhexidine is available only by prescription, and only as a commercially prepared 0.12% **rinsing solution** (e.g., Peridex®, Periogard®). In Europe, Scandinavia and elsewhere worldwide, CHX is available as a concentrated solution that can be diluted with water by the patient at home to establish higher concentrations (Saxer and Linden, 1977). Also in Europe, CHX is commercially available in the form of a **gel**, which a patient can apply topically at home to selected individual sites (Addy and Moran, 2000; Borer, 1978); however, gels require a concentration of at least 1.0% to be effective against microorganisms (Saxen et al, 1976; Zickert et al, 1982; Luthman et al, 1986; Gisselsson et al, 1994). Several chlorhexidine sprays, are now commercially available (Butler, HaWeKerr), and have been advocated by many authors because they can be targeted to specific sites, thus reducing side effects (Francetti, 2000). Chlorhexidine sprays (Peridex® or Periogard® in a simple plastic spray bottle) have been shown effective against gingivitis in institutionalized handicapped persons in whom tooth brushing is impossible (Dever, 1979; Burtner et al, 1991; Chitke et al, 1991; Hassell et al, 2000). CHX spray is also advocated in conjunction with "full mouth disinfection" (Quirynen et al, 1995; see also "Consequences for Periodontal Therapy" below).

Table 2 Attachment gain (AG) and reduction of probing depth (PD) following scaling and root planing, in comparison to initial values, in studies incorporating chlorhexidine and other adjunctive procedures

	4–6 mm		7+ mm		Remarks
Investigators	PD	AG	PD	AG	
Christie et al, 1998	1.9	0.8	3.9	2.5	12 mo, 0.2% CHX 2x/day
Quirynen, 2000					
Single rooted	1.0	0.2	1.8	0.5	C*, S/RP#
	1.9	1.0	3.5	1.0	Fdis**
	2.3	1.6	3.3	1.7	FRP## in 24 hr
Molars	0.8	0.0	1.0	0.5	C, S/RP q. 14 d
	1.5	0.8	3.0	2.0	Fdis
	1.8	1.3	3.0	2.3	FRP

* C = control
# S/RP = traditional scaling and root planing
** Fdis = full mouth disinfection
FRP = full mouth scaling and root planing in 24 hr

Subgingival irrigation with CHX, whether performed in the operatory by the dentist or hygienist, or by the patient at home (e.g., using the Pik-Pocket by WaterPik®; (Wennström, 1997)) can lead to a significant reduction in probing depths (Lander et al, 1986; Gustke, 1979). However, it has been shown that traditional ultrasonic tips used with simultaneous CHX rinsing seldom leads to adequate concentrations of CHX in the depth of the pocket, and the substantivity of CHX for the root's cementum surface is quite low (Stabholz et al, 1998). These facts probably account for the report of no clinical effect in some studies (Taggart et al, 1990; Chapple et al, 1992), and positive improvement in other investigations (Braatz et al, 1985; Reynolds et al, 1992). Studies have demonstrated that reduction of periodontal probing depth and/or gain of attachment will only be realized with optimum **daily** subgingival irrigation by the patient (Macaulay et al, 1986; Chapple et al, 1992); unfortunately, few patients are dextrous enough or sufficiently motivated to keep up such a daily regimen for very long. On the other hand, a skilled dental hygienist can access 90% of the pocket area with antibacterial solution if the irrigation tip reaches the fundus of the pocket (Eakle et al, 1986; Flemmig et al, 1990; Flemmig, 1993). In one recent long-term clinical trial, Christie et al (1998) thoroughly irrigated periodontal pockets with CHX immediately following scaling and root planing, and required patients to rinse twice daily with CHX for the subsequent 12 months. With this combined technique, significantly better results (PD reduction, attachment gain) were achieved compared to other treatment regimens (Table 2; see also Felo et al, 1997). Similar results were reported by Quirynen et al (2000) (see Table 2).

Chlorhexidine-containing **chewing gum** is commercially available in England, but not in the USA. Clinical results, in terms of plaque and gingivitis reduction after daily or twice daily chewing, have been inconsistent (Ainamo and Etemadzadeh, 1987; Ainamo et al, 1990; Imfeld, 1999).

Rapidly gaining acceptance is the CHX-containing **varnish** (e.g., Chlorzion, EC-40, Cervitec), developed mainly for the battle against root surface caries and cervical sensitivity (Emilson, 1994), but shown subsequently to also be effective in reducing supragingival plaque accumulation and gingivitis (Araujo, 2002). Numerous recent clinical trials showed that CHX varnish reduced plaque on proximal tooth surface for up to three months (Twetman and Heintze, 1999; Anusavice, 1998;

Microorganism	CHX	Iodine	SnF2
A. actinomycetemcomitans	2.0	0.5	4.0
P. gingivalis	0.5	0.25	0.5
P. intermedia	2.0	0.5	8.0

* Caulfield et al, 1987

Table 3 Minimal bactericidal concentration ("MBC") expressed as a percentage (1% = 10,000 ppm), for chlorhexidine digluconate, providone iodine and stannous fluoride against three periodontopathic microorganisms*

Investigator(s)	Medication	PD reduction
Soskolone et al, 1997	"PerioChip"	1.1 mm
	Scaling/root planing	0.7 mm
Jeffcoat et al, 1998	"PerioChip"	0.9 mm
	Scaling/root planing	0.7 mm

Table 4 Pocket probing depth (PD) reduction after scaling and supplementary topical medication with the "PerioChip," in relation to initial PD. Initial PD 6–7 mm. Observation time 3–6 months

Investigator(s)	Medication	PD reduction
Garrett et al,	Doxycycline	1.5
1999, 2000	S/RP	1.7
	Vehicle only	1.2
Caton et al, 2000	Doxycycline, 20 mg/d	1.7
	S/RP	1.1
van Steenberghe et al,	2% Minocycline	1.7
1993	S/RP	1.4
van Steenberghe et al,	2% Minocycline	1.2–1.5
1999	S/RP	1.1
Stelzel et al,	Metronidazole	1.4
1999, 2000	S/RP	1.1
Lie et al, 1998	Metronidazole	1.6
	S/RP	1.1
Riep et al, 1999	Metronidazole	1.7
	S/RP	1.7
Lie et al, 1998	Tetracycline	1.6
	S/RP	1.1

Table 5 Pocket probing depth (PD) reduction after scaling (S/RP) and supplementary topical medication(s), in relation to initial PD. Initial PD 6–7 mm. Observation time 3–6 months

Ekenback et al, 2000; Fennis-le, 1998; Sköld et al, 1998; Twetman and Petersson, 1998; Forrgie et al, 2000; Hausen et al, 2000; Petersson et al, 2000; Van Lunsen et al, 2000; Zaura-Arite and ten Cate, 2000).

Chlorhexidine-containing **toothpaste** is available in Europe and England, but not in the USA. Even with a CHX concentration of 0.4–1.0%, however, the clinical effect is not significant. It has been speculated that the other ingredients in the dentifrice may inactivate the CHX (Gjermo and Roella, 1971; Barkvoll et al, 1989; Yates et al, 1993; Sanz et al, 1994).

The chlorhexidine-containing biodegradable gelatin "**chip**" (PerioChip®) designed for insertion into periodontal pockets of 5+ mm depth, has been tested clinically in the USA (Jeffcoat et al, 1998; Jeffcoat et al, 2000) and in Europe (Soskolne et al, 1997). The CHX concentration in the pocket over a 7-day period averaged 125µg/ml; unfortunately, this concentration is too low to markedly influence some periodontal pathogens such as

Actinomyces actinomycetemcomitans and *Porphyromonas gingivalis*. The "MBC" (minimum bactericidal concentration) for these microorganisms is 5,000–20,000 ppm (Table 3). In two clinical studies, it was reported that the "chip" led to better attachment gain than scaling and root planing alone (Table 4); however, the results in both test and control groups were considerably poorer when compared to data from previous S/RP studies incorporating other adjunctive therapies (Table 5), so the interpretation of a "clearly better effect" has been widely questioned. Finally, many studies have revealed that agents placed into the periodontal pocket are rapidly eliminated by the constant flow of sulcus fluid (Oosterwaal et al, 1989).

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