An overview of systematic reviews of the use of systemic antimicrobials for the treatment of periodontitis

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IN BRIEF

- Describes the methodological approach of assessing the overall body of evidence supporting systemic antimicrobials for improving tooth survival in patients with periodontitis.
- Reports the lack of information of tooth survival and adverse events in patients suffering from periodontitis and treated with systemic antimicrobials.

Background Systemic antimicrobials have been used as an adjunctive therapy for the treatment of periodontitis. Nevertheless, it is unclear whether the use of antimicrobials may improve tooth survival in patients with periodontitis. The main objective of this overview of systematic reviews (SRs) with meta-analyses was to assess the evidence supporting systemic antimicrobials for improving tooth survival in patients suffering from periodontitis. Information on adverse events was also extracted from SRs. **Methods** PubMed and EMBASE databases were searched independently (up to 1st August 2013) to identify SRs with meta-analyses on the use of systemic antimicrobials as an adjunctive treatment to scaling and root planing (SRP) in the treatment of periodontitis. Tooth survival and adverse events were assessed. Clinical effect was also assessed based on endpoints including clinical attachment level and probing depth. The methodological quality of the SRs was assessed by two authors using two checklists (AMSTAR and OQAQ). **Results** No data on tooth survival after treatment with SRP and antimicrobials were found. Nine SRs were included in this overview. Three SRs showed statistically significant outcome improvement with the use of antimicrobials, although the clinical relevance may be questionable. One SR showed better results based on surrogate endpoints; however, short-term adverse events were more pronounced with the use of antimicrobials. The reporting of long-term data on clinical effects, adverse events and bacterial resistance is scarce. The SRs were of heterogeneous quality. **Conclusions** Evidence of the efficacy of systemic antimicrobials on improving tooth survival is lacking. Further research focused on tooth survival and adverse events should be performed to provide more robust evidence of the benefits of using systemic antimicrobials for treating periodontitis.

INTRODUCTION

Periodontal diseases affect the soft and hard tissues surrounding the teeth, and can contribute to tooth loss. Although several therapeutic approaches have been suggested, mechanical debridement is the standard approach for treating periodontitis.^{1–6} To enhance the effectiveness of therapy, systemic antimicrobials have been used with mechanical root scaling. Many reports suggest that clinical endpoints such as clinical attachment level (CAL) and pocket depth (PD) are improved with the use of

systemic antibiotics.^{7–10} However, the risk of adverse events, such as bacterial resistance, also needs to be considered,^{11,12} and more data on whether systemic antimicrobial use improves tooth survival are needed. Improvements in surrogate endpoints such as CAL and PD do not necessarily indicate future tooth survival.

An overview of systematic reviews (SRs) allows the synthesis of data from several reviews in a single document. This may benefit practitioners, researchers and policy makers looking for a comprehensive view of the evidence about the topic of interest.¹³ Therefore, the main objective of this paper was to critically assess whether the adjunctive use of systemic antimicrobials for the treatment of periodontitis may lead to improved tooth survival. We analysed evidence from SRs with meta-analyses (MAs) which are considered the pinnacle of the hierarchy of evidence to support decision-making. Moreover, we also critically assessed and interpreted the results of SRs based on the surrogate endpoints CAL and PD and potential adverse events.

Table 1 Literature search strategy in PubMed database (filters: systematic reviews; meta-analysis)

- 1) anti-bacterial agents
- 2) antibiotics
- 3) anti-infective agents
- 4) antimicrobial
- 5) (amoxicillin OR metronidazole OR tetracycline OR doxycycline)
- 6) (periodontal disease OR periodontal diseases OR periodontitis)
- 7) (#1 OR #2 OR #3 OR #4 OR #5)
- 8) (#6 AND #7)

MATERIALS AND METHODS

Research question, data sources and search strategies

In order to guide this critical appraisal, the following research question was developed: 'Does the use of systemic antibiotics as an adjuvant to mechanical therapy improve tooth survival in patients suffering from periodontitis?' A structured literature search was performed in PubMed and EMBASE electronic databases using the keywords: antibiotics and periodontitis. The last search was performed

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Table 2 Characteristics of systematic reviews with meta-analyses

Studies	Study designs included	Disease classification	Intervention	Comparison	Endpoints reported	Is tooth survival reported?
Hayes <i>et al.</i> 1992 ¹⁹	RCTs and CCTs	Periodontitis	SRP + tetracycline, tetracycline	SRP, placebo	PD and CAL	No
Elter <i>et al.</i> 1997 ²⁰	RCTs	Periodontitis	SRP + metronidazole	SRP	CAL and PD	No
Herrera <i>et al.</i> 2002 ²¹	RCTs and CCTs	Aggressive and chronic periodontitis	SRP + tetracyclines (tetracycline CIH, doxycycline, minocycline), MET and ornidazole, penicillins (AMX, AMX/clavulanate, penicillin), macrolides (erythromycin, spiramycin, azithromycin, oxithromycin), clindamycin, ciprofloxacin, and different combinations of these drugs (AMX/MET, /spiramycin, etc.)	SRP	Mean change in CAL and PD	No
Haffajee <i>et al.</i> 2003 ²²	RCTs, CCTs, and cohorts	Aggressive and chronic periodontitis	Single systematically administered antibiotic alone or combined with SRP or surgery	Placebo, SRP, surgery	CAL mean, % of sites exhibiting AL over a given threshold, PD	No
Bono <i>et al.</i> 2010 ²³	RCTs		AMX+MET or AMX or MET	SRP	CAL and PD	No
Sgolastra <i>et al.</i> 2012 ²⁵	RCTs	Chronic periodontitis	SRP + AMX+MET	SRP	Full-mouth CAL, full-mouth PD, as well as CAL gain and PD reduction stratified according to baseline PD	No
Sgolastra <i>et al.</i> 2012 ²⁶	RCTs	Aggressive periodontitis	SRP + AMX+MET	SRP	Full-mouth CAL gain, full-mouth PD reduction, as well as CAL gain and PD reduction stratified according to baseline PD	No
Sgolastra <i>et al.</i> 2013 ²⁷	RCTs	Chronic periodontitis	SRP +MET	SRP	CAL and PD	No
Zandbergen <i>et al.</i> 2013 ²⁴	RCTs, CCTs, prospective clinical studies, or case series	Aggressive and chronic periodontitis	AMX+MET+SRP.	SRP	CAL and PD	No

RCTs: randomized controlled trials; SRP: scaling and root planning; PD: pocket depth; CAL: clinical attachment level; CCTs: controlled clinical trials; AMX: amoxicillin; MET: metronidazole

on 1st August 2013. The predefined search strategy was designed for maximal retrieval using MeSH (medical subject headings) and free text searching (Table 1). 'In the process of choosing key-words for the search, balance between more generic synonyms for antimicrobials and more specific terms designating the most used antimicrobials for treating periodontitis (that is metronidazole and amoxicillin) was sought. The thesaurus of each database was used to adapt the search terms. The timeframe was chosen to include older references and monitor the progression of the literature over time. In addition, reference lists of select journal articles, three periodontal journals (*Journal of Clinical Periodontology*, *Journal of Periodontology* and *Journal of Periodontal Research*), and existing reviews were manually searched for additional references. The authors conducted independent literature searches, and disagreements over the initial search outputs were resolved by discussion. All searches were limited to articles published in English.

Study selection and criteria

All SRs with meta-analyses that assessed

the effects of systemic antimicrobials use with non-surgical mechanical treatment of periodontitis were considered for inclusion in this review. SRs with meta-analyses that examined host modulatory therapies including sub antimicrobial-dose doxycycline, local anti-infective agents, both local and systemic antimicrobials, and systematic reviews including animal studies were excluded. Two authors scanned the references retrieved by the initial search to exclude irrelevant studies. Full-text articles were retrieved and reviewed independently by two authors to determine inclusion after consensus was reached.

Data extraction

The authors independently extracted data using standardised forms. The data included: 1) results based on true endpoints such as tooth survival,¹⁴ 2) surrogate endpoints including CAL and PD measurements, and 3) adverse events. Adverse events were defined as injuries related to medical management, not complications of disease. Medical management included all aspects of care including diagnosis, treatment, failure

to diagnose or treat, and the systems and equipment used to deliver care.¹⁵ The recommendations of the SRs regarding the use of antimicrobials as adjuvant treatment for periodontitis were also extracted. The assessments of the two reviewers were compared, the final dataset determined after discussion and a consensus was reached.

Quality assessment

The methodological quality of the SRs included was determined using the assessment of multiple systematic reviews (AMSTAR) checklist, which is a validated checklist comprising 11 items addressing specific, important aspects of an SR.^{16,17} This tool was used to assess search strategies, inclusion and exclusion criteria, and the methodological qualities of trials included in the review. A second checklist, the overview quality assessment questionnaire (OQAQ), was used to assess the methodological quality of reviews included.¹⁸ OQAQ consists of a scale that is divided into nine areas related to the search methodology, selection criteria, assessment of the included studies, methods used to combine the findings, and overall

Fig. 1 PRISMA flowchart describing the literature search

scientific quality of the conclusions. We did not include the tenth question from OQAQ, because it is related to a final quality score for the review assessed. This measure was taken due to the difficulty of weighing domains assessed to achieve a final quality score, as well as to keep homogeneity in the assessment with AMSTAR (which does not include a final score). For the sake of simplicity, each of the checklist items was scored 'Yes' or 'No'. 'Yes' indicated that the assessed criteria were explicitly met in the SR, and 'No' indicated that the assessed criteria were not met or that they were not described by the authors. The number of items assigned 'Yes' indicated higher methodological quality of the reviews. Two authors performed the methodological quality assessments of SRs independently, and disagreements were resolved by discussion until a consensus was achieved.

Training of reviewers

Before the SRs were analysed with the checklists, reviewers performed practice assessments to streamline the process. Three rounds with three SRs in each round were assessed independently and in duplicate. The results of each assessment were compared and disagreements were discussed to improve homogeneity.

RESULTS

The initial search retrieved 179 articles. After screening titles and abstracts, 146 articles were excluded. Full-text reviews of the remaining 33 articles resulted in the

exclusion of 24 articles, which left nine SRs for inclusion in the study (Table 2).^{19–27} Figure 1 illustrates the literature search results in detail.

Results

Tooth survival

No tooth loss was reported in the nine SRs assessed (Table 2).

CAL and PD (all periodontal pockets)

The use of systemic antimicrobials increased mean PD reductions by 0.18 mm²⁷ to 1.41 mm²⁴ on average, in comparison to SRP alone. The number of studies included in the SRS with meta-analyses that assessed changes in PD varied from 3²⁵ to 19²⁴, and the follow-up time ranged from 1 to 24 months (Table 3). In the antimicrobials group, CAL improvements ranged from 0.045 mm²² to 0.94 mm²⁴ on average. The number of studies included in the SRs with meta-analyses assessing changes in CAL varied from 4²⁵ to 27.²²

CAL and PD (deep periodontal pockets)

In cases of deep periodontal pockets, PD >6 mm at baseline, on average CAL measurements improved with the use of antimicrobials from 0.262 mm (with spiramycin) to 0.551 mm (with metronidazole) (Table 4).²¹ In cases of PD >6 mm at baseline, the use of amoxicillin and metronidazole and SRP produced an average improvement on CAL of 1.66 mm in comparison to SRP alone.²⁴ In cases of PD >7 mm at baseline, CAL average

values varied from 0.193 mm²⁰ to 2.66 mm.²⁴ The number of studies included in the SRs with meta-analyses assessing changes in CAL varied from two²¹ to eight.²⁴

In cases of PD >5 mm at baseline, tetracycline and SRP treatment reduced PD by 0.43 mm on average compared to SRP treatment alone.¹⁹ In cases of PPD >6 mm at baseline, spiramycin reduced PD by 0.407 mm on average more than SRP treatment.²¹ In cases of PD >6 mm, amoxicillin, metronidazole and SRP combined treatment only reduced PD by 2.59 mm on average more than SRP.²⁴ In cases of PD >7 mm at baseline, average PD reductions varied from 0.7 mm²⁰ to 3.72 mm compared to SRP treatment alone.²⁴ The number of studies included in the SRs assessing changes in PD varied from two to eight (Table 4).

Adverse events

The prevalence of adverse events in patients treated with systemic antimicrobials varied greatly. Most adverse events reported were gastrointestinal. The complaints included nausea, vomiting, headache and metallic taste (Table 5). One SR reported a temporary increase in bacterial resistance.²¹

Methodological quality of SRs

With the AMSTAR checklist, SRs were scored from 1 to 9 (median = 8). Some checklist criteria were met in almost all SRs. For example, the questions, 'were the characteristics of the included studies provided?' and 'was the scientific quality of the included studies assessed and documented?' were reported in eight of the nine SRs assessed. In contrast, two questions, 'was the status of publication used as an inclusion criterion?' and 'was the conflict of interest included' were not reported in any SRs assessed. The full AMSTAR assessment is reported in Table S1 in the Appendix.

With the OQAQ checklist, SRs were scored from 5 to 9 (median = 8). Some checklist criteria were met in all SRs, for example 'were the search methods used to find evidence (original research) on the primary question (s) stated?' and 'were the criteria used for deciding which studies to include in the overview reported?' In contrast, one criterion ('was bias in the selection of studies avoided?') was met in three of nine SRs.

DISCUSSION

This overview of SRs reveals the lack of robust evidence supporting the use of systemic antimicrobials as adjuvant therapy to SRP for the treatment of periodontitis. To date, all evidence of antimicrobial effectiveness is based on surrogate endpoints such as PD and CAL. In addition, adjunctive use of

Table 3 Systematic reviews with meta-analyses of systemic antibiotic use in the treatment of periodontitis (PD average measurements at baseline: 'all pockets')

Studies	Results on effectiveness (in mm)		Number of studies included in the meta-analyses*	Time of follow-up	Authors' conclusions†
	Fixed-effect model	Random-effect model			
Hayes <i>et al.</i> 1992 ¹⁹	No data on PD average measurements		NP	25 weeks	'We conclude that analysis of data from the published literature does not demonstrate that the use of systemic tetracycline is more beneficial than conventional treatment in the management of adult periodontal disease. More information is needed in order to perform an extensive meta-analysis of this subject'
Elter <i>et al.</i> 1997 ²⁰	No data on PD average measurements		NP	4 to 6 weeks	'These results suggest that MET in conjunction with SRP may offer a benefit over SRP alone in the treatment of adult periodontitis patients in managing pockets of 4 mm or greater, but the additional benefit was not evident if initial PD was less than 4 mm or follow-up was beyond 13 weeks'
Herrera <i>et al.</i> 2002 ²¹	No data on PD average measurements		NP	24 weeks	'Systemic antimicrobials in conjunction with SRP, can offer an additional benefit over SRP alone in the treatment of periodontitis, in terms of CAL and PD change, and reduced risk of additional CAL loss. However, differences in study methodology and lack of data precluded an adequate and complete pooling of data for a more comprehensive analyses. It was difficult to establish definitive conclusions, although patients with deep pockets, progressive or 'active' disease, or specific microbiological profile, can benefit more from this adjunctive therapy.'
Haffajee <i>et al.</i> 2003 ²²	CAL (0.045, range 0.09 to 1.10)		27 for CAL	12 to 96 weeks	'1) The use of systematically administered adjunctive antibiotics with and without SRP and/or surgery appeared to provide a greater clinical improvement in CAL than therapies not employing these agents. 2) The data supported similar effect sizes for the majority of the antibiotics; therefore, the selection for an individual patient has to be made based on other factors. 3) Due to lack of sufficient sample size for many of the antibiotics tested, it is difficult to provide guidance as to the more effective ones'
Bono <i>et al.</i> 2010 ²³		PD (-1.1355, CI: -2.5896 to 0.3186); CAL (-0.4548, CI: -1.3035 to 0.3940) (favoring test)	6 for PD 5 for CAL	4 to 48 weeks	'This meta-analysis showed absence of statistically significant difference between the effects studied'
Sgolastra <i>et al.</i> 2012 ²⁵		CAL (0.21, CI: 0.02 to 0.4); PD (0.43, CI: 0.24 to 0.63)	4 for CAL 3 for PD	12 to 96 weeks	'The findings of this meta-analysis seem to support the effectiveness of SRP + AMX/MET; however, future studies are needed to confirm these results'
Sgolastra <i>et al.</i> 2012 ²⁶		CAL (0.42, CI: 0.23 to 0.61); PD (0.58, CI: 0.39 to 0.77)	6 for CAL 6 for PD	8 to 24 weeks	'The findings of the meta-analysis seem to support the effectiveness and the clinical safety of FMSRP + AMX/ MET; however, future studies are needed to confirm these results'
Sgolastra <i>et al.</i> 2013 ²⁷		PD (0.18, CI: 0.09 to 0.28); CAL (0.10, CI: 0.08 to 0.12)	9 for PD 9 for CAL	12 to 48 weeks	'The meta-analysis results seem to support the effectiveness of adjunctive MET with SRP compared to SRP alone. However, given the low number of included studies and limitations of meta-analysis, future studies are needed to confirm these results'
Zandbergen <i>et al.</i> 2013 ^{†,24}	PD (-1.41, CI: -1.46 to -1.37); CAL (+0.94, CI: +0.90 to +0.98)		19 for PD 19 for CAL	8 to 96 weeks	'Systemic antimicrobial therapy using a combination of AMX and MET as an adjunct to SRP can enhance the clinical benefits of non-surgical periodontal therapy in adults who are otherwise healthy'

*At least 2 studies were included in the meta-analysis; †The conclusions were directly retrieved in full from the papers' abstracts; †authors do not report the type of meta-analytic model; NP: not performed (no studies included because no meta-analysis was performed taking "all pockets" into consideration); PD: probing pocket depth; NT: no treatment; SRP: scaling and root planning; CI: confidence interval; NR: not reported; CAL: clinical attachment level; AMX: amoxicillin; MET: metronidazole; FMSRP: full-mouth scaling and root planning; GAgP: generalized aggressive periodontitis.

antimicrobials seemed to increase the risk of side effects compared to SRP alone. Finally, we did not find much data reporting on bacterial resistance, which reduced our confidence that the use of antibiotics may be acceptable. Nevertheless, it is important to emphasise that most trials included in the SRs had a short follow-up which hinders more robust conclusions on the effects of antimicrobials on tooth survival and bacterial resistance.

It is important to clarify to the reader that the current overview is based on the assessment of SRs which evaluated primary data (that is, clinical trials on interventions). So, all data presented (for example, the data reported in tables) are derived from information already reported in the SRs included. No attention was paid to data extraction from primary studies. Moreover, some overlapping of primary studies included in the SRs

is to be expected because of the similarity of review objectives (that is, evaluation of the use of antimicrobials in the treatment of periodontitis). For example, four RCTs included in one SR²⁵ were found in another SR²⁴, which included a total of 19 trials.

The efficacy results based on surrogate endpoints showed statistical differences between the groups. These differences were reduced when the average depth of all

Table 4 Clinical effect of systemic antibiotics as an adjuvant treatment for periodontitis (PD >5 mm at baseline)

Studies	Results on effectiveness (in mm)		Number of studies included in the meta-analysis
	Fixed-effect model	Random-effect model	
Hayes <i>et al.</i> 1992 ¹⁹	(Initial PD ≥ 5 mm) PD (NT: 0.65; SRP: 2.02; only tetra: 1.98; tetracycline +SRP: 2.45)	–	2
Elter <i>et al.</i> 1997 ²⁰	PD (0.7, CI: 0.12 to 1.27) in PD ≥ 7 mm at baseline; CAL (0.193, CI: -0.23 to 0.62) in CAL ≥ 7 mm at baseline	–	3 for PD; 3 for CAL
Herrera <i>et al.</i> 2002 ²¹	(in PD >6 mm at baseline) PD (spyramicin: 0.407, CI: 0.081 to 0.733); CAL (spyramicin: 0.262, CI: -0.044 to 0.569), (AMX/MET: 0.450, CI: 0.192 to 0.709), (MET: 0.551, CI: -0.017 to 1.119)	–	2 for PD; 2 for CAL
Zandbergen <i>et al.</i> 2013 ²⁴	(in PD ≥ 6 mm at baseline) PD (-2.59, CI: -2.65 to -2.53); CAL (1.66, CI: 1.54 to 1.78) (in PD ≥ 7 mm at baseline) PD (-3.72, CI: -3.83 to -3.61); CAL (2.66, CI: 2.51 to 2.81)	–	5 for PD 4 for CAL 8 for PD 8 for CAL

*authors do not report the type of meta-analytic model; PD: probing depth; NT: not treated; CAL: clinical attachment level; CI: confidence interval; SRP: scaling and root planning; AMX: amoxicillin; MET: metronidazole; – indicates that authors only used fixed-effect model for evaluating the data.

Table 5 Reported side-effects in systematic reviews with meta-analyses

Studies	Results on side-effects	
	Test group	Control group
Hayes <i>et al.</i> 1992 ¹⁹	NR	NR
Elter <i>et al.</i> 1997 ²⁰	NR	NR
Herrera <i>et al.</i> 2002 ²¹	Gastrointestinal problems Temporary bacterial resistance	Gastrointestinal problems
Haffajee <i>et al.</i> 2003 ²²	Diarrhea	–
Bono <i>et al.</i> 2010 ²³	NR	NR
Sgolastra <i>et al.</i> 2012 ²⁵	Types of adverse events not reported	–
Sgolastra <i>et al.</i> 2012b ²⁶	Diarrhea and vomiting	–
Sgolastra <i>et al.</i> 2013 ²⁷	No serious side effects occurred	–
Zandbergen <i>et al.</i> 2013 ²⁴	Nausea, vomiting, and gastrointestinal discomfort; headaches and a metallic taste, general unwellness, burning sensation of the mouth or tongue, musculoskeletal disorder, respiratory disorder, tooth loss, taste alterations, dry mouth, erythema, oral ulceration, dizziness, staining of tongue or teeth, irritability, a rash on the face or neck, and nausea after the use of alcohol.	–

NR: not reported (means that authors did not mention any potential side-effect); AMX: amoxicillin; MET: metronidazole; –: means that authors only reported side effects in the test group.

pockets was used as a reference. The greatest difference in mean PD favouring the antimicrobials group was 1.41 mm.²⁴ The greatest CAL gain, 0.94 mm in the group treated with systemic antibiotics, was reported in the same SR.²⁴ The analyses of improvements of deeper pockets generated more pronounced differences, although they were reported in only one of the four SRs,²⁴ which reported

data based on PD sub-groups (Table 4). Herrera *et al.* 2002²¹ assessed the effect of amoxicillin and metronidazole, among several antimicrobials and their combinations. This SR²¹ showed less pronounced differences in CAL measurements in patients treated with amoxicillin and metronidazole than Zandbergen *et al.* 2013,²⁴ which reviewed the same combination of antimicrobials. Herrera

et al. (pockets >6 mm) and Zandbergen *et al.* (pockets >6 mm) reported that pockets >6 mm at baseline improved in the group using antimicrobials by 0.450 mm and 1.66 mm on average, respectively. Zandbergen *et al.* also reported a greater improvement in CAL measurements in the antimicrobials group with >7 mm pockets at baseline. The differences in the results reported in these studies may be explained by the time of publication. Many newer studies were included in the 2013 SR. In addition, the inclusion/exclusion criteria differed between them.

A limitation of the present overview of the effectiveness of antimicrobials in the treatment of periodontitis is that authors of SRs evaluated the data in different ways. Some authors assessed CAL or PD taking into account the average CAL or PD changes from 'all teeth' involved. Others used a specific threshold of severity (for example, PD at baseline >5 mm). Furthermore, some meta-analyses seem to be performed with the inclusion of patients with different disease classifications (aggressive *vs.* chronic periodontitis). This approach hinders a better understanding of whether there are in fact different outcomes after the use of antimicrobials in aggressive or chronic forms of periodontitis. The distinction between these two entities is, nevertheless, not easy to make,²⁸ and some misinterpretation by authors of primary studies in classifying the disease might be expected.

Although there is a lack of information on potential relevant side effects of antimicrobials such as bacterial resistance, the importance of the topic deserves a more in-depth discussion. The risk of bacterial resistance is an ongoing issue of concern in the literature.^{29,30} In the USA in 2009, more than three million kilograms of antimicrobials were administered to patients and, in 2010, 13 million kilograms were administered to animals.²⁹ The uncontrolled use of antimicrobials may contribute to increases in bacterial resistance. Although bacterial resistance was only noted in one of the MAs we studied, the data for reducing the use of antibiotics in all patients is compelling. A recently published SR with MA investigated subsequent antimicrobial resistance in individuals prescribed antimicrobials in primary care.¹² They found that individuals prescribed an antimicrobial for a urinary infection developed bacterial resistance to that antimicrobial (pooled odds ratio [OR] for resistance was 2.5 [95% confidence interval 2.1 to 2.9] within 2 months of antimicrobial treatment). Similarly, individuals prescribed an antimicrobial in primary care for a respiratory infection developed bacterial resistance to that antibiotic (pooled

OR for resistance was 2.4 [95% confidence interval 1.4 to 3.9] within two months of antibiotic treatment). Furthermore, the study found that higher quantities of prescribed antimicrobials, longer duration and multiple courses were associated with higher rates of resistance. While the normal prescription of antimicrobials for treating periodontitis is usually a few days, patients may receive more than one course to treat (or re-treat) periodontitis. Moreover, periodontitis patients may receive similar combinations of antimicrobials to treat other health conditions, perhaps with multiple courses, thus increasing the risk of bacterial resistance.

Theoretically therapeutic improvements in CAL could lead to reduced tooth mortality, however, evidence suggests that clinical attachment loss might be moderately informative on overall tooth mortality.³¹ Moreover, increased PD might represent a risk factor for further periodontitis progression³² and tooth loss.³³ The question then is whether the 'extra CAL gain' or 'PD reduction' provided by the use of SRP plus antimicrobials in comparison to SRP alone outweighs the potential side-effects and the potential threat of bacterial resistance to the patient's overall health and welfare. There are, however, methodological limitations to answering this question such as the need to continue the study over many years because the rates of tooth loss are generally low. This would also necessitate large numbers of patients (with greater costs) to allow an adequate sample size after potential patient drop-outs to reach more robust conclusions.

The methodological qualities of SRs with meta-analyses were heterogeneous. Generally, SRs published more recently (from 2012 to present) had better AMSTAR scores than earlier SRs (Table S1 in the Appendix). This difference may be explained by the increasing awareness of the methods for producing methodologically robust studies. Another important consideration is that the interventions in primary studies varied. For example, different dosages and lengths of treatments were used, different instruments were used, and the experience of providers varied. Overall, the OQAQ checklist provided more positive results than AMSTAR. This might be explained by the grade of subjectivity on the checklist questions, which apparently allows a more positive judgement than AMSTAR. There was also heterogeneity among SRs regarding the type and combinations of antimicrobials (Table 2). Thus, in order to allow a reasonable comparison of the clinical effect of antimicrobials, only information that could be directly compared was retrieved (for example, in the case of Herrera *et al.* 2002²¹ and Zandbergen *et al.* 2013²⁴).

Future research directions

Long-term studies of sufficient sample size, that also record outcomes such as tooth survival are required,³⁴ funding permitting. Currently, systematic reviewers must use lower quality studies to find data on tooth survival. Furthermore, the dental community should reach a consensus on the definition of the most appropriate endpoints, other than tooth survival, to evaluate the benefits of antimicrobials in periodontitis treatment. Additional research efforts could, for example, focus on high quality studies on strategies to moderate host inflammation in response to infections.²⁹ The efficacy of host modulatory therapies for the treatment of periodontitis, as well as potential side-effects, have not been determined.³⁵ Other treatments such as immune-based therapies or biologic agents that do not kill bacteria, but change the disease processes²⁹ may be alternative treatments that do not contribute to bacterial resistance.

CONCLUSION

This overview of SRs revealed that the reporting of data on true endpoints such as tooth survival and bacterial resistance is lacking. So, due to the lack of confidence on the benefit of antimicrobials in improving tooth survival following periodontal treatment, clinicians are advised to discuss these limitations with their patients in order to carefully weigh benefits and potential harm when this therapy is proposed.

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APPENDIX

Table S1 AMSTAR results. The numbers on the top of the columns refer to the AMSTAR items (reported in the checklist). 1: criterion met; 0: criterion not met

Study	1	2	3	4	5	6	7	8	9	10	11
Hayes <i>et al.</i> 1992 ¹⁹	0	0	0	0	0	0	1	1	0	0	0
Elter <i>et al.</i> 1997 ²⁰	0	0	0	0	0	1	0	0	0	0	0
Herrera <i>et al.</i> 2002 ²¹	1	1	1	0	1	1	1	1	1	0	0
Haffajee <i>et al.</i> 2003 ²²	1	0	0	0	0	1	1	0	1	0	0
Bono <i>et al.</i> 2010 ²³	0	0	1	0	0	1	1	1	1	0	0
Sgolastra <i>et al.</i> 2012 ²⁵	1	1	1	0	1	1	1	1	1	1	0
Sgolastra <i>et al.</i> 2012 ²⁶	1	1	1	0	1	1	1	1	1	1	0
Sgolastra <i>et al.</i> 2013 ²⁷	0	1	1	0	1	1	1	1	1	1	0
Hayes <i>et al.</i> 1992 ¹⁹	1	1	1	0	1	1	1	1	1	0	0

Table S2 OQAQ results. The numbers on the top of the columns refer to the OQAQ items (reported in the checklist). 1: criterion met; 0: criterion not met

Study	1	2	3	4	5	6	7	8	9
Hayes <i>et al.</i> 1992 ¹⁹	1	0	1	0	1	1	0	0	1
Elter <i>et al.</i> 1997 ²⁰	1	1	1	0	1	1	1	1	1
Herrera <i>et al.</i> 2002 ²¹	1	1	1	0*	1	1	1	1	1
Haffajee <i>et al.</i> 2003 ²²	1	1	1	1	1	1	1	1	1
Bono <i>et al.</i> 2010 ²³	1	1	1	0	1	1	0	0	1
Sgolastra <i>et al.</i> 2012 ²⁵	1	1	1	0*	1	1	1	1	1
Sgolastra <i>et al.</i> 2012 ²⁶	1	1	1	0*	1	1	1	1	1
Sgolastra <i>et al.</i> 2013 ²⁷	1	1	1	1	1	1	1	1	1
Hayes <i>et al.</i> 1992 ¹⁹	1	1	1	1†	1	1	1	0	1

*authors did not report 'consensus'; †third reviewer used to resolve disagreements;

Table S3 AMSTAR checklist

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a 'yes'.

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (for example, Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select 'yes' (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

4. Was the status of publication (that is, grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for 'grey literature' or 'unpublished literature', indicate 'yes' SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select 'no'.

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed for example, age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (for example, for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, for example, Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ('low' or 'high' is fine, as long as it is clear which studies scored 'low' and which scored 'high'; a summary score/range for all studies is not acceptable).

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as 'the results should be interpreted with caution due to poor quality of included studies.' Cannot score 'yes' for this question if scored 'no' for question 7.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (that is, Chi-squared test for homogeneity, I²).

If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (that is, is it sensible to combine?).

Note: Indicate 'yes' if they mention or describe heterogeneity, that is, if they explain that they cannot pool because of heterogeneity/variability between interventions.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (for example, funnel plot, other available tests) and/or statistical tests (for example, Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score 'no'. Score 'yes' if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a 'yes', must indicate source of funding or support for the systematic review AND for each of the included studies.

Yes/No/Can't answer/Not applicable

Shea et al. *BMC Med Res Method* 2007; 7: 10. doi:10.1186/1471-2288-7-10

Table S4 OQAQ checklist

The purpose of this index is to evaluate the scientific quality (that is, adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews.

The index is for assessing overviews of primary ('original') research on pragmatic questions regarding causation, diagnosis, prognosis, therapy or prevention. A research overview is a survey of research. The same principles that apply to epidemiologic surveys apply to overviews: a question must be clearly specified, a target population identified and accessed, appropriate information obtained from that population in an unbiased fashion, and conclusions derived, sometimes with the help of difference between overviews and epidemiologic surveys the unit of analysis, not the scientific issues that the questions in this index address.

Since most published overviews do not include a methods section it is difficult to answer some of the questions in the index. Base your answer, as much as possible, on the information provided in the overview. If the methods that were used are reported incompletely relative to a specific item, score that item as 'partially'. Similarly, if there is no information provided regarding what was done relative to a particular question, score it as 'can't tell', unless there is information in the overview to suggest either that the criterion was or was not met.

Were the search methods used to find evidence (original research) on the primary question (s) stated?

☐ yes ☐ partially ☐ no

Yes is given to meta-analysis reporting categories of sources, including years (for example, databases-Medline) used, and whether these categories were named (for example, Medline). Partial points are given for the category of sources (for example, electronic, hand, register) are named.

Was the search for evidence reasonably comprehensive?

☐ yes ☐ can't tell ☐ no

Yes is given if at least three categories, one of which must be electronic with key words stated, and any two others (for example, hand, register) are reported. Key words and/or MESH terms must be stated.

Were the criteria used for deciding which studies to include in the overview reported?

☐ yes ☐ partially ☐ no

This item was thought to be reasonably explicit. If 2 or more items mentioned, yes, if <2 mentioned, partially, if none mentioned, no.

Was bias in the selection of studies avoided?

☐ yes ☐ can't tell ☐ no

Yes is given if at least two reviewers independently assess for inclusion. A consensus must be reached.

Were the criteria used for assessing the validity of the included studies reported?

☐ yes ☐ partially ☐ no

It was felt that the issues relating to publication bias should not be included in the assessment of this. Yes is given to those meta-analysis reporting 'a priori' methods of validity assessment (for example, if the author(s) chose to include only randomized, double-blind, placebo controlled trials, or allocation concealment as inclusion criteria).

Was the validity of all studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?

☐ yes ☐ can't tell ☐ no

This item relates to validity assessment. Yes is given if there is a description of any criteria (either internal or external) used either for inclusion, or for analysis (for example, sensitivity analysis).

Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

☐ yes ☐ partially ☐ no

This item was thought to be reasonably explicit.

Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?

☐ yes ☐ can't tell ☐ no

For question 8, if no attempt was made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check 'no'. If a summary (general) estimate is given anywhere in the abstract, the discussion or the summary section of the paper, and it is not reported how the estimate was derived, mark 'no' even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt mark 'can't tell'.

Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?

☐ yes ☐ partially ☐ no

For an overview to be scored as 'yes' on question 9, data (not just citations) must be reported that supports the main conclusions regarding the primary question(s) that the overview addresses. If the overview concerns diagnostic/prognostic tests, 'retest is not required' (this ensures that diagnostic/prognostic papers are not scored more rigorously than clinical papers).

How would you rate the scientific quality of the overview?

Extensive Flaws		Major Flaws		Minor Flaws		Minimal Flaws	
☐	☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7	

The score for question 10, the overall scientific quality, should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score. If the 'can't tell' option is used one or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (that is, a score of 4 or lower). If the 'no' option is used on question 2, 4, 6 or 8, the review is likely to have major flaws (that is, a score of 3 or less, depending on the number and degree of the flaws).