A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients

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Authors' objectives
To compare scaling and root planning (SRP) plus systemic antibiotics with SRP alone in patients with periodontitis.

Searching
MEDLINE, PubMed, EMBASE and the Cochrane Oral Health Group's Specialised Trials Register were searched to April 2001 for reports in the English language; the search terms were stated. The Journal of Periodontology, Journal of Clinical Periodontology and the Journal of Periodontal Research were searched to April 2001. In addition, reference lists in reviews, identified reports, the European Workshops (1994, 1997, 1999), World Workshops (1998, 1996) and position papers of the Journal of Periodontology were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were eligible for inclusion. Case reports and reviews were excluded. Some studies were of a split-mouth design.

Specific interventions included in the review
Studies that compared SRP plus systemic antibiotics with SRP alone for at least 6 months were eligible for inclusion. However, studies lasting 22 weeks or more were included. Studies were included if they used any of the following antibiotics: tetracyclines (tetracycline C1H, doxycycline, minocycline); metronidazole and ornidazole; penicillins (amoxicillin, amoxicillin-clavulanate, penicillin); macrolides (erythromycin, spiramycin, azithromycin, roxithromycin); clindamycin; ciprofloxacin; different combinations of these drugs; or long-term use of low-dosages of doxycycline. Studies that used local antibiotic therapy were excluded.

In most of the included studies SRP was full-mouth (except in split-mouth studies). The studies used different doses of antibiotics and different SRP protocols including more than one full-mouth SRP, a scaling session before root planning, or localised debridement before the start of antibiotic treatment. Antibiotics were usually prescribed during and immediately after SRP, although some studies delayed antibiotic treatment for 4 to 6 weeks. Most of the studies also advised patients on oral hygiene. The therapists in the studies were mostly dental hygienists, but some studies used dental students. The time spent in mechanical therapy ranged, where stated, from 30 minutes to 8 hours. Most of the studies were located in hospitals, universities, or specialist referral units.

Participants included in the review
Studies of patients with a diagnosis of aggressive or chronic periodontitis were eligible for inclusion. Studies that used terms such as early onset periodontitis, rapidly progressive periodontitis, adult periodontitis, 'refractory' periodontitis, or 'recurrent' periodontitis were eligible. In most studies, patients were either untreated or had been treated more than 6 months before. Some studies excluded smokers while others recruited only smokers.

Outcomes assessed in the review
Studies that assessed clinical outcomes were eligible for inclusion. The primary outcomes assessed in the review were the change in clinical attachment level (CAL) and the change in probing pocket depths (PPD). Most of the included studies assessed CAL and PPD using manual probes, but some studies used force probes. The secondary outcomes included change in bleeding on probing, changes in plaque control, changes in gingival inflammation, long-term patient-based outcomes and adverse effects (pharmacological and microbiological). The duration of follow-up ranged from 22 weeks to 3 years with most studies lasting 22 weeks to 9 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened titles and abstracts and resolved any disagreements by discussion. Two reviewers
assessed full articles and resolved any disagreements by discussion. Inter-reviewer agreement for both parts of the selection process was assessed using the kappa statistic.

Assessment of study quality
Validity was assessed using the method of randomisation, allocation concealment, blinding of the patients, examiners and therapists, and completeness of follow-up. The review also assessed the reporting of reasons for drop-outs and the use of intention-to-treat analysis. Two reviewers independently assessed validity and results were entered onto a specifically designed form. Inter reviewer agreement was assessed using the Kappa statistic.

Data extraction
One reviewer extracted data that were verified by a second reviewer. The authors of reports with missing information were contacted for additional data. The standard error was estimated for studies in which it was not reported. The tables included details of the mean change in CAL and PPD for all pockets, moderate pockets (4 to 6 mm deep) and deep pockets (greater than 6 mm deep) for each treatment group, and the difference between treatment groups.

Methods of synthesis
How were the studies combined?
The characteristics of the participants and interventions were summarised narratively. Studies of spiramycin, amoxicillin plus metronidazole, and metronidazole that reported mean change in CAL or PPD with standard errors were combined in meta-analyses. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for CAL and PPD. The studies were combined using fixed-effect models. The studies were grouped by antibiotic and depth of pocket (4 to 6 mm and greater than 6 mm). A narrative synthesis of studies reporting other outcomes was undertaken.

How were differences between studies investigated?
Statistical heterogeneity was assessed in the meta-analysis and forest plots were presented. Differences in CAL and PPD were examined by tabulating the data from each study and 'vote counting' how many showed a beneficial effect of SRP plus antibiotics.

Results of the review
Twenty-three RCTs (approximately 1,300 patients) and 2 CCTs (92 patients) met the inclusion criteria for the review. Three of these studies were excluded from the meta-analyses since they reported duplicate data.

Most of the studies did not report the method of randomisation or allocation concealment, and most did not clearly define blinding.

All of the meta-analyses were based on data from 2 studies for each drug. The meta-analysis showed that spiramycin significantly increased the mean change in PPD for deep pockets (greater than 6 mm) (WMD 0.407 mm, 95% CI: 0.081, 0.733), but there was no difference for change in CAL (WMD 0.262 mm, 95% CI: 0.044, 0.569). Amoxicillin plus metronidazole significantly increased the mean change in CAL for deep pockets (WMD 0.450 mm, 95% CI: 0.192, 0.709), but not for moderate pockets (4 to 6 mm) (WMD 0.154 mm, 95% CI: 0.172, 0.480). Metronidazole increased the mean change in CAL for deep pockets but the increase was not statistically significant (WMD 0.551 mm, 95% CI: 0.017, 1.119). No significant heterogeneity was detected in any of the meta-analyses (P>0.1).

The review also reported results for CAL change and PPD change for different antibiotics, different pocket depths and different patient groups in the other individual included studies.

Long-term outcomes: none of the studies reported the loss of teeth. The frequency of sites losing CAL were reported in several studies examining different antibiotics; 79 to 100% of patients experienced loss of CAL with placebo treatment and 0 to 45% with doxycycline (2 studies) and clindamycin or amoxicillin plus clavulanate (1 study).

Bleeding index change: the studies generally showed similar results between treatments, but the results varied among
studies.

Plaque index: the studies generally reported similar results between treatment groups with little improvement from baseline.

Adverse effects: few studies reported adverse effects. One study found more adverse effects with doxycycline than with control. Most of the reported adverse effects were gastrointestinal problems. Few studies assessed the increase in antibiotic resistance in subgingival bacteria.

**Authors' conclusions**
The addition of systemic antibiotic treatment to SRP in patients with periodontitis can improve the change in CAL and PPD, especially for deep pockets. Detailed analysis and definitive conclusion were not possible due to the differences in study methods and the lack of appropriate data.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched for published studies and the search terms were stated, but the apparently limited attempt to locate unpublished studies raises the possibility of publication bias. Limiting the included studies to those in the English language may have omitted some relevant studies. More than one reviewer independently selected the studies and assessed validity, which reduces the potential for bias and errors. One reviewer extracted the data with the results checked by a second reviewer. Validity was assessed using defined criteria and some relevant information on the included studies was tabulated. From the data extraction tables, it appeared that a number of studies had considerable drop-out rates and this may have influenced the results. Data from studies with similar antibiotic regimens and enrolling patients with similar types of periodontitis were appropriately combined in meta-analyses and statistical heterogeneity was assessed. As the authors correctly stated, the evidence was limited due to a lack of data and differences among the studies.

**Implications of the review for practice and research**
Practice: The authors stated that systemic antibiotics used with SRP compared with SRP alone can improve change in CAL and PPD, reduce further CAL loss in patients with progressive or 'active' disease, and that spiramycin and amoxicillin plus metronidazole can reduce PPD and increase CAL gain in deep pockets.

Research: The authors stated that well-designed and well-conducted RCTs with follow-up lasting at least 6 months and preferably one year are required. They stated that studies should recruit homogeneous populations and report age, previous treatments and smoking status; that interventions and cointerventions should be clearly described; and that the outcomes should include CAL, PPD, adverse effects and microbiological outcome measures. They also stated that long-term outcomes such as tooth survival and additional CAL loss should be assessed.

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