



The use of systemic antibiotics in the treatment of refractory periodontitis

A systematic review

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The most common forms of periodontitis—chronic and aggressive—are oral diseases associated with an accumulation of a bacteria-specific subgingival dental biofilm that elicits an exaggerated immune response, which leads to the destruction of the supporting tissues of teeth.^{1,2} Conventional treatment of such types of periodontitis is centered on the elimination of the bacteria present, mainly via biofilm mechanical debridement alone (surgical or nonsurgical) or, as better established for aggressive periodontitis, supplemented by antibiotic therapy.^{3,4} Adequate personal biofilm control via oral hygiene measures also is considered an essential part of treatment, as is the control of predisposing or modifying factors.⁴

Mechanical debridement alone (surgical or nonsurgical) is effective in the treatment of most patients with periodontitis.^{3,5} However, in a small number of cases (0.5-4%), it does not eliminate or control the disease.⁶ Although not a disease category explicitly included in the American Academy of Periodontology (AAP) 1999 Classification of Periodontal Diseases and Conditions, the AAP has defined periodontitis that responds poorly to conventional treatment as *refractory periodontitis* (RP).^{7,8}

Thus, rather than a single disease entity, RP describes destructive periodontal diseases—initially diagnosed as chronic, aggressive, or other types of periodontitis—in patients who, when longitudinally monitored, demonstrate additional attachment loss at 1 or more sites, despite well-executed therapeutic and patient efforts to stop the disease.⁸ Possible explanations for disease persistence include the presence of intraoral microbial

ABSTRACT

Background. The goal in treating refractory periodontitis (RP) is to arrest or slow disease progression, which usually has included the use of systemic antibiotics adjunct to conventional mechanical debridement. The aim of this systematic review was to evaluate the evidence that the association of systemic antibiotics with conventional mechanical debridement increases the efficacy of periodontal therapy in the treatment of RP.

Types of Studies Reviewed. The authors searched for studies in PubMed MEDLINE, Cochrane Central Register of Controlled Trials, Thomson Reuters Web of Science, Scopus, Latin American and Caribbean Center on Health Sciences Information, and Scientific Electronic Library Online electronic databases by using selected key words from the earliest records up through October 31, 2014.

Only clinical intervention studies in which investigators compared the treatment of participants with RP with either mechanical debridement alone or associated with systemic antibiotics were eligible for selection. Two authors independently assessed the risk of bias of each selected study.

Results. The authors identified 13 articles and included 6 of them. Investigators in all studies reported greater reductions in probing depth or in loss of clinical attachment level after adjunct systemic antibiotic therapy when compared with mechanical debridement alone. Antibiotics tested included metronidazole, clindamycin, tetracycline hydrochloride, amoxicillin, and amoxicillin and potassium clavulanate. Five studies presented a high risk of bias, and 1 study presented an unclear risk.

Conclusions and Practical Implications. The overall quality of the evidence does not allow the conclusion that adjunct systemic antibiotics are of additional benefit to conventional mechanical debridement alone.

Key Words. Periodontitis; systemic antibiotic therapy; periodontal treatment.

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reservoirs of infection, the activity of or superinfection by opportunistic bacteria, or a hyperactive oral neutrophil phenotype.^{7,9-12}

Treatment success is achieved when disease progression is prevented or at least slowed down. It is widely believed that a key aspect of the treatment strategy is the use of systemic antibiotics as an adjunct to mechanical debridement of the biofilm.^{10,11} Although a number of different antibiotics have been tested for this purpose, a successful standardized antibiotic regimen has not been established. The difficulty or impossibility of identifying an optimal antibiotic may be explained by the heterogeneous microbiological profile of the disease sites of patients with RP.^{11,13} Although putative bacteria usually are present in large numbers, uncommon species sometimes also are found in substantial quantities.¹³ The heterogeneous nature of the microbiota, as well as the presence of uncommon species may contribute to the contrasting results observed in different studies. If on one hand there are studies with results indicating that the use of adjunctive antibiotics markedly and sustainably reduces pathogenic species,^{6,12} others show the persistence, in high numbers, of both known and less well-established potential periodontal pathogens.^{11,14}

The aim of this systematic review was to evaluate the scientific evidence that supports the use of adjunct systemic antibiotic therapy in treating RP. Investigators in recent systematic reviews have concluded that there is solid evidence for the use of adjunct systemic antibiotics in treating both chronic and aggressive periodontitis.^{15,16} Therefore, we hypothesized that there also may be sufficient evidence that this approach (which the AAP recommends) similarly could be advantageous for treating RP.

METHODS

Focused question. We conducted this systematic review according to the Cochrane Collaboration¹⁷ and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁸ Thus, we developed the following focused question in accordance with the recognized Patient, Intervention, Comparison, and Outcome¹⁹ format: what is the clinical efficacy of systemic antibiotics as an adjunctive therapy to mechanical debridement, when compared with mechanical debridement alone in terms of clinical attachment level (CAL) gain and probing depth (PD) reduction, in patients with RP?

Search strategy. We searched for articles of interest in PubMed MEDLINE, Cochrane Central Register of Controlled Trials, Thomson Reuters Web of Science, Scopus, Latin American and Caribbean Center on Health Sciences Information, and Scientific Electronic Library Online databases and included studies published from inception of the databases up through October 31, 2014. We used the following search algorithm to explore

databases by using Boolean phrases: (“anti-bacterial agents” [medical subject headings {MeSH}] OR “systemic antibiotics” OR “antibiotic therapy”) AND (“refractory periodontitis” OR “chronic refractory periodontitis” OR “aggressive refractory periodontitis” OR “periodontal diseases” [MeSH] OR “periodontitis” [MeSH] OR “clinical attachment level” or “probing depth” OR “clinical attachment loss” OR “bleeding on probing”).

Eligibility criteria. We selected studies only if they met the following inclusion criteria: represented a patient-based study in which an intervention was provided, included patients with explicitly diagnosed RP, included both a mechanical debridement and systemic antibiotic (test) group and a mechanical debridement alone (control) group, the patient received only the systemic antibiotics and mechanical debridement in at least 1 of the study groups, investigated the effect of the intervention on CAL and PD, and followed up for at least 6 months. We excluded articles from consideration if the study population included participants with systemic disease or who had used antibiotics or other medication (within 30 days of the beginning of the study) known to affect periodontal tissues or treatment.

Selection strategy. Using a predefined protocol (Figure 1), 2 previously calibrated examiners (R.S.S., R.F.M.) performed all described stages independently. Figure 1 shows the overall process used for selecting the articles used in the final analysis.

After database identification of articles and the elimination of studies in duplicate, the first step in the selection process was the title-based screening of articles. To be selected for further consideration, the article had to contain in its title 1 or more key words, synonyms of these, or a word that was relevant to the topic of interest.

In the second step of the selection process, we performed abstract-based screening. We tentatively investigated compliance with the established inclusion criteria. We eliminated in vitro and animal studies, as well as studies in which no intervention was provided to the study population. If there were any doubt during the title-based or abstract-based screening stages about whether the inclusion criteria were being met, we kept

ABBREVIATION KEY. *Aa*: *Aggregatibacter actinomycetemcomitans*. **AAP**: American Academy of Periodontology. *Bf (Tf)*: *Bacteroides forsythus (Tannerella forsythensis)*. **BOP**: Bleeding on probing. **CAL**: Clinical attachment level. **GI**: Gingival index. **MeSH**: Medical subject headings. **PD**: Probing depth. *Pg*: *Porphyromonas gingivalis*. **PI**: Plaque index. *Pi*: *Prevotella intermedia*. **RP**: Refractory periodontitis. **SRP**: Scaling and root planing. **UBA**: Uncontrolled before and after.

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