ABSTRACT

Evaluation of the use of adjunct systemic antibiotic therapy in treating refractory periodontitis

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 one 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.

The use of systemic antibiotics in the treatment of refractory periodontitis

A systematic review

Rayane S. Santos, graduate student, Paraiba State University, Campina Grande-PB, Brazil

Rodrigo F. Macedo, dental student, Paraiba State University, Campina Grande-PB, Brazil

Emanuel A. Souza, graduste student, University of São Paulo-SP Brazil

Renata S.C. Soares, assistant professor, ph.d., Periodontics, Paraiba State University, Campina Grande-PB, Brazil

Daniela S. Feitosa, assistant professor, ph.d., Periodontology, Federal University of Pernambuco, Recife-PE, Brazil

Carlos F.M. Sarmento, assistant professor, ph.d.,Periodontology, Federal University of Pernambuco, Av professor Moares Rego, Recife-PE, Brazil

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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 Classication of Periodontal Diseases and Conditions, the AAP has defined

EMNEORD

Periodontitis; systemic antibiotic therapy; periodontal treatment

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 one 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 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 Collaboration (17) 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 outcome (19) 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 one 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 (Fig. 1), two previously calibrated examiners (R.S.S., R.F.M.) performed all described stages independently. Fig. 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 / 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 the study for a more detailed evaluation during the next stage.

The third step of the article selection process was a full-text–based analysis in which we investigated compliance with the

Udvælgelse af artikler

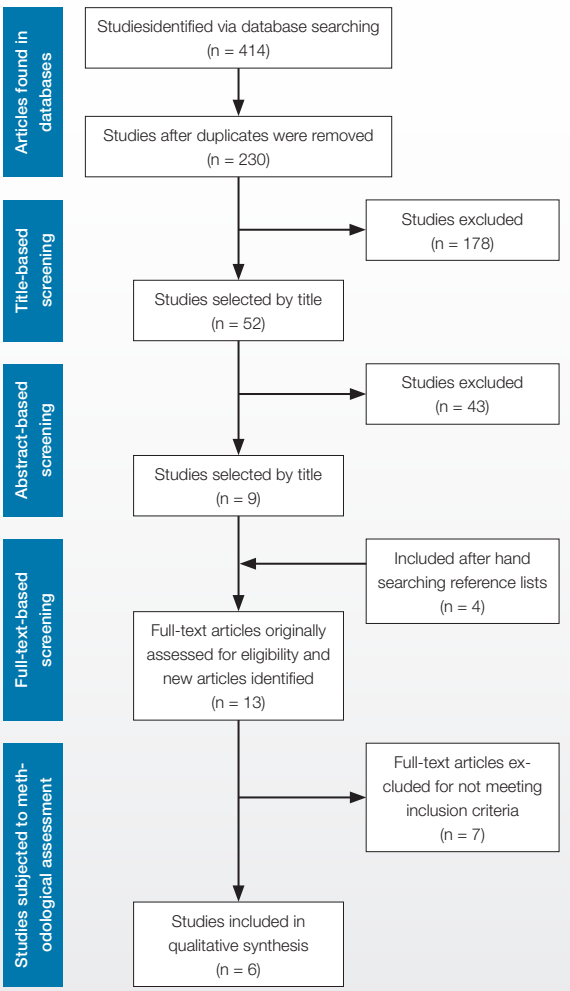

Fig. 1. Key words and search strategy.

Fig. 1. *Emneord og søgestrategi.*

inclusion criteria in greater detail. In addition, we performed a hand search of the reference lists of all articles that reached this third stage to identify any additional studies we may have missed during the electronic database searches.

Data extraction

Two independent investigators (C.F.M.S., R.S.C.S.) performed data extraction. From each article, we collected the following information: author names, year of publication, study design, participants (number, age, and previous treatment history), interventions used, evaluation method (including follow-up), and results.

Outcome assessment

The primary outcomes of interest were changes in CAL and PD from baseline up to the end of follow-up. In addition, we investigated secondary outcomes of interest such as bleeding on probing (BOP), gingival recession changes in gingival index, plaque index, and microbiological and immunologic parameters.

Quality assessment

We evaluated the methodological quality of each study on the basis of the revised recommendations of the Consolidated Standards of Reporting Trials statement (20). Thus, evaluation took into account random sequence generation, allocation concealment, adequate masking of all involved, completeness of outcome data, selective reporting, and other sources of bias. Two independent masked reviewers (C.F.M.S., R.S.C.S.) provided the overall risk of bias for each study and across studies through the guidelines recommended by the Cochrane Collaboration (17). In brief, the risk of bias (low, unclear, or high) within an individual study is based on whether all key domains evaluated show, respectively, either a low risk of bias or at least one key domain with an unclear or high risk of bias. The overall risk of bias (across studies) is then dependent on whether most of the individual studies present either a low, unclear, or high risk. A low risk of bias suggests that the results are unlikely to alter the results seriously, an unclear risk of bias raises some doubt about the results, and a high risk of bias indicates that the bias detected seriously weakens confidence in the results.

Results

Using the search strategy established, we identified 414 articles of potential relevance in all databases investigated. We identified most articles by using PubMed (n ¼ 356). After elimination of studies identified as duplicates, we subjected 230 studies to title-based screening. Of these, we eliminated 178 because they did not satisfy the inclusion criteria. Thus, 52 articles underwent abstract-based screening, resulting in the selection of nine articles for full-text–based analysis.

In the next phase, we further examined inclusion criteria compliance by means of full-text analysis, resulting in the elimination of foue articles. During this investigation, we identified a further four studies by means of hand searching and assessed them regarding fulfillment of the inclusion criteria. Of these, two did not meet the minimum criteria established, and we eliminated another study because its data were included in a subsequent article selected for final evaluation. Thus, only 6 studies reached the final stage of analysis (methodological evaluation).

The 6 studies examined in the final analysis were one randomized controlled trial (RCT) and 5 uncontrolled before and after (UBA) studies. In the UBA studies, all participants initially received the control intervention and subsequently the intervention being tested; the idea was that each patient would serve as his or her own control. Thus, in these studies, test and control interventions were not provided simultaneously.

In all studies, results were provided in regard to improvement of clinical parameters related to loss of clinical attachment (CAL, PD) and BOP. Table 1 (21-26) shows that the antibiotics tested included metronidazole (25), clindamycin (23), tetracycline hydrochloride (22), amoxicillin and metronidazole (24,26), and amoxicillin and potassium clavulanate (21). The investigators performed microbiological testing in three studies (21,23,24).

There was complete agreement about the overall risk of bias for all studies evaluated. As indicated, we considered five studies (21-25) to have high risk of bias and one study (26) to have an unclear risk. Thus, the overall risk of bias across studies (Fig. 2) (17,21-26) was high.

Discussion

We performed this review to answer the question of whether the use of adjunct systemic antibiotics in treating RP, a practice the AAP recommends (7), is of any additional benefit when compared with mechanical debridement alone. Although results from all six studies showed that mechanical treatment and systemic antibiotics resulted in the improvement of periodontal parameters from baseline to investigated time points, investigators in five of the six studies did not adequately evaluate whether such effects are superior to those achieved with mechanical debridement alone. Thus, there is insufficient evidence that it produces any additional benefit.

CLINICAL RELEVANCE

Although the investigators in the studies we evaluated in this review reported greater success in treating RP with adjunct antibiotic therapy, the overall body of evidence still does not support its use unequivocally.

Bias analyse

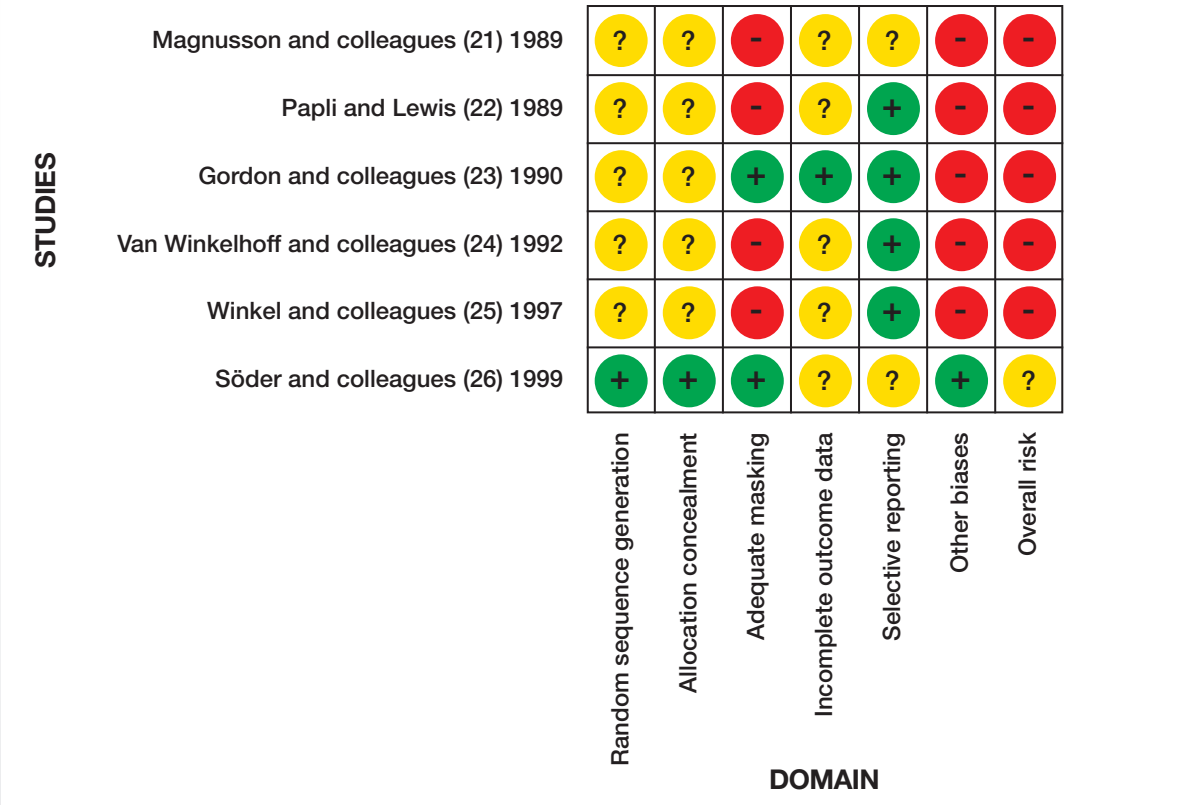

Fig. 2. Risk of bias analysis. (+): Low risk of bias. (-): High risk of bias. (?): Unclear risk of bias. Source: Higgins and Green (17).

Fig. 2. *Risiko for bias analyse. (+): Lav risiko for bias. (-): Høj risiko for bias. (?): Uklar risiko for bias. Kilde: Higgins og Green (17).*

De 6 inkluderede studier

Study	Design/ Follow-up	Nº of participants/Mean age (range or standard deviation)	Interventions	Antibiotic selection based on microbiologic testing	Parameters
Magnusson et al, 1989 (21)	UBA/ 1 year	10/52 (36-58)	**Control:** SRP. **Test:** SRP and amoxicillin 250 mg + potassium clavulanate 125 mg, 3x/day for 14 days.	Culture and antibiotic sensitivity testing.	CAL, PD, BOP, GI, PI, suppuration at day 0 and after 3, 6, 9 and 12 months.
Papli and Lewis, 1989 (22)	UBA/ 2 years	16/42.5	**Control:** SRP. **Test:** SRP + tetratracycline hydrochloride 250 mg 1h before root planning and then 1000 mg/day for 6 days.	No	PD, GR.
Gordon et al, 1990 (23)	UBA/ 2 years	30/47	**Control:** SRP. **Test:** SRP + clindamycin 150 mg 4x/d during 7 days.	Antibiotic sensitivity testing.	CAL, PD, BOP, PI
Van Winkelhoff et al, 1992 (24)	UBA/ 3 to 9 months	40/36.6±7.8	**Control:** SRP and/or periodontal surgery **Test:** SRP and amoxicillin 375 mg amoxicillin + metronidazole 250 mg, 3x/d for 7 days.	Identification and quantification of *Aa* in subgingival samples + antibiotic sensitivity testing.	CAL, PD, BOP, numbers an percentages of *Aa*, *Pg* and *Pi* (at day 0 and 3 to 9 months after therapy)
Winkel et al, 1997 (25)	UBA/ 1 year	27/ 45	**Control:** SRP. **Test:** SRP + metronidazole 500 mg, 3x/d during 7days at the beginning of study (day 0) and after 6 months. (quantas x / dia?)	No	CAL, PD, BOP, PI, presence of obligatory anaerobes and *Aa* (at day 0 and after 6 months).
Soder et al, 1999 (26)	RCT/ 5 years	98 (smokers and non smokers)/ 36±3.0	**Control:** SRP. **Test:** SRP (in some cases periodontal surgery was also performed) and amoxicillin 500 mg + metronidozole 400 mg, 3x/day during 7 days.	No	CAL, PD, BOP, PI, GI. From GCF: host cells, *Aa* and obligatory anaerobes.

RCT, randomly controlled trial; UBA, uncontrolled before and after; SRP, scaling and root planing; PI, plaque index; GI, gingival index; BOP, bleeding on probing; PD, probing depth; GR, gingival recession; CAL, clinical attachment level; *Aa, Aggregatibacter actinomycetemcomitans; Pg, Porphyromonas gingivalis; Pi, Prevotella intermedia.* (*), changes calculated for each group by the difference between the means (in mm) at the end of follow-up and baseline. (§), mean values (in mm) after (intervention) and before (control) treatment.

Table 1. Summary of methodology and results of studies selected.

***Tabel 1**. Resumé af metodologi og resultater af udvalgte undersøgelser.*

	PD Values (mm)	CAL Values (mm)	Statistical Analysis	Results
	2,5 mm decrease from baseline	2,0 mm gain from baseline	Statistical analysis was not performed.	**Primary outcomes:** In comparison to baseline measurements (proposed control), test intervention was associated with a 10% increase in the number of sites with gain of attachment, and a 15 increase in sites that underwent PD reduction >1 mm. **Secondary Outcomes:** The frequency of BOP and PI was practically unaltered throughout the study.
	Increase in % of pockets 1-3 mm (Test: 20.4%, Control: 11,6% Decrease in % of pockets 4-6 mm (Test: 84.3, Control: 57.4% and of pockets 7-10 mm (Test: 78.9%, Control: 44,4%)	Not applicable	Whether there was significant change in PD (of single and multirooted teeth) from baseline in response to test treatment was investigated by multivariate ANOVA.	**Primary Outcomes:** In comparison to baseline measurements (proposed control), test intervention resulted in reduction of PD in most sites throughout the duration of the study. Reductions in single-rooted teeth were greater. **Secondary Outcomes:** The number of sites with recession was small thus no further analysis was performed.
	Control: 7.6±1.5§ Test: 5.6±0.9§	Control: 7.8±1.4§ Test: 6.4±1.2§	ANOVA was used to investigate differences in clinical parameters and differences between observation periods were analyzed using the t test for paired samples. Differences between groups were calculated using the Wilcoxon matched-pairs signed-ranks test.	**Primary outcomes:** In comparison to baseline measurements (proposed control), test intervention resulted (at 12 and 24 months) in increases in the percentage of sites with a CAL gain of at least 3.0 mm and reductions in PD. **Secondary outcomes:** Increase in the time to detect active disease. Reduction in BOP and no significant changes in the presence of plaque at any time period.
	Control: 7.6±1.5§ Test: 5.6±0.9§	Control: 7.8±1.4§ Test: 6.4±1.2§	Differences in clinical parameters were analyzed with ANOVA and differences between observation periods were investigated using t tests for paired samples. Differences between groups were examined using Chi-square.	**Primary outcomes:** In comparison to baseline measurements (proposed control), test intervention resulted in gains in CAL and reductions in PD.
	Control: 6.8±1.0§ Test: 5.3±1.2§	Control: 7.7±1.6§ Test: 6.7±1.6	Differences in clinical parameters before (control) and after (test) therapy were analysed using the Wilcoxon-test. Clinical response to test treatment of sites with different microbiological profiles were analysed with ANOVA.	**Primary outcomes:** In comparison to baseline measurements (proposed control), test intervention resulted in significant reductions in CAL and PD. Greatest reduction in PD and gain in CAL observed in patients that at start of study were simultaneously *Bf (Tf), Pg* and *Pi* positive. **Secondary outcomes:** Reduction in BOP and no significant reduction in PI. Reduction in most patients in numbers of *Bf (Tf), Pg* and *Pi.*
	In non-smokers Control: 0.0±0.0* Test: 0.7±0.4* **In smokers** Control: 0.6±0.3* Test: 0.6±0.6*	**In non-smokers** Control: 3.3±0.0* Test: 0.7±0.4* **In smokers** Control: 0.9±0.7* Test: 1.0±0.7*	Differences between baseline (control) and 5 year measurements (test) were analyzed using the paired Student´s t test. Mann-Whitney U-test was used for non-parametric statistics on continuous variables. Chi square test to investigate differences between control and test groups in the number of sites ≥5 mm.	**Primary outcomes:** From baseline, significant improvements in both test intervention and placebo groups in CAL and PD among non smokers. However, no significant differences between intervention and placebo groups (this was not stated in the article). **Secondary outcomes:** Improvement in intervention and placebo groups among smokers and non-smokers of BOP GI and PI. Decrease in *Aa* and *Pg* in all intervention and placebo groups. Among smokers significant increase in granulocytes. **OBS:** Dropout rate: over 50%.

The studies available were low in numbers and, with one exception (26), were small-scale clinical trials without adequate controls, which presents a high risk of bias. Investigators in the only RCT (26) evaluated showed unclear risk of bias and failed to show any significant improvement when compared with mechanical debridement alone. Moreover, a further analysis of the overall reported benefits on outcomes (for example, metaanalysis) is hampered by the various ways by which the investigators reported quantitative assessments. For example, whereas Winkel and colleagues (25) reported results relative to PD reduction in terms of mean millimeter reduction after treatment, Söder and colleagues (26) assessed improvement on the basis of absence of inflamed sites with a PD less than 5 mm, and Gordon and colleagues (23) assessed improvement on the time for incidence of active disease. Which of these measurements are more or less important is open to debate.

That the body of evidence is inconclusive is not surprising when one considers the number and types of studies that reached the final stage of evaluation. Although ideally only RCTs would be included to answer the question posed in this systematic review, the literature consulted before the conception of the study, mainly traditional reviews, books, and AAP position papers, indicated that the number of RCTs on the subject was scarce. Thus, the decision to include other types of intervention trials, although not desirable, in some cases is acceptable (21). Another consideration is that none of the studies included had as the stated purpose the comparison of the effects of systemic antibiotics and mechanical debridement with those of mechanical debridement alone (26). However, data were reported and discussed and conclusions drawn by the respective authors regarding the issue (7). At least in the case of the UBA studies, their conclusions may be related to the authors' recognition of the limitations of such types of studies. In the case of the RCT evaluated, it is difficult to speculate. Nevertheless, two UBA studies are referenced in the AAP position paper on the parameters of care for RP, so we considered these and the four other similar studies included relevant to the aims of our review.

Despite this somewhat unsurprising lack of evidence, the process of performing this review, in itself, raises a number of issues that encourage further research. First, antibiotic use was associated with improvement in periodontal parameters when compared with baseline values (in patients who previously underwent unsuccessful mechanical treatment). This finding may indicate that there may be an additional benefit and that failure to detect this in Söder and colleagues (26) (who used metronidazole) may be due to deficiencies in study design or power. Second, the investigators in the studies analyzed reported significant improvement, and no participants were excluded because of adverse effects, even with a possible tendency of both authors and journals to attribute greater value to positive effects (27). Third, improvements in periodontal parameters were achieved using different antibiotics. These included antibiotics selected either empirically or via microbiological testing. As to the former, one can speculate that they were chosen because of their previous effects in other forms of periodontitis or known effects on specific microbiota. Regardless of the selection method, the improvement of periodontal parameters observed with the different agents is consistent with data indicating that the microbiota associated with RP appears to be case specific—that is, heterogeneous in nature (11-13). This heterogeneity may explain at least in part why a number of antibiotics have been tested or used to manage RP over the years (11-13,22,24-26,28). Because of the different experimental designs and parameters of evaluation used it was not possible, in our review, to identify any clear differences between the effects of the different antibiotics investigated.

However, further confirmation of the microbiota heterogeneity in RP with stronger evidence would indicate that microbiological testing may be paramount to more predictable successful treatment outcomes (29,30).

This testing would be associated with the possibility of identifying the most effective antibiotics against the case-specific microflora, including, possibly, agents that have not been used before. Another advantage of antimicrobial testing is related to the observation that patients with RP frequently have undergone previous attempts to control the disease, which may have involved the use of a number of different antibiotics and, thus, show an increased risk for the emergence of antibiotic-resistant bacteria (14). Hence, in contrast to how systemic antibiotics are selected for the treatment of other forms of periodontal disease, for RP, it has been recommended that microbiological testing should be performed to select an appropriate agent (9,30).

Although the AAP recommends such a procedure in RP, the extent to which periodontal practitioners perform it is unknown. One can speculate, however, that it is low and that the additional costs and difficulties in performing the tests on subgingival biofilm, particularly in some parts of the world, may constitute important contributing factors.

Another line of thought is that the key to treating RP successfully may not be the elimination of specific microbiota. Instead, modulation of the host response may be a more effective strategy. This modulation could involve the control of known inflammatory mediators also produced in other periodontal diseases or of yet unknown factors that determine the type of host response mounted against the RP microbial challenge (10,29-31). Identification of the latter in the future may turn out to be the missing piece of the treatment puzzle.

There is also the need for a more precise understanding of what in fact is RP. The uncertainty is such that the most recent AAP classification no longer contains a category termed refractory periodontitis. Instead, discussion at the 1999 International Workshop for a led to the conclusion that all forms of periodontitis can be nonresponsive to therapy and that the refractory designation could be added to any type of periodontitis (8).

Today, terms such as refractory chronic periodontitis, refractory aggressive periodontitis (as if describing a subset of these diseases) or the more generic refractory periodontitis are used for disease that initially was diagnosed as a known type of periodontitis but that did not respond to its modality of conventional treatment (9-11,32,33).

Thus, it still is not clear whether refractory periodontitis is a term that describes, for example, a single condition with patient-specific features, a group of distinct conditions with a similar or differing etiopathogenesis, a variation of more well-defined periodontal diseases, or simply any of the destructive periodontal diseases that, unknown to the periodontist, have not been treated adequately. "Inadequate" treatment may include, for example, the failure to control undiagnosed or still unknown contributing factors.

In addition, there is still no consensus regarding the specific clinical parameters used to determine a lack of response to periodontal treatment, which, as discussed, is a defining characteristic of RP. In the studies examined in this article, for example, parameters included "patients who had at least 3 teeth with inflamed pockets and probing depth of 5 mm associated with radiographic bone loss after initial scaling and root planing" (19); "subjects with an unsuccessful periodontal treatment history, showing advanced periodontal breakdown at > 6 sites with bleeding and/or suppuration upon probing" (25); and patients showing sites with 3.0 mm or greater loss in attachment from baseline or the occurrence of a periodontal abscess (24). Mean attachment loss or 3 sites with attachment loss greater than 2.5 mm is an example of the diagnostic criteria for RP used in a 2012 microbiological study (11).

Despite these numerous considerations, as mentioned previously, in a small number of cases conventional periodontal treatment does not eliminate or control the disease (7). Such patients receive a diagnosis of RP, which though poorly understood is considered a condition somewhat distinct from the other more well-established forms of periodontal disease (9-11,32,33).

Study limitations

The most glaring limitation of this review was that five of the six studies did not have a parallel design and, consequently, the investigators in these did not compare the effects of mechanical debridement alone against mechanical debridement and systemic antibiotics adequately. A second limitation was the small number of studies available for evaluation. One can speculate that this may be due to both the low prevalence of the condition and the difficulty in unequivocally confirming the diagnosis of RP. In addition, only 1 of the studies was an RCT (26) in which the investigators typically evaluated the effects of a single antibiotic. Third, although in most studies statistically significant differences were shown after treatment, the numbers of participants were invariably small. Finally, the studies considered important enough for evaluation were performed more than 17 years ago. A frequent reason why newer studies (11,12) were not eligible for analysis in this review was that, although showing favorable shifts in microbial profiles after antibiotic treatment, they failed to provide data on the effects on clinical parameters (11) or to adopt mechanical debridement alone as a control (12).

Evaluation of the strength of the evidence produced in intervention studies in general is still not a clear-cut procedure. Moreover, there appears to be no widely accepted standardized approach for the evaluation of non-RCT clinical intervention studies. Thus, in this review, we evaluated both RCT and non-RCT studies with the Cochrane Collaboration risk of bias assessment tool (17). This tool has become popular for evaluating RCTs; however, it has not been validated formally, and, as Hartling and colleagues (27) have shown, levels of inter-examiner agreement sometimes vary widely across the 6 domains considered. Despite not being specifically developed for the evaluation of quasi-experimental studies, its use for that purpose nevertheless has been recommended (34). Its use in our review seems to have been adequate for evaluating the deficiencies of both types of intervention studies subjected to analysis.

In view of these limitations, it seems clear that more well-controlled RCTs with greater numbers of participants are needed. Considering that RP is a relatively rare diagnosis, such RCTs potentially could be achieved via multicentric studies in which the investigators use identical designs and procedures. Studies in which the investigators test the effectiveness of different antibiotics also seem relevant. In these, the possible benefits of antibiotic sensitivity testing could be evaluated further and used to optimize the antibiotic selection process.

In addition, RCTs in which the investigators use technological advances available today, such as modern microbiological or host response molecular techniques, always should include data on the corresponding effects of the antimicrobial tested on relevant clinical parameters. The use of existing advanced tools for measurement of clinical parameters, as well as standardized procedures for reporting such effects, also seems essential. As suggested earlier, further clarification of what

constitutes RP also should be sought. The new information obtained potentially could guide the development of alternative treatment strategies.

The clinical implications of the results we reported are that, for now, the use of adjunct antibiotic therapy to treat RP will remain just barely empirical. We can hope that in the coming years additional evidence will become available to direct the clinician better in treating this challenging condition.

Conclusion

Although the investigators in the studies we evaluated in this review reported greater success in treating RP with adjunct antibiotic therapy, the overall body of evidence still does not support its use unequivocally.

Disclosure. None of the authors reported any disclosures.

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.

ABSTRACT (DANSK)

Brugen af systemisk antibiotika i behandlingen af refraktær marginal parodontitis

Baggrund *– Målet med at behandle refraktær marginal parodontitis (RMP) er at standse eller reducere sygdomsudviklingen. Denne behandling har ofte anvendt systemisk antibiotikum som supplement til den konventionelle mekaniske behandling. Formålet med denne systematiske oversigt var at evaluere evidensen for, at systemisk anvendelse af antibiotikum som supplement til konventionel mekanisk behandling øger effekten af behandlingen af RMP.*

Typer undersøgelser, som er inkluderet *– Forfatterne søgte efter studier i PubMed Medline, Cochrane Central Register of Controlled Trials, Thomson Reuters Web of Science, Scopus, Latin American and Caribbian Center on Health Sciences Information og Scientific Electronic Library Online elektroniske databaser ved hjælp af udvalgte emneord fra de tidligste registreringer og op til den 31. oktober 2014. Kun kliniske interventionsstudier, hvor forskere i behandlingen af deltagere med RMP med enten konventionel mekanisk rengøring alene eller suppleret med systemisk antibiotika var berettiget til udvælgelse. To forfattere vurderede uafhængigt af hinanden risikoen for bias i hver af de udvalgte undersøgelser.*

Resultater *– Der identificeredes 13 artikler, og forfatterne inkluderede seks af dem. Forskere rapporterede i alle undersøgelser om større reduktioner i pochedybde eller tab af klinisk fæste efter supplerende systemisk antibiotisk behandling sammenlignet med konventionel mekanisk rengøring alene. De antibiotika, der blev undersøgt, omfattede: metronidazol, clindamycin, tetracyklin hydrochlorid, amoxicillin, og amoxicillin med clavulansyre. Fem undersøgelser blev præsenteret med en høj risiko for bias, og ét studie blev præsenteret med en uklar risiko.*

Konklusioner og praktiske implikationer *– Kvaliteten af den samlede dokumentation tillader ikke den konklusion, at supplerende systemisk antibiotika i behandlingen af refraktær marginal parodontitis forøger effekten sammenlignet med konventionel mekanisk behandling alene.*

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