ADA CE Program ARTICLE 1

COVER STORY

Effectiveness of systemic antimicrobial therapy in combination with scaling and root planing in the treatment of periodontitis

A systematic review

Pablo Garcia Canas, DDS, MS; Ismael Khouly, DDS, MS, PhD; Javier Sanz, DDS, MS; Peter M. Loomer, BSc, DDS, PhD

ABSTRACT

Background. The use of systemic antibiotics in conjunction with scaling and root planing (SRP) may improve the clinical outcome and even could be essential for a successful treatment of periodontitis. However, the effectiveness and clinical safety of this combination of therapy remain unclear. The authors of this study reviewed the available literature related to this hypothesis, evaluating the effectiveness of the use of systemic antimicrobials in combination with SRP versus SRP alone in the treatment of chronic periodontitis (CP) or aggressive periodontitis (AgP).

Methods. The authors used 3 electronic databases and hand searched articles published from April 2001 through October 2013 in selected journals. The authors selected clinical trials with a minimum of 6 months follow-up during which patients with either CP or AgP had been treated with systemic antibiotics plus SRP in comparison with SRP alone or with placebo. The authors analyzed the gain in clinical attachment level (CAL), reduction in probing pocket depth (PPD), reduction in bleeding on probing (BOP), and patient-related variables (that is, adverse effects).

Results. After the selection process, the authors included 23 clinical trials in this review. Assessment of the quality of the studies revealed the risk of bias as a common finding. Overall, there was a tendency toward improvement of the measured outcomes, CAL, PPD, and BOP in studies for which systemic antibiotics were used as adjunctive therapy with SRP.

Conclusion. Owing to the high level of heterogeneity of the studies included in this review, the authors could not establish definitive conclusions and guidelines regarding the use of adjunctive systemic antibiotics. However, within the limitations of this review, the use of systemic antibiotics with SRP may be beneficial for specific populations. Standardized clinical disease diagnostic criteria and additional randomized controlled clinical trials are necessary to verify the effectiveness of the use of adjunctive systemic antimicrobials with SRP.

Practical Implications. Owing to methodological differences and biases among clinical trials evaluating systemic antibiotics adjunctive to SRP, clinicians should base their decisions to prescribe on the results of weighing both benefits and risks for each patient.

Key Words. Periodontitis; antibiotics; scaling and root planing; systematic review.
JADA 2015:146(3):150-163

http://dx.doi.org/10.1016/j.adaj.2014.12.015

Periodontal diseases are considered to be inflammatory diseases that affect the supporting tissues of the tooth and are caused by microorganisms that reside in the subgingival area.[1] The organization of the bacteria in the oral microbiota provides favorable conditions for its growth and maturation. The microbiota responsible for these diseases are complex;

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

however, investigators have observed that only a small number of bacterial species are associated strongly with periodontal disease progression.[2,3] Although these bacterial pathogens initiate the periodontal inflammation, the host response to these pathogens is equally if not more important in mediating connective tissue breakdown, including bone loss.[4,5]

The standard treatment for periodontal disease remains nonspecific, consisting mainly of scaling and root planing (SRP) to reduce the total bacterial load.[6] Although the results of some studies have proven that using this therapy is efficient,[7-11] the mechanical treatment may not be predictable for removing certain periodontal pathogens and some sites and patients may not respond adequately.[12] Investigators have reported factors that can influence these nonresponsive sites or patients, including the deep locations of pathogens, the ability of pathogens to invade soft tissues, and the limitations of periodontal mechanical treatment.[13-15]

For decades, researchers have discussed the use of systematic antimicrobials as part of the therapy used in the management of periodontal diseases.[16-18] The authors of previous systematic reviews[16,17,19] and meta-analyses[18,20,21] have reported that antimicrobial agents systemically provide a significant clinical benefit. This antibiotic therapy has the advantage to reach microorganisms that are inaccessible to scaling instruments and local antibiotic therapy.[22] Investigators have reported several benefits of the adjunctive antimicrobial, especially in cases of aggressive periodontitis (AgP), active periodontitis, severe chronic periodontitis (CP), and in periodontitis associated with specific microbiological profiles.[16,19,23,24]

The aim of this systematic review is to update a previous systematic review[16] and to evaluate critically the available literature with respect to the clinical effects of combined antibiotic therapy as an adjunct to SRP compared with a treatment of only SRP.

METHODS

We conducted this systematic review in accordance with the guidelines provided in the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25] The study methodology, including the search strategy, inclusion criteria, and exclusion criteria, was similar to a previous systematic review.[16]

Focused question. First, we used a Population-Intervention-Comparison-Outcome question approach. In patients with CP or AgP, what is the clinical effect of systemic antimicrobial therapy in combination with SRP compared with a treatment of only SRP in the following mean treatment outcomes: clinical attachment level (CAL), probing pocket depth (PPD), bleeding on probing (BOP), and variables related to patient adverse events?

Search strategy. We used 3 Internet sources to search for appropriate studies that satisfied the study purpose. We searched the relevant articles published from April 2001, which was the end date of the previous systematic review,[16] through October 2013, in the following databases: PubMed (Medline), Excerpta Medica (Embase), and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we manually searched articles in the following journals: *Journal of Clinical Periodontology, Journal of Periodontal Research,* and *Journal of Periodontology*. To minimize the potential for reviewer bias, two masked reviewers (P.G.C. and J.S.) independently screened the articles, which were limited to articles written in English and Spanish, using the same criteria. We designed the search to include any published study that evaluated the adjunctive effect of combining systemic administration of antibiotics with SRP in the treatment of periodontitis.

We performed the search by using semantic fields, one of which was periodontal disease, and the other was antibiotic treatment. We included patients with CP or AgP on the basis of the criteria for the classification of periodontal diseases proposed by Armitage.[1] We also included studies whose authors described periodontal disease in the following forms: early-onset periodontitis, rapidly progressive periodontitis, adult periodontitis, "refractory" periodontitis, and recurrent periodontitis.

Within the semantic field "periodontal disease," we added the following searches: "Periodontal AND Diseases" OR Periodontal diseases OR periodontitis, both in medical subject headings (MeSH) terms, as in "All fields." In the semantic field of antibiotics, we added the following searches: "Anti bacterial AND agents OR anti bacterial agents OR antibiotics OR anti parasitic agents OR (anti parasitic AND agents) OR quinolones", both in MeSH terms, as in All fields and Pharmacological action.

We used the following full search strategy (key words): (((((("periodontal diseases"[MeSH Terms]) OR "periodontal diseases") OR (("periodontitis"[MeSH Terms]) OR "periodontitis")) OR (("periodontal") AND "diseases"))) AND ((((((((((("anti bacterial agents"[MeSH Terms]) OR "anti bacterial agents") OR (("anti bacterial") AND "agents")) OR "antibiotics") OR "anti bacterial agents"[Pharmacological Action]) OR "antiparasitic agents"[MeSH Terms]) OR (("antiparasitic") AND "agents")) OR "antiparasitic agents") OR "antiparasitic agents"[Pharmacological Action]) OR

ABBREVIATION KEY. **AgP:** Aggressive periodontitis. **AM:** Amoxicillin. **AZ:** Azithromycin. **BOP:** Bleeding on probing. **CAL:** Clinical attachment level. **CCT:** Controlled clinical trial. **CLAR:** Clarithromycin. **CP:** Chronic periodontitis. **DOX:** Doxycycline. **M:** Metronidazole. **MeSH:** Medical subject heading. **MOX:** Moxifloxacin. **NA:** Not applicable. **ORN:** Ornidazole. **PPD:** Probing pocket depth. **RCCT:** Randomized controlled clinical trial. **SRP:** Scaling and root planing.

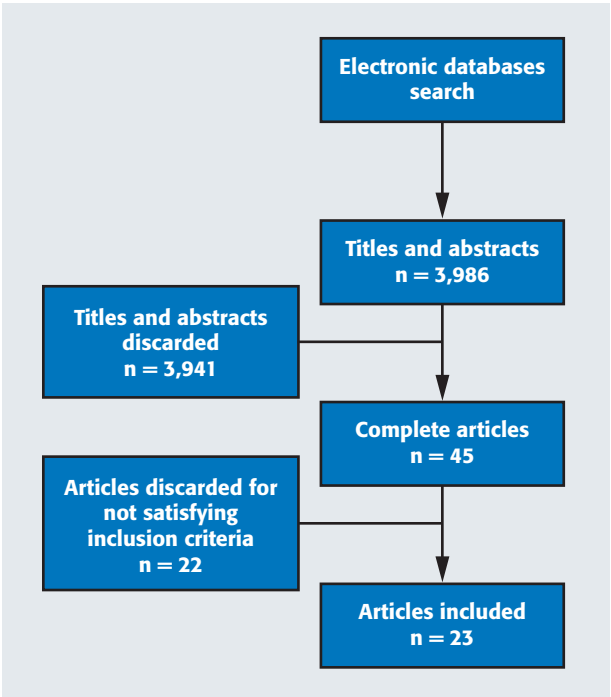

Figure. Flowchart of the search strategy.

"metronidazole"[MeSH Terms]) OR "quinolones" [MeSH Terms]).

Study inclusion and exclusion criteria. In the first phase, we analyzed studies according to the following inclusion criteria: randomized controlled clinical trials (RCCTs), controlled clinical trials (CCTs), or prospective clinical studies; all patients should be treated with mechanical periodontal therapy (that is, SRP), there had to be one experimental group in which one or more antibiotics were added to the basic therapy, and a control group which was not given any further treatment except placebo; patients with diagnosed periodontitis; minimum follow-up of 6 months or more; types of systemic antimicrobials included in this review were tetracyclines (doxycycline [DOX], minocycline), nitroimidazoles (metronidazole [M], ornidazole [ORN]), penicillins (penicillin, amoxicillin [AM], amoxicillin/clavulanate), macrolides (erythromycin, spiramycin, azithromycin [AZ], roxithromycin, clarithromycin [CLAR]), clindamycin, quinolones (ciprofloxacin, moxifloxacin [MOX]), and different combinations (AM/M, spiramycin/M); and clinical parameters of interest of PD and CAL as primary outcome parameters, with BOP and patient-related variables (that is, adverse effects) as secondary outcome parameters.

We admitted only studies that met all inclusion criteria to the second phase, which consisted of analysis of the preselected studies according to the following exclusion criteria: studies whose authors did not report numerical full-mouth CAL or PD; studies whose investigators used tetracyclines as antibiotics in low doses over time; duplicate studies; and studies whose investigators used in vitro and experimental animal models.

Selection process. Two reviewers (P.G.C. and J.S.) independently screened titles and abstracts. If the search key words and the relevant information to the eligibility criteria were present in the title, the abstract, or both, they selected the study for full-text reading. The reviewers also selected for full-text screening studies without abstracts but with titles suggesting that the results were related to the objectives of this review. After selection, two reviewers (P.G.C. and J.S.) read in detail the full text of the studies. They processed those studies that fulfilled all of the selection criteria for data extraction. Two reviewers (P.G.C. and J.S.) hand searched the reference lists of all selected studies for additional relevant articles. In addition, the reviewers scanned the references of all selected full-text articles and related reviews. The reviewers (P.G.C. and J.S.) resolved discrepancies with regard to the inclusion or exclusion of studies by discussion until they reached consensus.

Quality assessment. Two masked reviewers (P.G.C. and J.S.) independently performed quality assessment of the methodologies of all included studies. The quality assessment followed the same criteria established by Montenegro and colleagues.[26] This quality criteria checklist included the assessment of randomization; allocation concealment; masking of patient, caregiver, and examiner separately; and withdrawals and dropouts.

We calculated the level of agreement between reviewers as reported previously. We performed quality assessment in two phases. During the first phase, we based the quality assessment on the published full-text articles; in the second phase, we reconsidered all studies according to the additional information provided by the corresponding authors. After determining the scores at the conclusion of the second phase of quality assessment, we estimated the overall plausible risk of bias (low, moderate, or high) for each selected study. We estimated that a study had a low risk of bias when all of the criteria were met, we estimated a moderate risk when one criterion was met partially or was inadequate, and we estimated a high risk of bias when one or more criteria were not met.

RESULTS

Study selection. During the electronic and manual searches, we found a total of 3,986 abstracts (Figure). In the first step of the study selection process, we excluded 3,941 publications on the basis of an evaluation of titles and abstracts. During the second phase, we obtained the complete full-text articles of the remaining 45 publications and we assessed their quality and main

study characteristics. We excluded a total of 22 articles in this phase, because the studies that were described did not fulfill the inclusion criteria. We found 23 articles eligible for inclusion in this review according the defined selection criteria.[27-49] The figure depicts a flowchart of the study selection process. Table 1 summarizes the main characteristics of the 23 included studies.[27-49]

TABLE 1

Characteristics of study design and participants.

STUDY	TYPE OF STUDY	FOLLOW-UP TIME (MO)	GROUPS	PATIENTS (NO.)	
				Baseline	Posttreatment
Rooney and Colleagues,[27] 2002	RCCT,* parallel	6	4	66	62
Ehmke and Colleagues,[28] 2005	CCT,† parallel	24	2	48	35
Guerrero and Colleagues,[29] 2005	RCCT, parallel	6	2	41	40
Mascarenhas and Colleagues,[30] 2005	RCCT, parallel	6	2	31	30
Xajigeorgiou and Colleagues,[31] 2006	RCCT, parallel	6	4	47	43
Gomi and Colleagues,[32] 2007	RCCT, parallel	6	2	34	34
Haffajee and Colleagues,[33] 2007	RCCT, parallel	12	4	98	92
Guentsch and Colleagues,[34] 2008	RCCT, parallel	12	3	102	92
Haas and Colleagues,[35] 2008	RCCT, parallel	12	2	25	24
Cionca and Colleagues,[36] 2009	RCCT, parallel	6	2	51	47
Yashima and Colleagues,[37] 2009	RCCT, parallel	12	3	30	30
Oteo and Colleagues,[38] 2010	RCCT, parallel	6	2	29	27
Yek and Colleagues,[39] 2010	RCCT, parallel	6	2	32	28
Pradeep and Kathariya,[40] 2011	RCCT, parallel	9	2	40	37
Sampaio and Colleagues,[41] 2011	RCCT, parallel	12	2	40	38
Aimetti and Colleagues,[42] 2012	RCCT, parallel	6	2	39	39
Emingil and Colleagues,[43] 2012	RCCT, parallel	6	2	36	32
Feres and Colleagues,[44] 2012	RCCT, parallel	12	3	118	101
Goodson and Colleagues,[45] 2012	RCCT, parallel	24	8	231	187
Han and Colleagues,[46] 2012	RCCT, parallel	6	2	36	28
Mestnik and Colleagues,[47] 2012	RCCT, parallel	12	2	30	26
Pradeep and Colleagues,[48] 2012	RCCT, parallel	6	2	58	50
Silva-Senem and Colleagues,[49] 2013	RCCT, parallel	12	2	35	31

* RCCT: Randomized controlled clinical trial.
† CCT: Controlled clinical trial.

Characteristics of the study design and participants. All the selected studies were randomized clinical trials (Table 1).[27-49] The evaluation period varied among the studies from 6 to 24 months. Some studies were performed with a test group and a control group,[28-30,32,35,36,38-43,46-49] or multiple test groups and a control group (from 3 to 8 groups).[27,31,33,34,37,44,45] Study participants in the control groups were given a placebo in 14 studies.[27,29,35,36,38,40-44,46-49] At baseline, the studies included 25[35] to 231 participants.[45] Fifteen studies[27,28,30,32-34,36-38,40,41,45,46,48,49] included patients with CP, and 8 studies included participants with AgP.[29,31,35,39,42,43,47,49] All studies were parallel type.

The variable tobacco was taken into account, by means of different stratifications, in 10 of the 23 studies analyzed.[29,35,36,38,39,41,43,45,46,49] The stratification in 3 studies[39,43,46] was performed only with smokers of fewer than 10 cigarettes per day; the rest of the smokers were excluded. Cionca and colleagues[36] performed a regression model analysis to assess the impact of the patient's smoking habit on the persistence of periodontal pockets. In the study by Mascarenhas and colleagues,[30] the investigators included only study participants who were smokers in the trial. In 6 of the 14 studies whose investigators did not take into consideration the variable tobacco,[32,40,42,44,47,48] the investigators excluded both smokers and former smokers.

Characteristics of intervention. In the studies reviewed, the investigators used the following antibiotics: AM, AM in combination with M, AZ, CLAR, DOX, metronidazole, MOX, and ORN (Table 2[27-49]). The largest number of studies was conducted with a group of AM combined with M (11 studies),[27,28,29,31,36,39,42,44,45,47,49] followed by AZ (9 studies),[30,32,33,35,37,38,41,43,46] M (4 studies),[27,31,33,44] DOX (2 studies),[31,34] MOX (1 study),[34] CLAR (1 study),[40] ornidazole (1 study),[48] and AM (1 study).[27] Regarding dose, there was a high level of heterogeneity, especially in the group of AM combined with M. AZ doses (generally 500 milligrams daily for 3 days) tended to be more homogenous.

Intervals between visits of SRP were variable (from 24 hours to 7 weeks), as were the durations of the procedures (30 minutes to 2 hours).

The investigators of 17 studies[28,30,31,33,35,36,38-47,49] reported patient compliance with taking medication. Most of the investigators confirmed compliance by counting the remaining capsules at the review visit at the end of the antibiotic treatment. In some cases, the investigators telephoned patients to ensure compliance with taking medication.[35,41,42,44,47,49]

Quality assessment. As shown in Table 3,[27-49] 12 of 23 studies did not meet at least 1 of the methodological quality criteria; therefore, we noted that these studies had a high or moderate risk of bias.[27,28,30-34,37,39,40,45,48] Two of the studies with larger sample sizes had a high risk of bias,[34,45] which is important because in the

TABLE 2

Study interventions.

STUDY	DISEASE	ANTIBIOTICS					SRP*		
		Dose	Frequency	Duration (Days)	When Taken	Compliance	Sessions	Duration	During
Rooney and Colleagues,[27] 2002	Severe chronic periodontitis	AM†: 250 mg‡ + M§: 200 mg	3 times daily	7	After SRP	NA¶	4	45 min	4 to 7 wk
		AM: 250 mg							
		M: 200 mg							
Ehmke and Colleagues,[28] 2005	Moderate to severe chronic periodontitis	AM: 375 mg + M: 250 mg	3 times daily	8	After SRP	Counting done	4	2 h	10 d
Guerrero and Colleagues,[29] 2005	Generalized aggressive periodontitis	AM: 500 mg + M: 500 mg	3 times daily	7	Before SRP	NA	2	2 h	24 h
Mascarenhas and Colleagues,[30] 2005	Moderate to severe chronic periodontitis	AZ#: 250 mg	Once daily; double dose first day	5	After SRP	Counting done + questionnaires	2	NA	2 wk
Xajigeorgiou and Colleagues,[31] 2006	Generalized aggressive periodontitis	AM: 500 mg + M: 500 mg	3 times daily	7	6 weeks after SRP	Patient asked	4	NA	2 wk
		DOX**: 100 mg	Once daily; double dose first day	14					
		M: 500 mg	3 times daily	7					
Gomi and Colleagues,[32] 2007	Severe chronic periodontitis	AZ: 500 mg	Once daily	3	3 days before SRP	NA	4 to 6	90 min	1 to 5 wk
Haffajee and Colleagues,[33] 2007	Chronic periodontitis	AZ: 500 mg	Once daily	3	During SRP therapy	Counting done	4	NA	4 wk
		M: 250 mg	3 times daily	14					
Guentsch and Colleagues,[34] 2008	Severe chronic periodontitis	DOX: 100 mg	Once daily; double dose first day	9	During SRP therapy	NA	NA	2 h	24 h
		MOX††: 400 mg	Once daily	7					
Haas and Colleagues,[35] 2008	Aggressive periodontitis	AZ: 500 mg	Once daily	3	During SRP therapy	Phone call	4 to 6	NA	14 d
Cionca and Colleagues,[36] 2009	Chronic periodontitis	AM: 375 mg + M: 500 mg	3 times daily	7	After SRP	Counting done	2	NA	48 h
Yashima and Colleagues,[37] 2009	Chronic periodontitis	AZ: 500 mg	Once daily	3	Before SRP	NA	1 to 3	30 to 120 min	1 to 7 d
Oteo and Colleagues,[38] 2010	Moderate chronic periodontitis	AZ: 500 mg	Once daily	3	After SRP	Patient asked	2	90 min	1 wk
Yek and Colleagues,[39] 2010	Generalized aggressive periodontitis	AM: 500 mg + M: 500 mg	3 times daily	7	During SRP therapy	Counting done	2	NA	48 h

* SRP: Scaling and root planing.
† AM: Amoxicillin.
‡ mg: Milligrams.
§ M: Metronidazole.
¶ NA: Not applicable.
# AZ: Azithromycin.
** DOX: Doxycycline.
†† MOX: Moxifloxacin.
‡‡ CLAR: Clarithromycin.
§§ ORN: Ornidazole.

TABLE 2 (CONTINUED)

STUDY	DISEASE	ANTIBIOTICS					SRP*		
		Dose	Frequency	Duration (Days)	When Taken	Compliance	Sessions	Duration	During
Pradeep and Kathariya,[40] 2011	Chronic periodontitis	CLAR‡‡: 500 mg	Twice daily	3	After SRP	Patient asked + counting done	NA	NA	NA
Sampaio and Colleagues,[41] 2011	Generalized chronic periodontitis	AZ: 500 mg	Once daily	5	After SRP	Phone call + counting done	4 to 6	2 h	2 wk
Aimetti and Colleagues,[42] 2012	Generalized aggressive periodontitis	AM: 500 mg + M: 500 mg	3 times daily	7	During SRP therapy	Phone call + counting done	2	NA	24 h
Emingil and Colleagues,[43] 2012	Generalized aggressive periodontitis	AZ: 500 mg	Once daily	3	After SRP	Patient asked	4	NA	4 d
Feres and Colleagues,[44] 2012	Generalized chronic periodontitis	AM: 500 mg + M: 400 mg M: 400 mg	3 times daily	14	During SRP therapy	Phone call + counting done	4 to 6	1 h	14 d
Goodson and Colleagues,[45] 2012	Moderate to severe chronic periodontitis	AM: 500 mg + M: 250 mg	AM: Twice daily M: 3 times daily	14	During SRP therapy	Patient asked	4	NA	4 wk
Han and Colleagues,[46] 2012	Severe generalized chronic periodontitis	AZ: 500 mg	Once daily	3	After SRP	Patient asked	4	NA	NA
Mestnik and Colleagues,[47] 2012	Generalized aggressive periodontitis	AM: 500 mg + M: 400 mg	3 times daily	14	During SRP therapy	Phone call + counting done	4 to 6	1 h	10 to 14 d
Pradeep and Colleagues,[48] 2012	Moderate to advanced chronic periodontitis	ORN§§: 500 mg	Twice daily	7	After SRP	NA	NA	NA	NA
Silva-Senem and Colleagues,[49] 2013	Generalized aggressive periodontitis	AM: 500 mg + M: 250 mg	3 times daily	10	Before SRP	Phone call + counting done	4	1 h	4 to 6 wk

statistical analysis of the data (that is, the meta-analysis), studies with larger sample sizes had greater weight and, in this case, could alter the external validity of the results.

Study outcomes. Table 4,[29-49] Table 5,[29-49] and Table 6[27-38,41-44,46,47,49] show the study outcomes, which we classified according to the type of antibiotics used.

AM in combination with M. In terms of CAL (Table 4), 4[29,42,44,45] of the 9 studies using AM with M reported statistically significant benefits, especially in deep pockets greater than 6 millimeters, in the test group versus the control group. In 4 of the 9 studies,[31,39,47,49] the group receiving antibiotics had improved CAL; however, these differences were not statistically significant. The study that reported the best results in terms of CAL was Goodson and colleagues[45] (0.61 mm average extra gain versus the control group). Cionca and colleagues[36] reported the least beneficial result, with no differences in CAL between the test group and the control group.

In terms of reducing PPD (Table 5), 8 of the 9 studies[29,31,39,42,44,45,47,49] (one study's investigators[36] obtained no group differences) reported benefits in the test group participants versus the control group participants. The benefit in the group receiving the antibiotic was statistically significant in all of the studies except 3.[31,39,49] The greatest pocket reduction was found in the study of Xajigeorgiou and colleagues[31] with 0.82 mm intergroup difference (not statistically significant), followed by Feres and colleagues[44] and Goodson and colleagues[45] with 0.55 mm extra pocket reduction in the test group (statistically significant).

In terms of BOP (Table 6), all the studies whose investigators recorded this parameter[27-29,31,36,42,44,47,49] found benefits in participants receiving the adjuvant treatment of AM and M compared with the participants in the control group. The greatest reduction in BOP was observed in the study by Rooney and colleagues[27] (a 19.1% extra reduction in BOP in the test group compared with the control group). The least reduction was reported by Ehmke and colleagues,[29] with 1.6% extra reduction when these antibiotics were used.

TABLE 3

Quality of assessment.

STUDY	RANDOMIZATION	CONCEALMENT	MASKED	FOLLOW-UP		RISK OF BIAS
				Dropouts	Sample (No.)	
Rooney and Colleagues,[27] 2002	Not explained (unclear)	Adequate	Patient, caregiver, and examiner	Not explained	66-62	Elevated
Ehmke and Colleagues,[28] 2005	Alternate assignment (inadequate)	None	None	Explained	48-35	Elevated
Guerrero and Colleagues,[29] 2005	Randomly permuted blocks (adequate)	Adequate	Patient, caregiver, and examiner	Explained	41-40	Low
Mascarenhas and Colleagues,[30] 2005	Bag (adequate)	NA*	Caregiver and examiner	Explained	31-30	Moderate
Xajigeorgiou and Colleagues,[31] 2006	Random tables (adequate)	Adequate	Examiner	Explained	47-43	Moderate
Gomi and Colleagues,[32] 2007	Not explained (unclear)	NA	None	No drop outs	34	Elevated
Haffajee and Colleagues,[33] 2007	Random number table (adequate)	NA	Examiner	Explained	98-92	Elevated
Guentsch and Colleagues,[34] 2008	Not explained (unclear)	NA	Examiner	Explained	102-92	Elevated
Haas and Colleagues,[35] 2008	Draw (adequate)	Adequate	Patient, caregiver, and examiner	Explained	25-24	Low
Cionca and Colleagues,[36] 2009	Random computer-generated table (adequate)	Adequate	Patient, caregiver, and examiner	Explained	51-47	Low
Yashima and Colleagues,[37] 2009	Not explained (unclear)	NA	Caregiver and examiner	No drop outs	30	Elevated
Oteo and Colleagues,[38] 2010	Computer-generated randomization list (adequate)	Adequate	Patient, caregiver, and examiner	Explained	29-27	Low
Yek and Colleagues,[39] 2010	Coin toss (adequate)	NA	Caregiver and examiner	Explained	32-28	Moderate
Pradeep and Kathariya,[40] 2011	Computer-generated randomization list (adequate)	NA	Patient and examiner	Not explained	40-37	Elevated
Sampaio and Colleagues,[41] 2011	Computer-generated table (adequate)	Adequate	Patient, caregiver, and examiner	Explained	40-38	Low
Aimetti and Colleagues,[42] 2012	Randomly permuted blocks (adequate)	Adequate	Patient, caregiver, and examiner	No drop outs	39	Low
Emingil and Colleagues,[43] 2012	Computer-generated randomization list (adequate)	Adequate	Patient, caregiver, and examiner	Explained	36-32	Low
Feres and Colleagues,[44] 2012	Computer-generated table (adequate)	Adequate	Patient, caregiver, and examiner	Explained	118-101	Low
Goodson and Colleagues,[45] 2012	Randomly permuted blocks (adequate)	NA	Examiner	Explained	231-187	Elevated
Han and Colleagues,[46] 2012	Computer generated randomization list (adequate)	Adequate	Patient, caregiver, and examiner	Explained	36-28	Low
Mestnik and Colleagues,[47] 2012	Computer-generated table (adequate)	Adequate	Patient, caregiver, and examiner	Explained	30-26	Low
Pradeep and Colleagues,[48] 2012	Computer-generated table (adequate)	Adequate	Patient, caregiver, and examiner	Not explained	58-50	Moderate
Silva-Senem and Colleagues,[49] 2013	Randomly permuted blocks (adequate)	Adequate	Patient, caregiver, and examiner	Explained	35-31	Low

* NA: Not applicable.

AZ. In terms of CAL (Table 4), the investigators of 9 studies that evaluated the effect of AZ in participants in a test group compared with participants in a control group reported improvement.[30,32,33,35,37,38,41,43,46] We found the biggest differences between the test group and placebo for CAL in Gomi and colleagues,[32] with 1.15 mm improvement when AZ was used (not statistically significant) and Haas and colleagues[35] with 0.71 mm extra gain (statistically significant). However, Han and colleagues[46] reported the lowest intergroup difference (0.01 mm gain).

Regarding the reduction in PPD (Table 5), 5 studies showed statistically significant intergroup differences.[32,33,35,37,38] Haas and colleagues[35] reported the

TABLE 4

Clinical attachment level.

ANTIBIOTIC	STUDY	BASELINE CAL* (mm†)		POSTTREATMENT CAL (mm)		INTERGROUP DIFFERENCE
		Test	Control	Test	Control	
Amoxicillin and Metronidazole	Guerrero and colleagues,[29] 2005	4.70	4.80	3.90	4.30	SS‡
	Xajigeorgiou and colleagues,[31] 2006	4.97	4.55	4.05	4.07	Not SS
	Cionca and colleagues,[36] 2009	5.50	5.40	4.60	4.50	Not SS
	Yek and colleagues,[39] 2010	3.80	3.31	2.82	2.39	Not SS
	Aimetti and colleagues,[42] 2012	4.70	5.00	3.30	4.00	SS
	Goodson and colleagues,[45] 2012	6.35	5.84	4.82	4.92	SS
	Mestnik and colleagues,[47] 2012	4.47	4.23	3.32	3.63	Not SS
Azithromycin	Mascarenhas and colleagues,[30] 2005	5.02	3.92	3.89	3.46	X§
	Gomi and colleagues,[32] 2007	7.47	7.21	4.85	5.74	Not SS
	Haffajee and colleagues,[33] 2007	3.42	3.03	3.23	2.88	SS (+ 6 mm)¶
	Haas and colleagues,[35] 2008	5.9	5.7	4.22	4.73	SS
	Yashima and colleagues,[37] 2009	4	3.96	2.99	3.21	SS
	Oteo and colleagues,[38] 2010	3.46	3.56	2.7	3.32	SS
	Sampaio and colleagues,[41] 2010	5.51	5.74	4.44	4.69	Not SS
	Emingil and colleagues,[43] 2012	5.33	4.93	3.57	3.35	Not SS
	Han and colleagues,[46] 2012	5.68	5.32	4.13	3.78	Not SS
Clarithromycin	Pradeep and Kathariya,[40] 2011	NA#	NA	1.75**	0.68**	Not SS
Doxycyline	Xajigeorgiou and colleagues,[31] 2006	5.03	4.55	4.22	4.07	Not SS
	Guentsch and colleagues,[34] 2008	5.64	5.15	3.9	3.61	Not SS
Moxifloxacin	Guentsch and colleagues,[34] 2008	5.5	5.15	3.58	3.61	SS
Metronidazole	Xajigeorgiou and colleagues,[31] 2006	5.35	4.55	4.11	4.07	Not SS
	Haffajee and colleagues,[33] 2007	3.21	3.03	2.83	2.88	SS (+ 6 mm)
	Feres and colleagues,[44] 2012	4.09	4.32	3.19	3.59	SS
Ornidazole	Pradeep and colleagues,[48] 2012	7.48	6.96	4.56	6.04	SS

* CAL: Clinical attachment level.
† mm: Millimeters.
‡ SS: Statistically significant.
§ X: Indicates that there were differences between groups before any treatment, besides the randomization.
¶ SS (+ 6 mm): Statistically significant in clinical attachment level of 6 mm or more.
# NA: Not applicable.
** Mean clinical attachment level improvement in mm.

greatest reduction in PPD (1.03 mm extra reduction in test group versus placebo), and the only study whose investigators did not find a benefit in the test group was Sampaio and colleagues[41] with an extra 0.22 mm reduction in PPD favorable to the control group.

In BOP (Table 6), Oteo and colleagues[38] obtained the best results (with a 16.9% improvement in BOP in test group participants versus control group participants), but the intergroup differences were not statistically significant. The next best statistically significant results were from the study by Yashima and colleagues,[37] who found a 5.48% difference between AZ and placebo. Sampaio and colleagues[41] found benefits in the control group participants with respect to the test group participants, whereas the rest of the study investigators[30,32,33,35,37,38,43,46] noted beneficial results in the test group participants (that is, 8 studies[30,32,33,35,37,38,43,46] versus 1 study[41]).

M. Four studies evaluated the additional effect of M as an adjunct to mechanical periodontal therapy (Tables 4, 5, and 6).[27,31,33,44] These studies reported additional benefits in CAL and PPD when M was used. Xajigeorgiou and colleagues[31] noted the best results in terms of CAL (0.76 mm improvement, Table 4) and also reported the best reduction in PPD (1.16 mm extra pocket reduction in the antibiotic group, Table 5). Feres and colleagues[44] were the only investigators who reported statistically significant differences between groups, whereas Haffajee and colleagues[33] found statistically significant differences only in pockets deeper than 6 mm.

However, there were no significant differences between groups in terms of BOP (Table 6).[27,31,33,44]

TABLE 5

Probing pocket depth.

ANTIBIOTIC	STUDY	BASELINE PPD* (mm†)		POSTTREATMENT PPD (mm)		INTERGROUP DIFFERENCE
		Test	Control	Test	Control	
Amoxicillin and Metronidazole	Guerrero and colleagues,[29] 2005	4.1	4.1	2.9	3.4	SS‡
	Xajigeorgiou and colleagues,[31] 2006	4.63	4.21	3.12	3.52	Not SS
	Cionca and colleagues,[36] 2009	4.3	4.4	3	3.1	Not SS
	Yek and colleagues,[39] 2010	4.07	3.7	2.53	2.42	Not SS
	Aimetti and colleagues,[42] 2012	4.3	4.5	2.7	3.3	SS
	Feres and colleagues,[44] 2012	3.88	3.84	2.54	3.05	SS
	Goodson and colleagues,[45] 2012	6.01	6.17	3.65	4.36	SS
	Mestnik and colleagues,[47] 2012	4.27	4.09	2.61	2.48	SS
	Silva-Senem and colleagues,[49] 2013	4.31	4.19	3.01	3.19	Not SS
Azithromycin	Mascarenhas and colleagues,[30] 2005	4.23	3.51	2.9	3.06	X§
	Gomi and colleagues,[32] 2007	3.98	4.05	2.36	3.3	SS
	Haffajee and colleagues,[33] 2007	3.11	2.92	2.68	2.59	SS (+ 6 mm)¶
	Haas and colleagues,[35] 2008	6.7	6.3	3.82	4.45	SS
	Yashima and colleagues,[37] 2009	5.07	5.07	3.48	3.85	SS
	Oteo and colleagues,[38] 2010	2.99	2.84	2.18	2.57	SS
	Sampaio and colleagues,[41] 2011	4.82	5.02	3.36	3.34	Not SS
	Emingil and colleagues,[43] 2012	4.05	3.79	2.17	2.11	Not SS
	Han and colleagues,[46] 2012	4.02	3.84	2.21	2.18	Not SS
Clarithromycin	Pradeep and Kathariya,[40] 2011	NA#	NA	1.99**	0.81**	Not SS
Doxycycline	Xajigeorgiou and colleagues,[31] 2006	4.24	4.21	3.35	3.52	Not SS
	Guentsch and colleagues,[34] 2008	5.16	5.03	3.22	3.18	Not SS
Moxiflxacin	Guentsch and colleagues,[34] 2008	5.17	5.03	3.07	3.18	SS
Metronidazole	Xajoigeorgiou and colleagues,[31] 2006	4.71	4.21	2.86	3.52	Not SS
	Haffajee and colleagues,[33] 2007	3	2.92	2.54	2.59	SS (+ 6 mm)
	Feres and colleagues,[44] 2012	3.69	3.84	2.61	3.05	SS
Ornidazole	Pradeep and colleagues,[48] 2012	8.36	8.16	5.52	7.24	SS

* PPD: Probing pocket depth.
† mm: Millimeters.
‡ SS: Statistically significant.
§ X: Indicates that there were differences between groups before any treatment, besides the randomization.
¶ SS (+ 6 mm): Statistically significant in pockets of 6 mm or greater.
# NA: Not applicable.
** Mean pocket reduction in millimeters.

Although Rooney and colleagues[27] and Feres and colleagues[44] obtained beneficial results when antibiotics were used with test group participants compared with control group participants, Haffajee and colleagues[33] found no differences between groups, and Xajigeorgiou and colleagues[31] reported better results in the control group (that is, a 4% extra reduction) than in the test group who received antibiotics.

CLAR. The only study whose investigators evaluated the effect of CLAR was by Pradeep and Kathariya.[40] They reported that the group of participants who received antibiotics had statistically significant benefits of 1.07 mm improvement in terms of CAL and 1.18 mm in PPD reduction. However, they did not assess BOP during this study.

DOX. The investigators of 2 studies evaluated the action of DOX against a control group[31,34] and reported improvement in CAL in the control group compared with the test group (0.33 and 0.20 mm extra, respectively), in PPD reduction (0.20 and 0.09 mm extra, respectively), as well as for BOP. However, the differences in these results were not statistically significant.

MOX. Only 1 study's investigators evaluated the additional benefits of MOX as an adjunct to mechanical therapy.[34] They found statistically significant differences in CAL (0.38 mm) and PPD (0.25 mm) reduction between the test group and the control group. This study reported a 5.7% reduction favorable to the test group in BOP (not statistically significant).

TABLE 6

Bleeding on probing.

ANTIBIOTIC	STUDY	BASELINE BOP* (%)		POSTTREATMENT BOP (%)		INTERGROUP DIFFERENCE
		Test	Control	Test	Control	
Amoxicillin and Metronidazole	Rooney and colleagues,[27] 2002	62.6	65.6	22.8	44.9	SS†
	Ehmke and colleagues,[28] 2005	44.3	63.4	34.7	55.4	Not SS
	Guerrero and colleagues,[29] 2005	61.5	55.0	29.5	34.0	SS
	Xajigeorgiou and colleagues,[31] 2006	87.0	78.0	15.0	15.0	Not SS
	Cionca and colleagues,[36] 2009	64.2	62.5	16.0	19.0	Not SS
	Aimetti and colleagues,[42] 2012	61.5	56.2	9.4	15.5	SS
	Feres and colleagues,[44] 2012	63.7	70.6	11.4	23.5	Not SS
	Mestnik and colleagues,[47] 2012	77.7	63.8	10.0	13.7	Not SS
	Silva-Senem and colleagues,[49] 2013	85.7	81.0	58.7	61.0	Not SS
Azithromycin	Mascarenhas and colleagues,[30] 2005	59.3	67.3	40.0	50.0	SS
	Gomi and colleagues,[32] 2007	31.4	31.4	5.4	7.6	SS
	Haffajee and colleagues,[33] 2007	34.3	32.7	11.1	14.4	Not SS
	Haas and colleagues,[35] 2008	65.9	76.4	20.9	31.94	Not SS
	Yashima and colleagues,[37] 2009	44.1	42.9	9.5	13.8	SS
	Oteo and colleagues,[38] 2010	54.5	38.6	19.3	20.3	Not SS
	Sampaio and colleagues,[41] 2011	75.8	81.9	10.0	9.5	Not SS
	Emingil and colleagues,[43] 2012	66.0	65.3	14.2	15.6	Not SS
	Han and colleagues,[46] 2012	70.8	65.2	16.7	14.9	Not SS
Doxycycline	Xajigeorgiou and colleagues,[31] 2006	81.0	78.0	14.0	15.0	Not SS
	Guentsch and colleagues,[34] 2007	79.1	76.5	28.1	28.0	Not SS
Moxifloxacin	Guentsch and colleagues,[34] 2007	80.5	76.5	26.3	28.0	Not SS
Metronidazole	Rooney and colleagues,[27] 2002	61.8	65.6	32.5	44.9	Not SS
	Xajigeorgiou and colleagues,[31] 2006	80.0	78.0	21.0	15.0	Not SS
	Haffajee and colleagues,[33] 2007	39.4	32.7	21.1	14.4	Not SS
	Feres and colleagues,[44] 2012	74.6	70.6	16.8	23.5	Not SS
Amoxicillin	Rooney and colleagues,[27] 2002	61.8	65.6	33.9	44.9	Not SS

* BOP: Bleeding on probing.
† SS: Statistically significant.

ORN. We found only 1 clinical trial evaluating additional beneficial effects of ORN as an adjuvant mechanical periodontal treatment.[48] In terms of CAL, there was a significant improvement over the control group (2 mm extra attachment gain in the test group compared with the control group), as well as in reducing PPD (1.92 mm extra reduction). BOP was not recorded.

Characteristics of adverse effects. All of the studies, except 1,[30] reported adverse effects associated with medication (Table 7[27-29,31-49]). The group of antibiotics that produced more adverse effects was the combination of AM with M. Although most of the adverse effects appeared in a small percentage of patients, the investigators of 5 studies reported adverse effects that appeared in more than 15.0% of study participants.[31,36,42,44,49] It is important to note that adverse effects also were reported in the control group with similar[41] or higher[49] percentages of adverse effects' appearance in the placebo group than the antibiotic group. In general, the most prevalent adverse effects were gastrointestinal discomfort, diarrhea, nausea, and vomiting.

DISCUSSION

The main objective of this review was to update and add more evidence to a previous systematic review[16] by following its methodology and using a similar search strategy and inclusion and exclusion criteria. We reviewed data from 23 randomized clinical trials shown in several articles published since April 2001, when Herrera and colleagues[16] ended their search. In most studies, the effects of antibiotic therapy adjunctive to mechanical periodontal therapy may have had a beneficial effect on the outcomes of SRP in terms of the clinical parameters CAL, PPD, and BOP. This was evident in 25 of 27

TABLE 7

Adverse events.*

ANTIBIOTIC	STUDY	ADVERSE EFFECTS (NO.)
Amoxicillin and Metronidazole	Rooney and colleagues,[27] 2002	Test: 0
		Control: 0
	Ehmke and colleagues,[28] 2005	Test: 2 gastrointestinal discomfort (11.1%)
		Control: 0
	Guerrero and colleagues,[29] 2005	Test: 3 nausea/vomiting (15%), 1 diarrhea (5%), 1 headache (5%), 1 metallic taste (5%), 3 general unwellness (15%)
		Control: 2 intraoral tissue alterations (9.5%), 2 periodontal abscess (9.5%)
	Xajigeorgiou and colleagues,[31] 2006	Test: 2 gastrointestinal discomfort (16.6%)
		Control: 0
	Cionca and colleagues,[36] 2009	Test: 6 diarrhea (24%), 5 nausea/vomiting (20%), 5 cramps (20%), 4 headache (16%)
		Control: 3 diarrhea (12%), 4 nausea/vomiting (15%), 1 cramps (4%), 4 headache (15%)
	Yek and colleagues,[39] 2010	Test: 1 intestinal problems (8.3%), 1 vertigo (8.3%)
		Control: 0
	Aimetti and colleagues,[42] 2012	Test: 3 gastrointestinal discomfort (15.7%)
		Control: 0
	Feres and colleagues,[44] 2012	Test: 2 diarrhea (5.12%), 3 vomiting (7.29%), 5 headache (12.82%), 5 metallic taste (12.82%), 1 irritability (2.56%)
		Control: 1 metallic taste (2.5%), 2 irritability (5%)
	Goodson and colleagues,[45] 2012	Test: 1 nausea and vomiting (1.05%), 1 candidiasis (1.05%)
		Control: 0
	Mestnik and colleagues,[47] 2012	Test: 1 diarrhea, vomiting (6.66%)
		Control: 1 diarrhea, vomiting (6.66%)
	Silva-Senem and colleagues,[49] 2013	Test: 2 diarrhea (11.1%), 2 nausea (11.1%), 1 dizziness (5.5%), 3 metallic taste (16.6%), 3 oral ulcers (16.6%), 3 tongue staining (16.6%), 7 teeth staining (38.8%), 6 taste alterations (33.3%), 7 mouth burning (38.8%)
		Control: 1 diarrhea (5.8%), 3 nausea (17.6%), 3 dizziness (17.6%), 3 metallic taste (17.6%), 3 oral ulcers (17.6%), 2 tongue staining (11.7%), 5 teeth staining (29.4%), 11 taste alterations (64.7%), 4 mouth burning (23.5%)
Azithromycin	Gomi and colleagues,[32] 2007	Test: 1 diarrhea (5.8%)
		Control: 0
	Haffajee and colleagues,[33] 2007	Test: 1 allergic reaction (4%), 1 difficulty swallowing tablets (4%)
		Control: 0
	Haas and colleagues,[35] 2008	Test: 1 headache (8.3%)
		Control: 0
	Yashima and colleagues,[37] 2009	Test: 1 diarrhea (5%)
		Control: 0
	Oteo and colleagues,[38] 2010	Test: 1 diarrhea (6.6%)
		Control: 0
	Sampaio and colleagues,[41] 2011	Test: 2 diarrhea (10%), 1 headache and dizziness (5%), 2 metallic taste (10%), 3 somnolence (15%), 1 general unwellness (5%)
		Control: 2 headache and dizziness (10%), 3 metallic taste (15%), 3 somnolence (15%), 1 general unwellness (5%)
	Emingil and colleagues,[43] 2012	Test: 0
		Control: 0
	Han and colleagues,[46] 2012	Test: 0
		Control: 0
Clarithromycin	Pradeep and Kathariya,[40] 2011	Test: 2 gastrointestinal discomfort (11.1%)
		Control: 0

* Note that the number of study participants and the percentages in the total size of population are provided.

TABLE 7 (CONTINUED)

ANTIBIOTIC	STUDY	ADVERSE EFFECTS (NO.)
Doxycycline	Xajigeorgiou and colleagues,[31] 2006	Test: 0
		Control: 0
	Guentsch and colleagues,[34] 2008	Test: 0
		Control: 0
Moxifloxacin	Guentsch and colleagues,[34] 2008	Test: 0
		Control: 0
Metronidazole	Rooney and colleagues,[27] 2002	Test: 0
		Control: 0
	Xajigeorgiou and colleagues,[31] 2006	Test: 1 metallic taste (8.3%)
		Control: 0
	Haffajee and colleagues,[33] 2007	Test: 1 diarrhea (4.16%)
		Control: 0
	Feres and colleagues,[44] 2012	Test: 1 diarrhea (2.56%), 3 vomiting (7.29%), 1 headache (2.56%), 7 metallic taste (17.94%), 1 irritability (2.56%)
		Control: 1 metallic taste (2.5%), 2 irritability (5%)
Ornidazole	Pradeep and colleagues,[48] 2012	Test: 2 nausea (7.14%), 1 vomiting (3.57%), 3 metallic taste (10.71%)
		Control: 0
Amoxicillin	Rooney and colleagues,[27] 2002	Test: 0
		Control: 0

antibiotics studied for CAL, in 25 of 27 antibiotics studied for PPD, and in 22 of 25 antibiotics studied in which investigators had recorded BOP. In addition, the results of this review are consistent with the results of previously published reviews whose authors used similar criteria.[9,16,23]

We observed the most dramatic statistically significant improvement in CAL in studies whose investigators used AZ and a combination of AM with M.[35,45] The best improvement in PPD was reported with the use of AZ,[35] and, in the case of BOP, the best improvement was reported with the use of AM with M.[27] In this review, we noted an optimum effect in deep pockets (greater than 6 mm) in patients with CP and in all cases of AgP.

The results of the use of ORN as adjunctive therapy demonstrated greater improvement in clinical outcomes compared with the results of other studies; however, this result may have less significance because only 1 study's investigators[48] evaluated its effects. This set of investigators[48] did not report BOP, although they found greater reduction in the gingival index in participants who used ORN. Nevertheless, additional studies are required to support the result that ORN has highly beneficial effects for the treatment of CP.

Cases of AgP have demonstrated the optimal benefit of adjunctive systemic antimicrobial use with mechanical periodontal therapy. Previous reviews have shown a greater benefit in deeper pockets in both AgP and CP.[16,23,24]

Our review has several limitations resulting from the high level of heterogeneity of the evaluated clinical studies. First, there was not a uniform criteria for defining the severity of periodontal disease, and thus each study's investigators used their own criteria to establish the boundary between health and disease. Only 12[29,31,35,38,39,41-44,46,47,49] of the 23 studies we analyzed followed the classification of the American Academy of Periodontology[1] to classify the periodontal diseases. Moreover, there was high level of heterogeneity in different antibiotic regimens, both drug type and dose, making it difficult to directly compare studies, even those studies whose investigators had used similar diagnostic criteria.

With regard to the timing of antibiotic use, we contend that no clear conclusions can be drawn from the results of this review because of the wide variability of protocols set forth in the studies analyzed. We noted a similar scenario with regard to the duration of mechanical therapy, although the final clinical outcome of complete removal of plaque and calculus was consistent between studies.

We noted many confounding variables in the studies. For example, in some studies, investigators used chlorhexidine mouth rinses during the mechanical phase. Other confounding variables that have been demonstrated to influence the outcomes of periodontal therapy were not necessarily adjusted for the study data analyses. One such confounder was smoking, which

investigators considered in fewer than one-half of the studies.[29,35,36,38,39,41,43,45,46,49] However, similar outcomes were found in studies in which investigators excluded smokers compared with studies in which investigators included smokers with[35,45] or without stratification.[27]

Although more than one-half of the studies we analyzed had a moderate or high risk of bias,[27,28,30-34,37,39,40,45,48] it is interesting to note that most of these studies were conducted before 2010, indicating that methodological quality is improving.

Regarding side effects of using adjunctive antibiotics, we noted that investigators reported low incidences (typically fewer than 15% of study participants). The selection of participants may be important to minimize complications from antibiotic use, as the authors of previous reviews have stated.[16,23,24] We also must note that unnecessary and inappropriate use of antibiotics has been associated with an increase in antimicrobial resistance of bacteria.[50,51] In fact, antimicrobial resistance has become a worldwide health threat. Clinicians must take special precautions to ensure that systematic antibiotics, including those given for the treatment of periodontal diseases, are used appropriately.

CONCLUSIONS

The findings from this review show that the use of systemic antibiotics as an adjunct to mechanical periodontal treatment may provide benefits in terms of PPD and CAL compared with mechanical periodontal treatment alone, especially in the cases of AgP and deep pockets (greater than 6 mm) of CP. Wide-spectrum antibiotics, represented in the combination of AM with M and AZ, were the most effective in improving the clinical parameters. Standardizing protocols regarding mechanical periodontal therapy and dosing of antimicrobials, as well as establishing specific diagnostic and severity criteria of periodontal disease, would facilitate comparisons between studies. Given the limitations of the evidence regarding the use of adjunctive antimicrobials with SRP, we conclude that the clinician should evaluate carefully the evidence and make a decision on the basis of the specific needs of the patient. ■

Dr. Garcia Canas is a clinical assistant fellow, Ashman Department of Periodontology and Implant Dentistry, College of Dentistry, New York University, 421 First Ave., 3W, New York, NY, 10010, e-mail pgcanas@gmail.com. Address correspondence to Dr. Garcia Canas.

Dr. Khouly is a clinical assistant professor, Department of Oral and Maxillofacial Surgery, College of Dentistry, New York University, New York, NY, and a clinical investigator, Bluestone Center for Clinical Research, College of Dentistry, New York University, New York, NY.

Dr. Sanz is a resident in periodontology, Faculty of Dentistry, Complutense University of Madrid, Madrid, Spain.

Dr. Loomer is a chairman, Ashman Department of Periodontology and Implant Dentistry, College of Dentistry, New York University, New York, NY; and a director of global health, Oral Health Science, Global Institute of Public Health, New York University, New York, NY.

Disclosure. None of the authors reported any disclosures.

1. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol.* 1999;4(1):1-6.
2. Zambon JJ. Periodontal diseases: microbial factors. *Ann Periodontol.* 1996;1(1):879-925.
3. Moore WE, Moore LV. The bacteria of periodontal diseases. *Periodontol 2000.* 1994;5:66-77.
4. Socransky SS, Haffajee AD. Microbial mechanisms in the pathogenesis of destructive periodontal diseases: a critical assessment. *J Periodontal Res.* 1991;26(3):195-212.
5. Pahkla ER, Koppel T, Naaber P, Saag M, Loivukene K. The efficacy of non-surgical and systemic antibiotic treatment on smoking and non-smoking periodontitis patients. *Stomatologija.* 2006;8(4):116-121.
6. Hung HC, Douglass CW. Meta-analysis of the effect of scaling and root planing, surgical treatment and antibiotic therapies on periodontal probing depth and attachment loss. *J Clin Periodontol.* 2002;29(11):975-986.
7. Nyman S, Sarhed G, Ericsson I, Gottlow J, Karring T. Role of "diseased" root cementum in healing following treatment of periodontal disease. An experimental study in the dog. *J Periodontal Res.* 1986;21(5):496-503.
8. Nyman S, Westfelt E, Sarhed G, Karring T. Role of "diseased" root cementum in healing following treatment of periodontal disease: a clinical study. *J Clin Periodontol.* 1988;15(7):464-468.
9. Kaldahl WB, Kalkwarf KL, Patil KD. A review of longitudinal studies that compared periodontal therapies. *J Periodontol.* 1993;64(4):243-253.
10. Mombelli A, Nyman S, Bragger U, Wennstrom J, Lang NP. Clinical and microbiological changes associated with an altered subgingival enviroment induced by periodontal pocket reduction. *J Clin Periodontol.* 1995;22(10):780-787.
11. Koshy G, Corbet EF, Ishikawa I. A full-mouth disinfection approach to nonsurgical periodontal therapy: prevention of reinfection from bacterial reservoirs. *Periodontol 2000.* 2004;36:166-178.
12. Walker CB, Gordon JM, Magnusson I, Clark WB. A role for antibiotics in the treatment of refractory periodontitis. *J Periodontol.* 1993;64(8 suppl):772-781.
13. Renvert S, Wikstrom M, Dahlen G, Slots J, Egelberg J. On the inability of root debridement and periodontal surgery to eliminate Actinobacillus actinomycetemcomitans from periodontal pockets. *J Clin Periodontol.* 1990;17(6):351-355.
14. Renvert S, Wikstrom M, Dahlen G, Slots J, Egelberg J. Effect of root debridement on the elimination of Actinobacillus actinomycetemcomitans and Bacteroides gingivalis from periodontal pockets. *J Clin Periodontol.* 1990;17(6):345-350.
15. Winkel EG, Van Winkelhoff AJ, Timmerman MF, Vangsted T, Van der Velden U. Effects of metronidazole in patients with "refractory" periodontitis associated with Bacteroides forsythus. *J Clin Periodontol.* 1997;24(8):573-579.
16. Herrera D, Sanz M, Jepsen S, Needleman I, Roldan S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. *J Clin Periodontol.* 2002;29(suppl 3):136-162.
17. Drisko CH. Non-surgical pocket therapy: pharmacotherapeutics. *Ann Periodontol.* 1996;1(1):491-566.
18. Elter JR, Lawrence HP, Offenbacher S, Beck JD. Meta-analysis of the effect of systemic metronidazole as an adjunct to scaling and root planing for adult periodontitis. *J Periodontal Res.* 1997;32(6):487-496.
19. van Winkelhoff AJ, Rams TE, Slots J. Systemic antibiotic therapy in periodontics. *Periodontol 2000.* 1996;10:45-78.
20. Moreno Villagrana AP, Gómez Clavel JF. Antimicrobial or subantimicrobial antibiotic therapy as an adjunct to the nonsurgical periodontal treatment: a meta-analysis. *ISRN Dent.* 2012;2012:581207.
21. Hayes C, Antczak-Bouckoms A, Burdick E. Quality assessment and meta-analysis of systemic tetracycline use in chronic adult periodontitis. *J Clin Periodontol.* 1992;19(3):164-168.
22. Bidault P, Chandad F, Grenier D. Systemic antibiotic therapy in the treatment of periodontitis. *J Can Dent Assoc.* 2007;73(6):515-520.
23. Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontal therapy: a systematic review. *Ann Periodontol.* 2003;8(1):115-181.
24. Herrera D, Alonso B, Leon R, Roldan S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. *J Clin Periodontol.* 2008;35(8 suppl):45-66.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012.

26. Montenegro R, Needleman I, Moles D, Tonetti M. Quality of RCTs in periodontology: a systematic review. *J Dent Res*. 2002;81(12):866-870.

27. Rooney J, Wade WG, Sprague SV, Newcombe RG, Addy M. Adjunctive effects to non-surgical periodontal therapy of systemic metronidazole and amoxycillin alone and combined: a placebo controlled study. *J Clin Periodontol*. 2002;29(4):342-350.

28. Ehmke B, Moter A, Beikler T, Milian E, Flemmig TF. Adjunctive antimicrobial therapy of periodontitis: long-term effects on disease progression and oral colonization. *J Periodontol*. 2005;76(5):749-759.

29. Guerrero A, Griffiths GS, Nibali L, et al. Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized placebo-controlled clinical trial. *J Clin Periodontol*. 2005;32(10):1096-1107.

30. Mascarenhas P, Gapski R, Al-Shammari K, et al. Clinical response of azithromycin as an adjunct to non-surgical periodontal therapy in smokers. *J Periodontol*. 2005;76(3):426-436.

31. Xajigeorgiou C, Sakellari D, Slini T, Baka A, Konstantinidis A. Clinical and microbiological effects of different antimicrobials on generalized aggressive periodontitis. *J Clin Periodontol*. 2006;33(4):254-264.

32. Gomi K, Yashima A, Nagano T, Kanazashi M, Maeda N, Arai T. Effects of full-mouth scaling and root planing in conjunction with systemically administered azithromycin. *J Periodontol*. 2007;78(3):422-429.

33. Haffajee AD, Torresyap G, Socransky SS. Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results. *J Clin Periodontol*. 2007;34(3):243-253.

34. Guentsch A, Jentsch H, Pfister W, Hoffmann T, Eick S. Moxifloxacin as an adjunctive antibiotic in the treatment of severe chronic periodontitis. *J Periodontol*. 2008;79(10):1894-1903.

35. Haas AN, de Castro GD, Moreno T, et al. Azithromycin as an adjunctive treatment of aggressive periodontitis: 12-month randomized clinical trial. *J Clin Periodontol*. 2008;35(8):696-704.

36. Cionca N, Giannopoulou C, Ugolotti G, Mombelli A. Amoxicillin and metronidazole as an adjunct to full-mouth scaling and root planing of chronic periodontitis. *J Periodontol*. 2009;80(3):364-371.

37. Yashima A, Gomi K, Maeda N, Arai T. One-stage full-mouth versus partial-mouth scaling and root planing during the effective half-life of systemically administered azithromycin. *J Periodontol*. 2009;80(9):1406-1413.

38. Oteo A, Herrera D, Figuero E, O'Connor A, Gonzalez I, Sanz M. Azithromycin as an adjunct to scaling and root planing in the treatment of Porphyromonas gingivalis-associated periodontitis: a pilot study. *J Clin Periodontol*. 2010;37(11):1005-1015.

39. Yek EC, Cintan S, Topcuoglu N, Kulekci G, Issever H, Kantarci A. Efficacy of amoxicillin and metronidazole combination for the management of generalized aggressive periodontitis. *J Periodontol*. 2010;81(7):964-974.

40. Pradeep AR, Kathariya R. Clarithromycin, as an adjunct to non surgical periodontal therapy for chronic periodontitis: a double blinded, placebo controlled, randomized clinical trial. *Arch Oral Biol*. 2011;56(10):1112-1119.

41. Sampaio E, Rocha M, Figueiredo LC, et al. Clinical and microbiological effects of azithromycin in the treatment of generalized chronic periodontitis: a randomized placebo-controlled clinical trial. *J Clin Periodontol*. 2011;38(9):838-846.

42. Aimetti M, Romano F, Guzzi N, Carnevale G. Full-mouth disinfection and systemic antimicrobial therapy in generalized aggressive periodontitis: a randomized, placebo-controlled trial. *J Clin Periodontol*. 2012;39(3):284-294.

43. Emingil G, Han B, Ozdemir G, et al. Effect of azithromycin, as an adjunct to nonsurgical periodontal treatment, on microbiological parameters and gingival crevicular fluid biomarkers in generalized aggressive periodontitis. *J Periodontal Res*. 2012;47(6):729-739.

44. Feres M, Soares GM, Mendes JA, et al. Metronidazole alone or with amoxicillin as adjuncts to non-surgical treatment of chronic periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. *J Clin Periodontol*. 2012;39(12):1149-1158.

45. Goodson JM, Haffajee AD, Socransky SS, et al. Control of periodontal infections: a randomized controlled trial I. The primary outcome attachment gain and pocket depth reduction at treated sites. *J Clin Periodontol*. 2012;39(6):526-536.

46. Han B, Emingil G, Özdemir G, et al. Azithromycin as an adjunctive treatment of generalized severe chronic periodontitis: clinical, microbiologic, and biochemical parameters. *J Periodontol*. 2012;83(12):1480-1491.

47. Mestnik MJ, Feres M, Figueiredo LC, et al. The effects of adjunctive metronidazole plus amoxicillin in the treatment of generalized aggressive periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. *J Clin Periodontol*. 2012;39(10):955-961.

48. Pradeep AR, Kalra N, Priyanka N, Khaneja E, Naik SB, Singh SP. Systemic ornidazole as an adjunct to non-surgical periodontal therapy in the treatment of chronic periodontitis: a randomized, double-masked, placebo-controlled clinical trial. *J Periodontol*. 2012;83(9):1149-1154.

49. Silva-Senem MX, Heller D, Varela VM, Torres MC, Feres-Filho EJ, Colombo AP. Clinical and microbiological effects of systemic antimicrobials combined to an anti-infective mechanical debridement for the management of aggressive periodontitis: a 12-month randomized controlled trial. *J Clin Periodontol*. 2013;40(3):242-251.

50. World Health Organization. The evolving threat of antimicrobial resistance: options for action. 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf. Accessed December 28, 2014.

51. Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance: threat report 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/. Accessed December 28, 2014.