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# Are topically delivered antibiotics beneficial as an adjunct to scaling and root planing in the treatment of periodontal diseases?

## A systematic review

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KEY WORDS *local antibiotics, mechanical therapy, periodontitis*

Local antibiotics have been reported successful in the treatment of destructive periodontitis. However, design, stringency and outcome of such studies seem variable. Thus our focused question was: are scaling and root planing (SRP) with adjunctive topical antibiotics superior to SRP alone in treating chronic periodontitis? Reports from 1990 and 15 years on were electronically searched in central databases using the terms 'periodontitis'/'periodontology' combined with 'local antibiotics'/'topical antibiotics'. Only randomised, blinded, controlled clinical trials (RCTs), comprising more than 20 patients diagnosed with chronic periodontitis, adjunctively treated with a single, topical antibiotic, and with a follow-up of more than 3 months were accepted. Treatment outcome was assessed by changes in clinical attachment level from baseline to end of study. The initial searches produced 198 articles, which eventually were reduced to 11 according to the inclusion criteria. The analyses of this group of articles gave no clear-cut answer to the focused question, but displayed a possible benefit of applying topical antibiotics in conjunction with SRP. However, the benefit was small and of doubtful clinical significance.

## ■ Introduction

Periodontal disease is a family of bacterial infections characterised by the destruction of periodontal supporting tissues. The bacterial flora in diseased sites is complex, with over 500 different species in the subgingival dental plaque[1], although only a limited number have been recognised as putative periodontal pathogens[2]. The standard treatment of periodontitis has been to mechanically reduce the number of bacteria present by scaling and root planing (SRP), thereby reducing the bacterial challenge in the sites showing disease progression. Although representing a non-specific form of treatment, it has proven effective in most cases[3–7].

However, a small – still significant – group of patients shows remaining inflammation as well as continuous destruction of periodontal support, despite adequate oral hygiene and proper mechanical treatment[8–10]. A widely discussed explanation for this recurrent failure is that certain virulent microorganisms may persist in the site after treatment.

These microorganisms, although in comparatively low numbers, may theoretically maintain the level of infection needed to continue periodontal destruction[11–14]. This situation is discussed under the designation 'microbial specificity in periodontitis', i.e. a specific host response to the bacterial attack[15]. In order to prohibit such remaining destructive infection, many researchers have suggested adjunct therapy by antibiotics (for review see[16]). The antibiotic should preferably be chosen based on microbiological diagnoses and the suggested pathogenic bacterial resistance profile[17,18].

Systemic antibiotics as an adjunct to mechanical therapy have been reported with a beneficial effect on clinical as well as microbiological parameters in single and double-blind controlled clinical studies[19–23], but several studies of comparable design oppose these results[24–27].

In order to maintain therapeutic concentrations of the drug at target sites when the antibiotic is delivered systematically, relatively high systemic doses are required. This increases the risk of developing adverse effects towards the prescribed drugs[28,29]. Moreover, the use of antibiotics per se will inevitably increase the risk for developing antimicrobial resistance in periodontal bacteria[30–33]. Consequently, several pharmaceutical companies have developed topical antibiotic formulas to counteract these negative effects, still maintaining the pharmaceutical properties of the drug. All of these formulations have been reported in the literature with varying effects on periodontal diseases[34]. However, a great variation in design and outcome are seen among these reports, giving rise to clinical concerns about which reports to act upon. Thus the purpose of this study was to present a systematic review on available formulations of topical antibiotics and their suggested effect on chronic periodontitis when used in conjunction with scaling and root planing.

## ■ Focused question

Is scaling and root planing (SRP) with single adjunct topical antibiotic superior to SRP alone in treating chronic periodontitis as assessed by changes in clinical attachment levels?

## ■ Study design

### ■ Inclusion criteria

Only randomised, blinded, controlled clinical trials (RCTs) were accepted into the systematic review. To be accepted, they should also comprise more than 20 patients diagnosed with chronic periodontitis treated with SRP alone as control procedure and SRP plus a single, defined topical antibiotic as test, and with a follow-up of 3 months or more. Treatment outcome was assessed by changes in clinical attachment level (CAL) from baseline to end of study. Topical antimicrobials allowed into the study were those existing on the European market; tetracyclines (minocycline, doxycycline, tetracycline), metronidazole, penicillins and macrolides. Metronidazole is still formally classified as a chemotherapeutic. However, the ongoing production of new synthetic and semisynthetic antibiotics has 'watered out' the nomenclature, and in medicine as well as odontology, metronidazole is regarded as an antibiotic. Thus articles on metronidazole were included in the study. Chemotherapeutics, like chlorhexidine products, were not included.

### ■ Search strategies

MEDLINE/PubMed, Cochrane Controlled Trials Register (Central CCTR) and WebSPIRS were researched. The search terms 'periodontitis'/'periodontology' combined with 'local antibiotics'/'topical antibiotics' were used. Only articles in the English and Scandinavian languages appearing in the journals from 1 January 1990 to 1 January 2006 were included in the study. Manual search was performed in the Journal of Clinical Periodontology, Journal of Periodontal Research and Journal of Periodontology. Additionally, all references in all selected publications were manually searched.

### ■ The selection process (Fig 1)

The initial search process produced 198 articles. All of these publications described the use of local antibiotics as a part of the treatment. These titles were then evaluated by two of the authors (EM, ER). One hundred and eight articles were discarded because: they were not RCTs; they included more than one con-

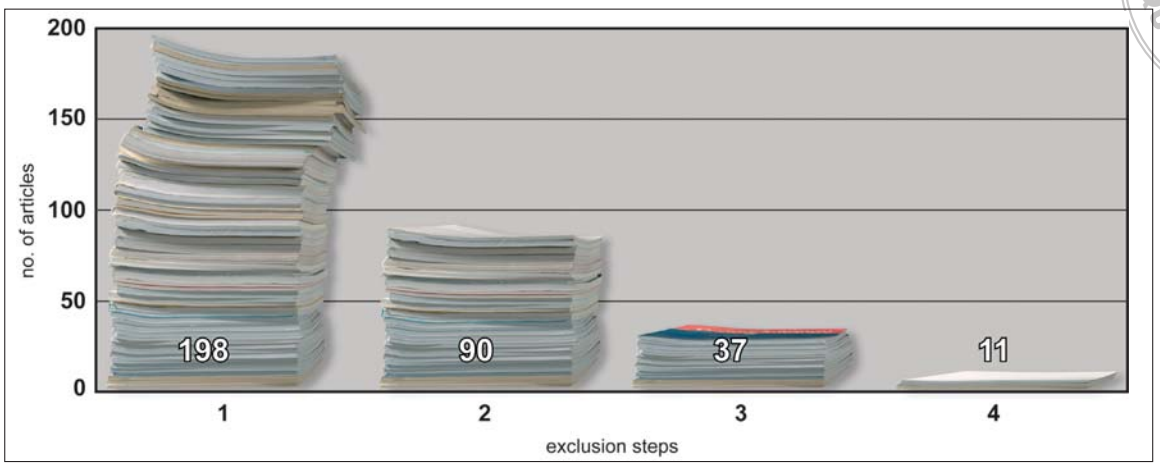


**Fig 1** The four-step selection process. (1) The initial search producing 198 articles. (2) Articles were discarded if: they were not RCTs; they included more than one concomitant antimicrobial in one and the same patient; they were performed in special patient groups; or if they contained surgery (in addition to SRP) as part of the treatment. This resulted in 90 articles. (3) Rejecting those that reported less than 20 participants and/or had a follow-up period of less than 3 months left 37 articles. (4) Only 11 articles were selected for final evaluation because they were also blinded RCTs.

**Table 1** Articles included in the systematic review.

| Autors | Year | Duration (d) | Drug | Design | Plaque | N | ΔCAL | Significant | Sponsor |
|---|---|---|---|---|---|---|---|---|---|
| Jones et al[40] | 1994 | 180 | min | p | no | 39 | –0.50 | **p<0.05** | yes |
| Drisko et al[45] | 1995 | 360 | tet | s | no | 116 | 0.06 | no | yes |
| Timmerman et al[41] | 1996 | 540 | min | p | yes | 20 | 0.19 | no | yes |
| Graça et al[42] | 1997 | 90 | min | p | yes | 26 | 0.36 | **p<0.05** | no info |
| Tonetti et al[44] | 1998 | 180 | tet | p | no | 123 | 0.00 | no | yes |
| Palmer et al[37] | 1998 | 180 | met | p | no | 84 | 0.04 | no | no |
| van Steenbherge et al[43] | 1999 | 450 | min | p | yes | 93 | 0.40 | **p<0.05** | yes |
| Kinane and Radvar[35]* | 1999 | 180 | tet | p | no | 39 | 0.15 | no | no info |
| Kinane and Radvar[35]* | 1999 | 180 | min | p | no | 41 | 0.04 | no | no info |
| Kinane and Radvar[35]* | 1999 | 180 | met | p | no | 39 | 0.00 | no | no info |
| Stelzel and Flores-de-Jacoby[38] | 2000 | 270 | met | s | no | 59 | 0.04 | no | yes |
| Eickholz et al[36] | 2002 | 180 | dox | s | yes | 108 | 0.38 | **p<0.05** | yes |
| Friesen et al[39] | 2002 | 180 | tet | s | no | 24 | 0.48 | no | yes |

**Kinane and Radvar[35] has been broken down into three different studies since they report on three different test groups against one single control group.*
*dox, doxycycline; met, metronidazole; min, minocycline; N, no. of patients completing the study; p, parallel design; s, split mouth design; tet, tetracycline; bold type indicates statistically significant.*

comitant antimicrobial in one and the same patient; they were performed in special patient groups; or they contained surgery (in addition to SRP) as part of the treatment. Of the remaining 90 articles, 53 studies were rejected because they reported less than 20 participants and/or had a follow-up period of less than 3 months. The criterion that only blinded RCTs should be included resulted in the rejection of another 26 articles, leaving 11 for final evaluation. During the selection process, all uncertainty regarding exclusion or inclusion of articles was discussed among the four authors until agreement was reached. The full text of these 11 articles (Table 1) was then examined closely, and their main characteristics were extracted and analysed. Single-blind studies were admitted into the study because there were so few double-blind studies found. One study[35] evaluated three different local antibiotics separately against one control group in one study design. In order to evaluate these in the present systematic review, we compared the different test groups against the controls as three different studies, which resulted in 11 articles proper plus 2 virtual ones[35]. This is displayed in Table 1 and Fig 1 as 13 studies in 11 articles.

### Summary of the individual studies

Of the 11 articles, three were performed in the USA. The others were published by European institutions (3 Great Britain; 2 Germany; 1 Italy; 1 The Netherlands; 1 Belgium) (Table 1). The publications were quite recent, the oldest being from 1994 and the most recent from 2002. Eight of the 11 publications acknowledged industrial support.

Two of the 11 studies reported inclusion of previously treated patients. The rest comprised previously untreated patients.

Different antibiotics were tested in the different publications: doxycycline[36], metronidazole[35,37–39], minocycline[35,40–43] and tetracycline[35,39,44,45] (Table 1). There was substantial variation in the number of study participants in each of the studies, from 123 in the study of Tonetti et al[44], to 20 reported by Timmerman et al[41] (Table 1).

## Results

Table 1 shows CAL changes in the different studies. Three of the studies reported a statistically significant CAL gain ($p < 0.05$), whereas one study showed significant CAL loss ($p < 0.05$) compared with the controls. Seven studies showed a non-significant CAL gain, whereas two showed no difference between the test and control groups. All studies with significant differences were using tetracycline as test substance.

## Discussion

In this systematic review we chose to exclude articles reporting on a combination of antimicrobials as well as studies with surgical techniques to facilitate the SRP. This was done because these factors themselves might have influenced treatment outcome. Treatment of special groups, such as smokers[46], was excluded since smoking itself has been reported as a cause of or a confounding factor for the progression of periodontal diseases and treatment outcome[47–49]. Also, studies performed on non-responders to mechanical therapy were excluded for the same reasons[50]. Thus all included studies were concerned with chronic marginal periodontitis.

We assumed that 'all types of local antibiotics used in the periodontal pocket have potentially the same effect on periodontitis' and that all delivery systems were equally effective, thereby viewing all topical antimicrobials as one xenobiotic in order to simplify the comparison of quantitative results from all studies. We realise that this is probably not a biologically correct assumption as some antibiotics are more effective towards certain bacteria than others, and a vehicle may be more successful than another in this particular biological system. In this context, Kinane and Radvar[35] showed that three different local antibiotics (+SRP) produced three different changes in CAL. However, none of them produced results significantly better than SRP alone. Three studies showed a significant gain of clinical attachment, all being on tetracyclines and all having a follow-up period of 180 days[36,42,43]. This may reflect the fact that tetracyclines are broad-spectrum antibiotics and produce better results in cases where microbiological testing has not been done. One can draw the analogous, although opposite, conclusion from the statistically significant loss of attachment reported in Jones et al[40]. This shows how difficult it may be to evaluate different antibiotics without knowing which bacteria have been identified, and how difficult it is to compare when the studies are so low in homogeneity. To test for statistical significance in these cases may therefore be of less value than describing the differences.

A large number of studies were rejected due to short post-treatment observation time. We decided to exclude all studies with less than 3 months observation post-treatment. In order to study the progression of repair after periodontal treatment, 3 months observation time is probably not sufficient, but changes in inflammation affect the recording of CAL and thus may act as a surrogate parameter for treatment success[51]. However, whether this is a feasible end point parameter for observing the effect upon destructive periodontal disease after treatment may be questioned, since further destruction of periodontal tissues and inflammation are not strongly associated[52].

Smoking is a factor in development of periodontal diseases. Only two studies described the distribution of smokers in both test and control groups[37,44]. Some studies vaguely described smoking habits, but did not report clearly enough to include it as a factor.

Smoking was not an exclusion criterion in any of the studies, and therefore one cannot evaluate the impact on smoking on the treatment modalities, nor can it be used as a factor in the analysis. Smokers have elevated risk for developing periodontal disease[47,49] and present themselves with more attachment loss than non-smokers[53]. It also seems as if approximately 90% of all refractory periodontitis patients are smokers[48] and studies have shown that there is a dose-response relationship between smoking and loss of periodontal support[47]. Thus, intervention studies should consider these factors in the future.

Gender seems to play a role in the epidemiology of periodontal diseases. Studies from the US showed that males displayed more CAL loss than females[54,55]. However, the same study showed that men displayed more plaque and calculus than the average woman[55]. In the present systematic review of 11 articles, five reported a selection with more women than men, one showed an equal distribution of the genders, whereas two had a majority of male participants. Three articles did not report the male/female ratio.

In this review we concentrated on average gain or loss of attachment, since this was the commonly reported parameter. However, in studies like this, it would be more clinically relevant to use cut-off levels of clinical interest in order to study, assess and possibly quantify patients that may obtain a clinically meaningful benefit from the treatment studied.

One can conclude from this systematic review that most of the studies demonstrated a possible benefit from the adjunct use of topical antibiotics with SRP. However, bearing in mind the limitation set by the low number of quality studies our review is based upon, one may say that the average gain in CAL must be regarded as small and in most instances insignificant, both from a statistical and clinical point of view.

## ■ Acknowledgements

This study was carried out with support from only the Dental Faculty at the University of Oslo, as it was a student research project. The authors thank Henriette Magnussen for valuable help in preparing the manuscript, and photographer Jan Unneberg for designing Fig 1.

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