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Periodontal therapy using local delivery of antimicrobial agents

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Periodontal diseases are bacterial infections that occur at or below the gingival margin. They occur in approximately 70% of the United States population and severely affect 20–30% of the United States population, who spend approximately $5 billion per year on therapy.

Optimum, cost-effective preventive therapy might logically lie in the elimination or control of the infection. Over the last century, numerous investigations attempted to define the etiologic agents of this disease. A small group of specific bacterial species are now considered to be the causative agents [1]. This group includes *Bacteroides forsythus, Porphyromonas gingivalis, Treponema denticola*, and *Actinobacillus actinomycetemcomitans*.

The recognition that specific microbes are the causative agents of periodontal disease stimulated the development of new tools to reduce the supra- and subgingival microbiota. Among the agents are chlorhexidine mouthwash, triclosan dentifrice, electronic toothbrushes, and systemic and local drug delivery. The purpose of these approaches is to attempt to disinfect pathogen reservoirs.

Local drug delivery is the focus of this article. Several treatments normally adjunctive to scaling and root planing have been tested. These include chlorhexidine disks, tetracycline fibers, and gels containing doxycycline, metronidazole, or minocycline microspheres. This article examines the efficacy of these local delivery systems.

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A MEDLINE search strategy was developed and implemented to identify studies on the efficacy of local antimicrobial drug delivery systems for the treatment of periodontal disease (Table 1). The search included articles from 1966 to September 2001 week 1, and was executed on the Ovid interface for MEDLINE (http://gateway.ovid.com). The five antimicrobial agents included in this search were local delivery products containing metronidazole (MET) (Elyzol®, a gel that can be injected into the periodontal pocket), chlorhexidine (CHX) (PerioChip®, a flat disk that can be inserted into the pocket), tetracycline (TTC) (Actisite®, a fiber that can be placed into the periodontal pocket), doxycycline (DOX) (Atridox®, a gel that can be injected into the pocket), and minocycline (MNC) (Arestin®, a microsphere gel that can be injected into the pocket).

Inclusion criteria were randomized controlled trials, in vivo human trials, publications in English, and trials that compared one or more of these agents in local delivery systems with each other, to scaling and root planing (SRP) or to another control group. From the identified articles, the Food and Drug Administration (FDA) pivotal studies were selected for detailed analysis to determine the number needed to treat (NNT). When a new drug comes to market, the FDA standard has been to require two controlled clinical trials that demonstrate efficacy of the product. Generally, the applicant company conducts several trials. Although not commonly appreciated, the FDA selects the trials it considers ''pivotal'' and allows the applicant company to write the package insert using data from those trials. Hence, identification of pivotal trials was accomplished by determining the trials that were cited in the package insert of each product.

Table 1
MEDLINE search

Step	Search history	Results
1	Exp periodontics/	13494
2	Exp periodontal diseases/	40247
3	1 or 2	45576
4	Chlorhexidine.tw.	2856
5	Metronidazole.tw.	6572
6	Tetracycline.tw.	12948
7	Doxycycline.tw.	3408
8	Minocycline.tw.	2024
9	4 or 5 or 6 or 7 or 8	25701
10	Fiber.tw.	39794
11	Chip.tw.	1532
12	Gel.tw.	130288
13	10 or 11 or 12	170862
14	Local delivery.tw. or *drug delivery/	566
15	13 or 14	171394
16	3 and 9 and 15	187
17	Limit 16 to (human and english language)	165

NNT was determined using the percentage of patients, sites, or teeth with either a probing depth (PD) reduction or attachment level (AL) gain of $\geq$2 mm:

$$\text{NNT} = 1/(\%\text{experimental sites} \geq 2\,\text{mm} - \%\,\text{control sites} \geq 2\,\text{mm})$$

We further analyzed the data to determine cost effectiveness for each drug:

$$\text{cost effectiveness} = (\text{estimated product cost} + \text{care cost}) \times \text{NNT}$$

Additional data for chlorhexidine and minocycline were obtained from their respective package inserts, and data for tetracycline were obtained from the author of the study.

The MEDLINE search (see Table 1) identified 165 articles, 52 of which fit the inclusion criteria. All 52 studies conducted randomized control trials examining the efficacy of five different local delivery systems for antimicrobial agents to treat periodontal disease.

Tables 2 through 6 provide details of the identified studies. Eighteen studies examined metronidazole (Table 2), with studies ranging in size from 10 to 206 subjects, and study lengths from 1.5 to 9 months. The chlorhexidine delivery system was examined in 12 studies (Table 3), with study sizes ranging from 10 to 418 subjects, and study length from 1 to 9 months.

Table 2
Metronidazole

Ref[a]	N	Experimental group—metronidazole	Control group (s)	Outcomes						Followup (m)
				BP	PD	AL	PI	GI	M	
[2]	84	+SRP	SRP	+	+	+			+	6
[3]	12	±SRP	SRP; UC	+	+		+	+		2
[4]	10	Alone	Placebo	+	+	+			+	3
[5]	12	Alone	UC		+		+	+		6
[6]	46	Alone	SRP		+	+			+	4.5
[7]	18	+SRP	TC; SRP	+	+	+			+	6
[8]	84	+SRP	SRP	+	+	+				6
[9]	30	Alone	SRP	+	+				+	6
[10]	206	Alone	SRP	+	+					6
[11]	24	Alone	SRP	+	+				+	6
[12]	61	Alone	SRP	+	+					3
[13]	59	+SRP	SRP	+	+	+			+	9
[14]	84	+SRP	SRP	+	+	+				9
[15]	29	+SRP	SRP	+	+	+	+			3
[16]	54	+SRP	TC; MC; SRP	+	+	+	+	+		1.5
[17]	10	±SRP	SRP; UC		+	+	+	+	+	1.5
[18]	12	±SRP	SRP; UC		+	+	+	+	+	1.5
[19]	69	±SRP	TC; CX; SRP	+	+	+				3

[a] Ref, reference number; N, number of total subjects completing the study; BP, bleeding on probing; PD, probing depth; AL, attachment level; PI, plaque index; GI, gingival index; M, microbiota; m, months; SRP, scaling and root planing; TC, tetracycline; UC, untreated control; MC, minocycline.

Table 3
Chlorhexidine

Ref	N	Experimental group—chlorhexidine	Control group (s)	Outcomes						Followup (m)
				BP	PD	AL	PI	GI	M	
[19]	69	Alone	MT; TC; SRP	+	+	+				3
[20]	10	+ SRP	SRP	+	+		+	+	+	2
[21]	10	Alone	Placebo	+	+		+	+	+	1
[22]	26	+ SRP	TC; SRP	+	+	+	+	+		8
[23]	10	+ SRP	SRP	+	+	+	+	+		8
[24]	418	+ SRP	SRP ± Placebo	+	+	+	+	+		9
[25]	10	+ SRP	SRP		+		+		+	8
[26]	22	+ SRP	TC; SRP	+	+	+	+	+		3
[27]	10	+ SRP	SRP + Placebo[a1]	+	+				+	9
[28]	42	+ SRP	SRP ± Placebo		+	+				9
[29]	94	+ SRP	SRP	+	+	+	+	+		6
[30]	58	+ SRP	SRP[a2]		+		+	+	+	3

[a] Ancillary treatment: 1. Amine fluoride and stannous fluoride gels; 2. Chlorhexidine gluconate irrigation; H_2O irrigation.

Ref, reference number; N, number of total subjects completing the study; BP, bleeding on probing; PD, probing depth; AL, attachment level; PI, plaque index; GI, gingival index; M, microbiota; m, months; SRP, scaling and root planing; MT, metronidazole; TC, tetracycline.

Nineteen studies examined the efficacy of the tetracycline delivery system (Table 4), with study size ranging from 10 to 123 subjects, and study lengths ranging from 1-month to 5-year followup study. Five studies examined the efficacy of the doxycycline delivery system (Table 5) and engaged between 141 and 758 subjects, all with study lengths of 9 months. The minocycline delivery system was examined in five studies (Table 6), with study sizes ranging from 15 to 54 people and study lengths from 1.5 to 18 months.

Study outcomes and design varied considerably. For example, 85% of the studies examined bleeding on probing (BP), 96% examined pocket depth (PD), 77% examined attachment level (AL), 48% examined probing index (PI), 35% examined gingival index (GI), and 38% examined microbiota (M).

Because of variability in study design, we elected to examine in detail only the four agents with FDA pivotal trials. Table 7 summarizes the data derived from the FDA pivotal studies and articulates the NNT using this data. NNTs were calculated for change in probing depth (PD) and AL, with 2 mm selected as a statistically and clinically significant change. For pocket depth reduction, the efficacies of the products from most to least effective were, respectively, tetracycline fiber, chlorhexidine disk, and minocycline microspheres. For attachment level only the tetracycline delivery system study provided data that allowed us to determine NNT. For the doxycycline delivery system, the study design did not allow for a determination of NNT.

It should be noted that the pivotal studies all exhibited variability in clinical characteristics. For example, all of the studies lasted 9 months, except for the tetracycline delivery system studies, which lasted 6 months.

Table 4
Tetracycline

Ref	N	Experimental group—tetracycline	Control group (s)	Outcomes						Followup (m)
				BP	PD	AL	PI	GI	M	
[7]	18	+SRP	MT; SRP	+	+	+			+	6
[16]	54	+SRP	MT; MC; SRP	+	+	+	+	+		1.5
[19]	69	Alone	MT; CX; SRP	+	+	+				3
[22]	26	+SRP	CX; SRP	+	+	+	+	+		3
[26]	22	+SRP	CX; SRP	+	+	+	+	+		3
[31]	107	Alone	SRP; UC; Placebo	+		+				2
[32]	16	±SRP	SRP[a]	+	+	+	+		+	3
[33]	105	+SRP	SRP	+	+	+				6
[34]	116	±SRP	SRP	+	+	+	+			12
[35]	116	±SRP	SRP	+	+	+	+			12
[36]	26	+SRP	SRP	+	+	+				60
[37]	18	Alone	UC	+	+	+				1
[38]	10	±SRP	SRP; UC	+	+		+	+	+	2
[39]	107	Alone	SRP; UC; Placebo	+		+				2
[40]	10	±SRP	SRP; UC		+	+				12
[41]	123	+SRP	SRP	+	+	+				6
[42]	19	+SRP	UC	+	+	+		+		6
[43]	10	Alone	SRP; UC; Placebo	+	+	+	+			6.5
[44]	17	+SRP	SRP	+	+	+		+	+	2

[a] Ancillary treatment: citric acid.

Ref, reference number; N, number of total subjects completing the study; BP, bleeding on probing; PD, probing depth; AL, attachment level; PI, plaque index; GI, gingival index; M, microbiota; m, months; SRP, scaling and root planing; UC, untreated control; CX, chlorhexidine; MT, metronidazole; MC, minocycline.

The studies also varied in number of drug placements and use of scaling and root planing in the experimental groups. Thus, the interpretation of the NNT needs careful consideration.

Although clinical efficacy is a desired outcome, cost effectiveness is a concern of the provider and payer. We therefore estimated cost effectiveness for these agents. Determination of the care cost includes the following variables:

Table 5
Doxycycline

Ref	N	Experimental group—doxycycline	Control group (s)	Outcomes						Followup (m)
				BP	PD	AL	PI	GI	M	
[45]	758	Alone	SRP; Placebo; UC	+	+	+	+			9
[46]	141	Alone	SRP; UC	+	+	+				9
[47]	170	Alone	Placebo[a]	+	+	+	+			9
[48]	317	Alone	SRP	+	+	+				9
[49]	170	Alone	Placebo[a]	+	+	+	+			9

[a] Ancillary treatment: sanguinarium chloride.

Ref, reference number; N, number of total subjects completing the study; BP, bleeding on probing; PD, probing depth; AL, attachment level; PI, plaque index; GI, gingival index; M, microbiota; m, months; SRP, scaling and root planing; UC, untreated control.

Table 6
Minocycline

Ref	N	Experimental group—minocycline	Control group (s)	Outcomes						Followup (m)
				BP	PD	AL	PI	GI	M	
[16]	54	+SRP	TC; MT; SRP	+	+	+	+	+		1.5
[50]	26	+SRP	SRP + Placebo	+	+	+				3
[51]	20	+SRP	SRP + Placebo	+	+	+	+	+	+	18
[52]	15	Alone	SRP; SS	+	+	+			+	1.5
[53]	39	±SRP	SRP; UC	+	+	+	+	+	+	6

SS, supragingival scaling; TC, tetracycline; MT, metronidazole; UC, untreated control.

Ref, reference number; N, number of total subjects completing the study; BP, bleeding on probing; PD, probing depth; AL, attachment level; PI, plaque index; GI, gingival index; M, microbiota; m, months; SRP, scaling and root planing.

cost of the agent, cost of wastage, number of drug placements, cost of scaling and root planing, and cost associated with clinician time. Assuming the effectiveness is accounted for by the NNT values calculated for PD reduction of $\geq$2 mm, we estimated the treatment cost for each local delivery system for treatment of a single tooth and a complete quadrant (Table 8, Fig. 1). Table 9 uses these calculations to estimate cost effectiveness. When treating a single tooth, total cost per tooth was least for the tetracycline delivery system ($99). The tetracycline delivery system was also approximately 3–4 times more cost effective than either the chlorhexidine or minocycline delivery systems, respectively ($495 versus $1260–$2016).

When treating a quadrant as an additional procedure to another dental treatment, cost analysis indicated that total cost per tooth for the chlorhexidine and minocycline delivery systems was half that of the tetracycline delivery system. Cost effectiveness was similar for the tetracycline and chlorhexidine delivery systems ($195 and $200), however, both of which were approximately 1.5 times more cost effective than the minocycline delivery system ($320).

Because data submitted to the FDA for validation of the doxycycline delivery product considered only equivalence of the product compared with SRP, cost effectiveness could not be determined. Cost comparison, however,

Table 7
Number needed to treat

Drug	Delivery system	Brand	Study length (m)	# SRP (expt)[a]	# Drug placements (expt)	NNT PD[b]	NNT AL
Tetracycline	Fiber	Actisite	6	1	1	5	9
Chlorhexidine	Chip	PerioChip	9	1	3	10	NA
Minocycline	Microsphere	Arestin	9	1	3	16	NA
Doxycycline	Gel	Atridox	9	0	2	NA	NA

[a] Expt, SRP received by experimental group; NTT; number needed to treat.

[b] CHX, MNC mean values for PD $\geq$2 mm from the two FDA studies.

SRP, scaling and root planing; PD, probing depth; AL, attachment level; FDA, Food and Drug Administration; NA, not available.

Table 8
Treatment cost

Assumptions						
Product[a]	Cost/unit purchase[b]	Teeth treated/unit[b]	Treatment visits required	Non treatment visits	Placement time (min/tooth)	Total setup cost[c]
TTC	$24	2	1	1	15	$50
CHX	$12	1	3	0	3	$75
MNC	$12	1	3	0	3	$75
DOX	$24	6	2	0	2	$50

Treatment of one tooth					
Product	Used product cost	Waste product cost	Placement cost[c]	Cost/tooth	As an add-on[d]
TTC	$12	$12	$25	$99	$49
CHX	$36	$0	$15	$126	$51
MNC	$36	$0	$15	$126	$51
DOX	$8	$40	$7	$105	$55

Treatment of one quadrant[d]					
Product	Used product cost	Waste product cost	Placement cost	Cost/tooth	As an add-on[e]
TTC	$84	$12	$175	$46	$39
CHX	$36	$0	$105	$31	$20
MNC	$36	$0	$105	$31	$20
DOX	$36	$40	$49	$28	$20

[a] TTC, tetracycline; CHX, chlorhexidine; MNC, minocycline; DOX, doxycycline; SRP, scaling and root planing.

[b] Assumptions: Tetracycline @ $24 per fiber, 2 teeth per fiber, $12 per tooth, 15 min for placement per tooth, 1 treatment and 1 removal visit. Chlorhexidine @ $12 per chip, 1 tooth per chip, $12 per tooth, 1 min for placement per tooth, 3 treatment visits. Minocycline @ $12 per cartridge, 1 tooth per cartridge, $12 per tooth, 1 min per placement per tooth, 3 treatment visits. Doxycycline @ $24 per cartridge, 6 teeth per cartridge, $4 per tooth, 1 min per placement per tooth, 2 treatment visits

[c] Assumptions: Setup cost = $25 per visit (treatment or nontreatment). Chair time = $100 per h × (placement time per tooth/60 min).

[d] Assumptions: One quadrant = 7 teeth (treatment cost − $200/quadrant = $29/tooth).

[e] Assumptions: When used as an additional or addon procedure, setup costs have been covered by the first procedure.

revealed that total cost associated with the doxycycline delivery system alone was approximately $28 per tooth, whereas the cost associated with SRP alone was $29 per tooth (Table 8[C], Assumption 4).

This systematic review was conducted to identify the available literature and to determine cost effectiveness of locally delivered antimicrobial agents in the treatment of periodontal disease. All 52 articles found in our search examined the efficacy of at least one of five different local delivery systems to one another or to scaling and root planing. Because there was a significant variability among the studies, we chose to more closely examine the FDA pivotal studies, and because metronidazole is not approved for use in the United States, it was excluded from further evaluation. Because of the

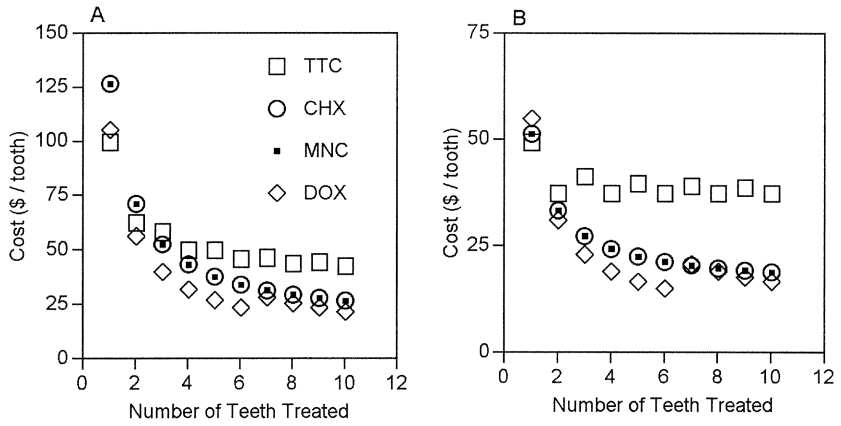

Fig. 1. (A) The cost of treatment of teeth ($/tooth) with periodontal disease by local delivery products as a visit scheduled solely for local delivery treatment. (B) The added cost of treatment of teeth ($/tooth) with periodontal disease by local delivery products.

variability in study design and reported results, a comprehensive product comparison was not possible. The available data only allowed for an NNT determination for pocket depth reduction, not for attachment level gain. The following comments speak to the overall results and their interpretation, based on study variability.

The FDA pivotal studies provided data for a determination of the NNT for three products: tetracycline fibers (Actisite), chlorhexidine disks (PerioChip), minocycline microspheres (Arestin). We were unable to make this determination for the doxycycline gel (Atridox) in that this product was not used as an adjunct to SRP. Inspection of the doxycycline gel data, however,

Table 9
Cost effectiveness[a]

To treat one tooth			
Product[b]	Total cost ($)/tooth	NNT	Cost effectiveness ($)
TTC	99	5	$99 \times 5 = 495$
CHX	126	10	$126 \times 10 = 1260$
MNC	126	16	$126 \times 16 = 2016$
Cost/tooth when treating one quadrant as an additional procedure			
Product[b]	Total cost ($)/tooth	NNT	Cost effectiveness ($)
TTC	39	5	$39 \times 5 = 195$
CHX	20	10	$20 \times 10 = 200$
MNC	20	16	$20 \times 16 = 320$

[a] Cost, over and above SRP, to have one additional pocket reduced by $\geq$2 mm.
[b] TTC, tetracycline; CHX, Chlorhexidine; MNC, minocycline.
SRP, scaling and root planing; NNT, number needed to treat.

demonstrated that the therapeutic effects of doxycycline gel alone were similar to those for SRP alone.

The NNTs suggest that at $\leq$9 months and compared with SRP alone, SRP plus the tetracycline fiber drug delivery system (Actisite) was most effective in reducing pocket depth (lowest NNT of five). This compares with an NNT of 10 and 16 for the chlorhexidine disk and the minocycline gel, respectively.

The NNT, although an awkward name and concept, has a useful clinical application. It allows one to provide a risk and benefit assessment to the patient. For example, for the tetracycline fiber, an NNT of five indicates the following risk and benefit. For every five teeth that are treated with SRP plus fibers (risk), one tooth will achieve $\geq$2 mm of pocket depth reduction when compared with SRP alone (benefit). Said differently, a patient may have five teeth treated with SRP plus fibers, but only one tooth will benefit by $\geq$2 mm more than SRP alone. Thus, the risk:reward ratio is 5:1.

As indicated, there were differing study designs. In addition, there were also differing drugs and drug delivery systems. Thus the differing results among the products may be attributable to study design, drug used, or drug delivery system. Although all three may be important, the available pharmacokinetic data suggest that the delivery system may have the greatest effect. The fibers sustain a constant high level of antibiotic in the gingival crevice for the week that they are in place. In contrast, the drug concentration for the other delivery systems decreases substantially over the first few days. Having a constant high level of drug in place over an extended period of time might account for the clinical effect.

The issue of study longevity could also have an impact on the results. The tetracycline fiber delivery system studies ranged from 2 to 6 months, whereas the other studies were 9 months in length (see Table 7). Thus one might suspect that the apparent efficacy of the tetracycline delivery system could degrade between 6 and 9 months. There is no evidence for or against this hypothesis.

The number of drug placements also varied within the studies being considered. The tetracycline delivery system was applied once, the doxycycline gel delivery system was applied twice, and the chlorhexidine disk and minocycline microsphere systems were applied three times (see Table 7). One would suspect that multiple placements would enhance the efficacy of the drug system, but this was not found to be the case.

Many complicating issues arise when attempting to determine the efficacy of these local delivery agents, most notably the cost effectiveness. The clinician and the patient must determine if the cost of the product is worth the possible benefit. The cost includes the price of the local delivery agent, the number of teeth treated, the number of drug placements required, the cost of product wastage, the cost associated with clinician time, and from the patient's perspective, the number of trips to the dentist.

Analysis revealed that when treating a single tooth, the tetracycline delivery system was the most cost effective, but when treating a quadrant the tetracycline and chlorhexidine delivery systems were equally cost effective. This

is because of the relative balance of lower cost per tooth and higher NNT for chlorhexidine versus higher cost per tooth and lower NNT for tetracycline. From a patient's cost:benefit perspective, the cost per tooth to achieve a benefit from the tetracycline fibers is $195–$495 per tooth (Table 9). At the other end of the spectrum, following treatment by the minocycline delivery system, a patient would spend $320–$2,016 per tooth to obtain a clinically meaningful improvement in one tooth (see Table 9).

The results of the cost analysis clearly indicate that for all local delivery systems, the most expensive treatment occurred as a single tooth treated at a dedicated visit (Fig. 1, Table 8). Considerable economy could be realized by treating multiple teeth. Treatment of a quadrant was estimated to cost $30–$45 per tooth (see Fig. 1). Treatment of a quadrant as an added procedure costs as little as $20 per tooth. Clearly, the economic argument favors the adjunctive use of local delivery products as for periodontal maintenance. If multiple teeth are treated as an added procedure, even less effective treatments (ie, higher NNT) become cost effective (see Table 9).

As with all treatments, it is the clinician's responsibility to explain the treatment options available, their cost, and their expected efficacy to the patients so that the patient can decide the relative worth of their possible benefits. To some patients, maximizing effectiveness may be the primary objective irrespective of cost. For these patients, treatments with low NNT values would be preferred. To others, maximizing cost effectiveness may be the primary objective. For these patients, an appeal to multiple tooth treatments as an adjunctive procedure would be desirable. Still other patients may believe that any treatment beyond scaling and root planing is not worth the extra expenditure. Only by combining benefit and cost analysis can the needs of each individual patient be met.

References

[1] Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25:134–44.

[2] Palmer RM, Matthews JP, Wilson RF. Adjunctive systemic and locally delivered metronidazole in the treatment of periodontitis: a controlled clinical study. Br Dent J 1998;184:548–52.

[3] Awartani FA, Zulqarnain BJ. Comparison of the clinical effects of subgingival application of metronidazole 25% gel and scaling in the treatment of adult periodontitis. Quintessence Int 1998;27:41–8.

[4] Needleman IG, Watts TLP. The effect of 1% metronidazole gel in routine maintenance of persistent furcation involvement in human beings. J Periodontol 1989;60: 699–703.

[5] Sander L, Frandsen EVG, Arnbjerg D, Warrer K, Karring T. Effect of local metronidazole application on periodontal healing following guided tissue regeneration. Clinical findings. J Periodontol 1994;65:914–20.

[6] Rudhart A, Rurucker P, Kage A, Hopfenmuller W, Bernimoulin JP. Local metronidazole application in maintenance patients. Clinical and microbiological evaluation. J Periodontol 1998;69:1148–54.

[7] Lie T, Bruun G, Boe OE. Effects of topical metronidazole and tetracycline in treatment of adult periodontitis. J Periodontol 1998;69:819–27.
[8] Palmer RM, Matthews JP, Wilson RF. Non-surgical periodontal treatment with and without adjunctive metronidazole in smokers and non-smokers. J Clin Periodontol 1999;26: 158–63.
[9] Stelzel M, Flores-de-Jacoby L. Topical metronidazole application compared with subgingival scaling. A clinical and microbiological study on recall patients. J Clin Periodontol 1996;23:24–9.
[10] Ainamo J, Ellingsen BH, Hansen BF, Johansson LA, Darring T, Kisch J, et al. Clinical responses to subgingival application of a metronidazole 25% gel compared to the effect of subgingival scaling in adult periodontitis. J Clin Periodontol 1992;19:723–9.
[11] Pedrazzoli V, Kilian M, Karring T. Comparable clinical and microbiological effects of topical subgingival application of a 25% metronidazole gel and scaling in the treatment of adult periodontitis. J Clin Periodontol 1992;19:715–22.
[12] Klinge B, Attstrom R, Karring T, Kisch J, Lewin B, Stoltze K. Three regimens of topical metronidazole compared with subgingival scaling on periodontal pathology in adults. J Clin Periodontol 1992;19:708–14.
[13] Stelzel M, Flores-de-Jacoby L. Topical metronidazole application as an adjunct to scaling and root planing. J Clin Periodontol 2000;27:447–52.
[14] Griffiths GS, Smart GJ, Bulman JS, Weiss G, Schroweder J, Newman HN. Comparison of clinical outcomes following treatment of chronic adult periodontitis with subgingival scaling or subgingival scaling plus metronidazole gel. J Clin Periodontol 2000;27: 910–7.
[15] Riep B, Purucker P, Bernimoulin JP. Repeated local metronidazole-therapy as adjunct to scaling and root planing in maintenance patients. J Clin Periodontol 1999;26:710–5.
[16] Radvar M, Pourtaghi N, Kinane DF. Comparison of 3 periodontal local antibiotic therapies in persistent periodontal pockets. J Periodontol 1996;67:860–5.
[17] Noyan U, Yilmaz S, Kuru B, Kadir T, Acar O, Buget E. A clinical and microbiological evaluation of systemic and local metronidazole delivery in adult periodontitis patients. J Clin Periodontol 1997;24:158–65.
[18] Yilmaz S, Kuru B, Noyan U, Kadir T, Acar O, Buget E. A clinical and microbiological evaluation of systemic and local metronidazole delivery in early onset periodontitis patients. J Marmara Univ Dent Faculty 1996;2:500–9.
[19] Moran J, Addy M, Wade W, Newcombe R. The use of antimicrobial acrylic strips in the non-surgical management of chronic periodontitis. Clin Mater 1990;6:123–35.
[20] Quirynen M, Bollen CML, Vandekerckhove BNA, Dekeyser C, Papaioannou W, Eyssen H. Full- vs. partial-mouth disinfection in the treatment of periodontal infections: short-term clinical and microbiological observations. J Dent Res 1995;74:1459–67.
[21] Kalaitzakis CJ, Tynelius-Bratthall G, Attstrom R. Clinical and microbiological effects of subgingival application of a chlorhexidine gel in chronic periodontitis. A pilot study. Swed Dent J 1993;17:129–37.
[22] Unsal E, Walsh TF, Akkaya M. The effect of a single application of subgingival antimicrobial or mechanical therapy on the clinical parameters of juvenile periodontitis. J Periodontol 1995;66:47–51.
[23] Vandekerckhove BNA, Bollen CML, Dekeyser C, Darius P, Quirynen M. Full- versus partial-mouth disinfection in the treatment of periodontal infections. Long-term clinical observations of a pilot study. J Periodontol 1996;67:1251–9.
[24] Jeffcoat MK, Bray KS, Ciancio SG, et al. Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. J Periodontol 1998;69:989–97.
[25] Bollen CML, Vandekerckhove BNA, Papaioannou W, Van Eldere J, Quirynen M. Full- versus partial-mouth disinfection in the treatment of periodontal infections. A pilot study: long-term microbiological observations. J Clin Periodontol 1996;23:960–70.

[26] Unsal E, Akkaya M, Walsh TF. Influence of a single application of subgingival chlorhexidine gel or tetracycline paste on the clinical parameters of adult periodontitis patients. J Clin Periodontol 1994;21:351–5.
[27] Oosterwaal PJM, Mikx FHM, van't Hof MA, Renggli HH. Comparison of the antimicrobial effect of the application of chlorhexidine gel, amine fluoride gel and stannous fluoride gel in debrided periodontal pockets. J Clin Periodontol 1991;18:245–51.
[28] Jeffcoat MK, Palcanis KG, Weatherford TW, Reese M, Geurs NC, Flashner M. Use of a biodegradable chlorhexidine chip in the treatment of adult periodontitis: clinical and radiographic findings. J Periodontol 2000;71:256–62.
[29] Soskolne WA, Heasman PA, Stabholz A, Smart GJ, Palmer M, Flashner M, et al. Sustained local delivery of chlorhexidine in the treatment of periodontitis: a multi-center study. J Periodontol 1997;68:32–8.
[30] Jolkovsky DL, Waki MY, Newman MG, Otomo-Corgel J, Madison M, Flemmig TF, et al. Clinical and microbiological effects of subgingival and gingival marginal irrigation with chlorhexidine gluconate. J Periodontol 1990;61:663–9.
[31] Goodson JM, Gugini MA, Kent RL, et al. Multicenter evaluation of tetracycline fiber therapy: II. Clinical response. J Periodontol Res 1991;26:371–9.
[32] Jeong S, Han S, Lee S, Magnusson I. Effects of tetracycline-containing gel and a mixture of tetracycline and citric acid-containing gel on non-surgical periodontal therapy. J Periodontol 1994;65:840–7.
[33] Newman MG, Kornman KS, Doherty FM. A 6-month multi-center evaluation of adjunctive tetracycline fiber therapy used in conjunction with scaling and root planing in maintenance patients: clinical results. J Periodontol 1994;65:685–91.
[34] Drisko CL, Cobb CM, Killoy WJ, et al. Evaluation of periodontal treatments using controlled-release tetracycline fibers: clinical response. J Periodontol 1995;66:692–9.
[35] Michalowicz BS, Pihlstrom BL, Drisko CL, et al. Evaluation of periodontal treatments using controlled-release tetracycline fibers: maintenance response. J Periodontol 1995;66:708–15.
[36] Wilson TG, McGuire MK, Greenstein G, Nunn M. Tetracycline fibers plus scaling and root planing versus scaling and root planing alone: similar results after 5 years. J Periodontol 1997;68:1029–32.
[37] Needleman IG, Gerlach RW, Baker RA, Damani NC, Smith SR, Smales FC. Retention, antimicrobial activity, and clinical outcomes following use of a bioerodible tetracycline gel in moderate-to-deep periodontal pockets. J Periodontol 1998;69:578–83.
[38] Heijl L, Dahlen G, Sundin Y, Wenander A, Goodson JM. A 4-quadrant comparative study of periodontal treatment using tetracycline-containing drug delivery fibers and scaling. J Clin Periodontol 1991;18:111–6.
[39] Goodson JM, Cugini MA, Kent RL, et al. Multicenter evaluation of tetracycline fiber therapy: I. Experimental design, methods, and baseline data. J Periodontol Res 1991; 26:361–70.
[40] Goodson JM, Hogan PE, Dunham SL. Clinical responses following periodontal treatment by local drug delivery. J Periodontol 1985;56:81–7.
[41] Tonetti MS, Cortellini P, Carnevale G, Cattabriga M, de Sanctis M, Pini Prato GP. A controlled multicenter study of adjunctive use of tetracycline periodontal fibers in mandibular class II furcations with persistent bleeding. J Clin Periodontol 1998;25: 728–36.
[42] Mombelli A, Lehmann B, Tonetti M, Lang NP. Clinical response to local delivery of tetracycline in relation to overall and local periodontal conditions. J Clin Periodontol 1997;24:470–7.
[43] Maze GI, Reinhardt RA, Agarwal RK, Dyer JK, Robinson DH, DuBois LM, et al. Response to intracrevicular controlled delivery of 25% tetracycline from poly (lactide/glycolide) film strips in SPT patients. J Clin Periodontol 1995;22:860–7.
[44] Yalcin F, Demirel K, Utku O. Evaluation of adjunctive tetracycline fiber therapy with scaling and root planing: short-term clinical results. Periodontal Clin Invest 1999;21:23–7.

[45] Garrett S, Johnson L, Drisko CH, et al. Two multicenter studies evaluating locally delivered doxycycline hyclate, placebo control, oral hygiene and scaling and root planing in the treatment of periodontitis. J Periodontol 1999;70:490–503.
[46] Garrett S, Adams DF, Bogle G, et al. The effect of locally delivered controlled-release doxycycline or scaling and root planing on periodontal maintenance patients over 9 months. J Periodontol 2000;71:22–30.
[47] Poson AM, Garrett S, Stoller NH, et al. Multi-center comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of periodontitis. I. Study design, procedures, and management. J Periodontol 1997;68:110–8.
[48] Ryder MI, Pons B, Adams D, et al. Effects of smoking on local delivery of controlled-release doxycycline as compared to scaling and root planing. J Clin Periodontol 1999; 26:683–91.
[49] Polson AM, Garrett S, Stoller NH, et al. Multi-center comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of periodontitis. II. Clinical results. J Periodontol 1997;68:119–26.
[50] Graca MA, Watts TLP, Wilson RF, Palmer RM. A randomized controlled trial of a 2% minocycline gel as an adjunct to non-surgical periodontal treatment, using a design with multiple matching criteria. J Clin Periodontol 1997;24:249–53.
[51] Timmerman MF, van der Weijden GA, van Steenbergen TJM, Mantel MS, de Graaff J, van der Velden U. Evaluation of the long-term efficacy and safety of locally-applied minocycline in adult periodontitis patients. J Clin Periodontol 1996;23:707–16.
[52] Yeom HR, Park YJ, Lee SJ, Rhyu IC, Chung CP, Nisengard RJ. Clinical and microbiological effects of minocycline-loaded microcapsules in adult periodontitis. J Periodontol 1997;68:1102–9.
[53] Jones AA, Kornman KS, Newbold DA, Manwell MA. Clinical and microbiological effects of controlled-release locally delivered minocycline in periodontitis. J Periodontol 1994; 65:1058–66.