No evidence to support benefit of 14-day courses of amoxicillin-plus-metronidazole as adjunct to non-surgical periodontal treatment at three months

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A Commentary on

McGowan K, McGowan T, Ivanovski S.
Optimal dose and duration of amoxicillin-plus-metronidazole as an adjunct to non-surgical periodontal therapy: A systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Periodontol* 2018; **45:** 56-67.

Practice points

- Antibiotic use as adjuvant to non-surgical periodontal therapy should be rationally selected in a case-by-case basis according to clinical criteria such as diagnosis, severity, flora or rate of progression.
- Principles of responsible use of antibiotics suggest the use of high doses and short duration. In this context, seven days of amoxicillin and metronidazole (500/500 or 500/400) three times per day should be recommended.

Abstract

Data sources Databases including Embase, MEDLINE, The Cochrane Central Register of Controlled Trials and the WHO International Clinical Trial Register Platform were screened by two reviewers. A manual search has been performed in references from included articles and relevant reviews.

Study selection Blinded, placebo-controlled, randomised clinical trials (RCTs) with a minimum follow-up of three months were included. Primary outcomes were periodontal pocket depth (PD) and clinical attachment level (CAL) changes after non-surgical periodontal treatment with adjunctive use of amoxicillin/metronidazole vs placebo in periodontitis patients. Secondary outcomes were adverse events and compliance.

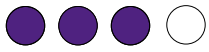
Data extraction and synthesis Data were extracted and compiled in a spreadsheet. Studies were grouped according to duration (seven days or fourteen days) and dose of amoxicillin/metronidazole regimen (lower dose (mg): 250/200, 375/250, 375/500, 500/250 and higher dose (mg): 500/400, 500/500). Meta-analyses were performed using inverse-variance method. Random-effect models were applied and weighted mean differences were estimated for PD reduction and CAL changes at three months. Risk of bias was assessed using the Cochrane Collaboration tool.

Results Eighteen studies were identified and included in the systematic review. Among them, 15 were pooled for meta-analysis. The use of a wide range of antibiotics concentrations (amoxicillin (from 250 to 500 mg) and metronidazole (from 200 to 500 mg)) was reported and the duration of antibiotic administration ranged from three to 14 days. Eleven studies were performed in chronic periodontitis patients and six in aggressive periodontitis patients. No significant differences were found regarding mean PD and mean CAL changes according to the duration or dose of administered antibiotics (Table 1). Risk differences for adverse events in the higher dose and longer duration groups were minimally greater (0.04 and 0.05 respectively).

Conclusions Longer courses (14 days) of antibiotics adjuvant to non-surgical therapy do not appear to provide better results in terms of PD reduction or CAL gain at three months. No differences were found between high and low dose groups. In this context, 400/500 mg or 500/500 mg of amoxicillin/metronidazole three times per day should be recommended for seven days.

Table 1 Mean PD and mean CAL changes at three months according to dose and duration of amoxicillin/metronidazole administration as an adjuvant to non-surgical periodontal treatment

	Dose		Duration	
	Lower	Higher	7-days	14-days
PD (mm)	-0.35 (-0.47, -0.24)	-0.37 (-0.46, -0.27)	-0.36 (-0.47, -0.25)	-0.38 (-0.49, -0.27)
CAL (mm)	-0.32 (-0.45, -0.19)	-0.25 (-0.42, -0.08)	-0.28 (-0.55, 0.00)	-0.28 (-0.47, -0.09)

GRADE rating 

Commentary

The combination of amoxicillin-metronidazole has demonstrated synergic effects and it has been recommended as an adjuvant to non-surgical periodontal treatment in the management of periodontitis. However, the use of such a combination during chronic periodontitis treatment remains controversial.[2] Although the administration of antibiotics improves results of non-surgical periodontal therapy,[3] most chronic periodontitis patients could be managed without.[4] According to the World Health Organization and the European Union, broad-spectrum or a combination of antibiotics should be avoided except in cases of severe infections that do not respond otherwise.[2] Responsible use of antibiotics also recommends high doses and shorter duration of administration[5] even if no clear recommendations are available, resulting in a wide range of doses and duration of administration depending on treated population, countries and diagnosis criteria.

The systematic review and meta-analysis by McGowan *et al.* addressed the optimal dose and duration of amoxicillin/metronidazole as an adjuvant to non-surgical periodontal

treatment. The study followed the PRISMA guidelines and included only RCTs, blinded and placebo-controlled. The study was well conducted and most of the included studies were classified as low risk of bias.[1]

Included studies evaluated different durations of antibiotics administration (3, 7, 10 and 14 days) but due to the low number of available studies, outcomes were compared only between seven and 14 days. Several doses were also reported in the included studies. Consequently, to allow comparisons, authors characterised studies as 'low dose' or 'high dose'. Both groups exhibited similar results for PD and CAL reduction at three months and no evidence suggested an optimal dose or duration. However, the threshold selected to define low and high dose may reduce the impact of such conclusion.

Efficacy of antibiotics is dampened when undisturbed biofilm is present. It has been recommended that the drug therapeutic levels should be achieved at the time of debridement completion.[4] In the present study it was not possible to evaluate the protocol effect due to the variability of the time of antibiotics administration (in one study prior to the first appointment, in seven studies after the first appointment and in nine studies immediately after the completion of the treatment).

Non-surgical periodontal treatment with and without systemic antibiotics leads to PD and CAL improvements during the first six months before reaching a plateau.[6] In this context, the short-term results analysed in this review (three months) could underestimate the therapeutic outcomes.

Finally, chronic and aggressive periodontitis were analysed together, and it was not possible to stratify results according to the severity of the disease. Such a parameter is of importance as antibiotics have been demonstrated to induce better clinical improvements in deep pockets than for moderate ones.[3] Therefore, an analysis of the effect at the site level would have been informative.

Nevertheless, biofilm composition, especially determination of the presence of main periodontal pathogens is of importance. Most of the periodontitis-associated flora is formed by anaerobic bacteria susceptible to metronidazole alone, while amoxicillin-plus-metronidazole is a broad-spectrum combination targeting facultative anaerobic bacteria, such as *Aggregatibacter actinomycetemcomitans*. Treating all periodontitis cases with this antibiotic combination could suppose an unnecessary use of antibiotics, against the general recommendations.[2]

In conclusion, the article addressed well the focused question and the evidence available suggests that 14 day antibiotic treatment achieves similar outcomes to seven day antibiotic treatment in combination with non-surgical periodontal treatment at three months. Higher doses and seven day courses should be preferred when antibiotic use is necessary according to responsible use of antibiotics.

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