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SYSTEMATIC REVIEW

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Adjunctive effect of systemic antimicrobials in periodontitis therapy: A systematic review and meta-analysis

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Abstract

Aim: To answer the following PICOS questions: in patients with periodontitis, which is the efficacy of adjunctive systemic antimicrobials, in comparison with subgingival debridement plus a placebo, in terms of probing pocket depth (PPD) reduction, in randomized clinical trials with at least 6 months of follow-up?

Material and Methods: A systematic search was conducted: 34 articles (28 studies) were included. Data on clinical outcome variables changes were pooled and analysed using weighted mean differences (WMDs), 95% confidence intervals (CI) and prediction intervals (PIs), in case of significant heterogeneity.

Results: For PPD, statistically significant benefits ($p < .001$) were observed in short-term studies (WMD = 0.448, 95% CI [0.324; 0.573], PI [−0.10 to 0.99]) and long-term studies (WMD = 0.485, 95% CI [0.322; 0.648], PI [−0.11 to 1.08]). Additionally, statistically significant benefits were also found for clinical attachment level, bleeding on probing, pocket closure and frequency of residual pockets. The best outcomes were observed for the combination of amoxicillin plus metronidazole, followed by metronidazole alone and azithromycin. Adverse events were more frequently reported in groups using systemic antimicrobials.

Conclusions: The adjunctive use of systemic antimicrobials in periodontal therapy results in statistically significant benefits in clinical outcomes, with more frequent adverse events in test groups using systemic antimicrobials.

KEYWORDS

meta-analysis, scaling and root planing, systematic review, systemic antimicrobials

1 | INTRODUCTION

Periodontitis is an infectious inflammatory disease triggered and aggravated by the dysbiosis of the subgingival microbiota. Periodontal treatments should promote significant clinical improvements and prevent further disease progression. There is compelling evidence that these clinical outcomes are achieved when the proportions of periodontal pathogens are reduced by treatment and the root surfaces are recolonized with a new microbial community harbouring higher proportions of host-compatible species (Haffajee, Teles, & Socransky, 2006; Teles, Teles, Frias-Lopez, Paster, & Haffajee, 2013). This striking shift in the subgingival microbial profile is not an easy undertaking, due to the organization of the oral microbiota in complex biofilm structures that help protect resident organisms from periodontal treatment and allow the survival of strict anaerobe pathogens, even in highly oxygenated areas of the mouth, such as shallow pockets, tongue, saliva and oral mucosa (Socransky & Haffajee, 2002).

Wim Teughels and Magda Feres contributed equally to this work.

The effectiveness of scaling and root planing (SRP), the standard periodontal treatment, is well documented (Badersten, Nilvéus, & Egelberg, 1981; Cobb, 2002). Despite its microbiologically unspecific nature, the clinical benefits promoted by SRP are associated with a specific beneficial change in the composition of the subgingival biofilm (Cugini, Haffajee, Smith, Kent, & Socransky, 2000; Teles, Haffajee, & Socransky, 2006). However, SRP does not always induce the ecological changes necessary to achieve and maintain the desired clinical improvements in all subjects in the long term, especially in severe cases with the presence of several deep periodontal pockets (Loesche & Grossman, 2001; Socransky & Haffajee, 2002). Therefore, other forms of therapies, including different debridement approaches (e.g. one-stage full-mouth disinfection) or adjunctive therapies (e.g. antimicrobials, probiotics, lasers and host modulators), have been proposed and tested. Among adjunctive therapies, a variety of antimicrobials have been used as adjuncts to SRP in order to improve the clinical and microbiological outcomes of this treatment (Feres, Figueiredo, Soares, & Faveri, 2015; Graziani, Karapetsa, Alonso, & Herrera, 2017; Herrera, Matesanz, Bascones-Martínez, & Sanz, 2012; Quirynen, Teughels, De Soete, & Steenberghe, 2002; van Winkelhoff, Rams, & Slots, 1996).

Antimicrobials can be used locally or systemically in the treatment of periodontitis. Systemic antimicrobials have the advantage of reaching all oral surfaces and fluids, in addition to having the potential to reach periodontal pathogens that eventually invade the host's tissues (Kim et al., 2010; Rudney, Chen, & Sedgewick, 2005).

The range of systemic antimicrobials used to treat periodontitis is rather extensive, and their effectiveness varies considerably depending on the agent and protocol used. Numerous randomized clinical trials (RCTs) and systematic reviews have shown benefits from the use of certain systemic antibiotic protocols over those obtained with mechanical treatment alone (Haffajee, Socransky, & Gunsolley, 2003; Herrera et al., 2012; Herrera, Sanz, Jepsen, Needleman, & Roldan, 2002; Keestra, Grosjean, Coucke, Quirynen, & Teughels, 2015a, 2015b; Rabelo et al., 2015; Sgolastra, Gatto, Petrucci, & Monaco, 2012; Sgolastra, Petrucci, Gatto, & Monaco, 2012; Sgolastra, Severino, Petrucci, Gatto, & Monaco, 2014; Zandbergen, Slot, Cobb, & Weijden, 2013; Zandbergen, Slot, Niederman, & Weijden, 2016). Although many of these RCTs have shown important clinical benefits with the use of systemic antibiotics, such as reduction in number of residual sites post-treatment or percentage of patients achieving a certain clinical endpoint for treatment, most systematic reviews have based their conclusions exclusively on mean full-mouth probing depth or clinical attachment level. Mean full-mouth changes may mask the main clinical improvements occurring in intermediate and deep sites, generating differences between treatments of small magnitudes. This kind of result has produced extensive debates about statistically significance versus clinical relevance. Systematic reviews evaluating a variety of clinical outcomes, including changes occurring in subsets of sites instead of only in the full mouth, could greatly contribute to clarify the knowledge regarding the proper use of systemic antibiotics in daily clinical practice.

Clinical Relevance

Scientific rationale for the study: The efficacy of the adjunctive use of systemic antimicrobials to scaling and root planing (SRP) on different clinical outcome measures is insufficiently clear to provide sharp recommendations in clinical practice.
Principal findings: Systemic antimicrobials, especially amoxicillin plus metronidazole and to a lesser extent, metronidazole and azithromycin, showed significant benefits on probing pocket depth, clinical attachment level, bleeding on probing, and frequency of pocket closure and of residual pockets, with more adverse effects in the groups using systemic antimicrobials.
Practical implications: There is consistent evidence, showing that the adjunctive use of systemic antimicrobials improves the outcomes of SRP.

Thus, the objective of the present systematic review was to answer the following PICOS questions: in patients with periodontitis, which is the efficacy of systemic antimicrobials, in comparison with subgingival debridement plus a placebo, in terms of probing depth reduction, in RCTs with at least 6 months of follow-up? A number of other outcome measures, such as reduction in residual deep pockets and percentage of pocket closure, were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

A protocol was prepared by the authors and presented to the Workshop Committee for the XVI European Workshop. Before starting the study, the protocol was approved and registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42019142370).

2.2 | Eligibility: inclusion and exclusion criteria for studies

2.2.1 | (P)opulation

Patients with periodontitis with any type of untreated periodontitis (aggressive periodontitis patients were analysed separately). Studies exclusively on patients with diabetes or smokers were excluded.

2.2.2 | (I)nterventions

For test groups: subgingival debridement (i.e. SRP, either conventional or "full-mouth approach"), plus an adjunctive systemic antimicrobial. Any type of antibiotics and systemic antimicrobials (e.g. metronidazole, quinolones) were considered, but not antimicrobial molecules used with non-antimicrobial purposes (e.g. low-dose doxycycline).

2.2.3 | (C)omparisons

For control groups: subgingival debridement plus a placebo.

2.2.4 | (O)utcome

Primary outcome was change in full-mouth probing pocket depth (PPD). Secondary clinical outcomes were as follows: changes in clinical attachment level (CAL), "pocket closure" (from PPD ≥ 4 to PPD ≤ 3 mm), frequency distribution of pockets in different categories, bleeding on probing (BOP), patient-reported outcome measures (PROMs), adverse effects and oral health-related quality of life (OHRQoL).

2.2.5 | (S)tudy design and duration

RCTs with at least 6 months of follow-up.

2.3 | Information sources and search

The search strategy is presented in Appendix S1. Due to time limits, no hand search was done and only publications written in English were searched in three databases: MEDLINE/PubMed, EMBASE and Cochrane.

2.4 | Study selection

Two reviewers selected eligible studies by reviewing the list of titles and abstracts and considering the inclusion and exclusion criteria. The complete articles sourced via eligible titles, and abstracts were obtained and examined independently to determine eligibility. Discrepancies between these reviewers pertaining to the selection and inclusion of any specific paper were discussed until either a consensus was reached, or a third reviewer determined inclusion or exclusion. All reports excluded at this stage were formally recorded, as well as the reason/s for their exclusion. Inter-observer agreement value for the screening of complete articles was assessed via kappa score.

2.5 | Data collection process and items

Data collection was done in specifically designed Excel sheets (Appendix S2). Based on the Cochrane recommendations, a standardized, pre-piloted data extraction form was designed and used. Data were extracted from eligible studies and recorded by an initial reviewer. Second and third examiners cross-checked the accuracy and validity of all the data obtained from the studies.

In case of missing data, an attempt to contact primary authors was done. Studies without enough data for meta-analyses were kept in the systematic review, but excluded from the meta-analyses.

2.6 | Risk of bias in individual studies

The risk of bias (RoB) and quality assessment were conducted, following the recommendations of Cochrane (Higgins, Thompson, & Spiegelhalter, 2009) for RCTs, by two reviewers. When the papers adequately showed a random sequence allocation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), no bias of outcome assessment (detection bias), complete outcome data (attrition bias), no selective reporting (reporting bias) and no other bias (conflict of interest bias), the studies were defined as low risk of bias. When one of these criteria was not fulfilled, the study was classified as moderate potential risk of bias and, when missing two or more criteria, as a high potential risk of bias (Ten Heggeler, Slot, & Weijden, 2011).

2.7 | Data analyses and synthesis of the results

Meta-analyses on the mean treatment effects were performed (changes from v1 to vn) with v1 being baseline, and vn being 6-month, 12-month and final visit.

To compare the selected studies, data on the primary and secondary outcomes were pooled and analysed using weighted mean differences (WMDs) and 95% confidence intervals (CI). When the differences between (Δ) baseline end were not reported, they were calculated using baseline and final values. The variance of ΔVar was estimated with the formula: SVar2 = SVar12 + SVar22 − (2*r*SVar1*SVar2), where SVar2 is the variance of the difference, SVar12 is the variance of the mean baseline value, and Svar22 is the variance of the mean end value. A correlation *r* of .5 was assumed.

The statistical heterogeneity among studies was assessed using the Q test according to (DerSimonian and Laird (1986). As a complement to the Q test, the I2 index was calculated in order to know the percentage of variation in the global estimate that was attributable to heterogeneity (I2 = 25%: low; I2 = 50%: moderate; I2 = 75%: high heterogeneity).

TABLE 1 Study design of the selected studies: systemic antimicrobials

References	Year	Blinding	Centre	Setting	Country	Follow-up (months)	Type	Pattern	Severity
Aimetti et al. (2012)	2012	Double blind	Single	University	Italy	6	Aggressive	Generalized	Severe
Al-Joburi et al. (1989)	1989	Double blind	Multi	University	Canada	6	Chronic	Unclear	Severe
Andere et al. (2017)	2017	Double blind	Single	University	Brazil	6	Aggressive	Generalized	Severe
Ardila, Martelo-Cadavid, Boderth-Acosta, Ariza-Garces, and Guzman (2015)	2015	Double blind	Single	University	Colombia	6	Aggressive	Generalized	Severe
Bain et al. (1994)	1994	Double blind	Multi	University	Canada	6	Chronic	Unclear	Severe
Basegmez et al. (2011)	2011	Double blind	Single	University	Turkey	6	Chronic	Unclear: ≥16 interproximal sites with PPD ≥ 4 mm	Moderate to severe
Berglundh et al. (1998)	1998	Double blind	Single	University	Sweden	24	Chronic	Unclear	Severe
Borges et al. (2017)	2017	Double blind	Single	University	Brazil	12	Chronic	Generalized	Severe
Casarin et al. (2012)	2012	Double blind	Single	University	Brazil	6	Aggressive	Generalized	Severe
Cionca et al. (2009)	2009	Double blind	Single	University	Switzerland	6	Chronic	Localized to generalized	Moderate to severe
Cosgarea et al. (2016)	2016	Double blind	Single	University	Romania	12	Chronic	Generalized	Severe
Emingil et al. (2012)	2012	Double blind	Single	University	Turkey	6	Aggressive	Generalized	Severe
Feres et al. (2012)	2012	Double blind	Single	University	Brazil	12	Chronic	Generalized	Moderate to severe
Guerrero et al. (2005)	2005	Double blind	Single	University	U.K.	6	Aggressive	Generalized	Severe
Haas et al. (2008)	2008	Double blind	Single	University	Brazil	12	Aggressive	Generalized & localized	Moderate to severe
Han et al. (2012)	2012	Double blind	Single	University	Turkey	6	Chronic	Generalized	Severe
Harks et al. (2015)	2015	Double blind	Multi	University	Germany	24	Chronic and aggressive	Localized to generalized	Moderate to severe
Heller et al. (2011)	2011	Double blind	Single	University	Brazil	12	Aggressive	Generalized	Severe
Martande et al. (2016)	2016	Double blind	Single	University	India	12	Chronic, *Aa* associated	Unclear: ≥4 teeth with PPD > 6 mm and CAL ≥ 4 mm	Moderate to severe
Mestnik et al. (2010)	2010	Double blind	Single	University	Brazil	12	Aggressive	Generalized	Severe
Morales et al. (2018)	2018	Double blind	Single	University	Chile	9	Chronic	Unclear: ≥5 teeth with PPD ≥ 4 mm and CAL ≥ 1 mm	Moderate to severe
Oteo et al. (2010)	2010	Double blind	Single	University	Spain	6	Chronic, *P. gingivalis* associated	Generalized	Moderate
Pradeep et al. (2012)	2012	Double blind	Single	University	India	6	Chronic	Generalized	Moderate to severe

(Continues)

TABLE 1 (Continued)

References	Year	Blinding	Centre	Setting	Country	Follow-up (months)	Type	Pattern	Severity
Pradeep and Kathariya (2011)	2011	Double blind	Single	University	India	9	Chronic	Generalized	Severe
Preus et al. (2013)	2013	Double blind	Single	Private practice	Norway	60	Chronic	Localized to generalized	Moderate to severe
Rooney, Wade, Sprague, Newcombe, and Addy (2002)	2002	Double blind	Single	University	UK	6	Chronic	Localized to generalized	Severe
Sampaio et al. (2011)	2011	Double blind	Single	University	Brazil	12	Chronic	Generalized	Severe
Taiete et al. (2016)	2016	Double blind	Single	University	Brazil	6	Aggressive	Generalized	Severe

Abbreviations: Aa, *Aggregatibacter actinomycetemcomitans*; CAL, clinical attachment level; PPD, probing pocket depth.

The study-specific estimates were pooled using both the fixed-effects model (Mantel–Haenszel–Peto test) and the random-effects model (Dersimonian–Laird test). If a significant heterogeneity was found, the random-effects model results was presented. For subgroup analysis, meta-regression was applied, in case of enough available data.

Forest plots were created to illustrate the effects in the meta-analysis of the global estimation and the different sub-analysis. STATA® 14 (StataCorp LP) intercooled software was used to perform all analyses. Statistical significance was set at $p \leq .05$.

In case of heterogeneity in the primary outcome, in addition to the summary estimate (WMD) and CI, prediction intervals (PI) were reported to allow more informative inferences and illustrate which range of true effects can be expected in future settings, presenting the heterogeneity in the same metric as the original effect size measure (IntHout, Ioannidis, Rovers, & Goeman, 2016).

2.8 | Risk of bias across studies: publication bias

Egger's test and Funnel plots, in case of a sufficient number of included studies (at least 10 studies), were used to assess publication bias. Sensitivity analysis was performed assessing the contribution made to the totality of the evidence by each study after omitting each of them.

3 | RESULTS

3.1 | Study selection

The electronic search resulted in 12,772 unique articles. After title and abstract reading (κ = .629, 95% CI [0.559; 0.699]), 12,670 articles were excluded. Full-text reading resulted in an additional exclusion of 68 articles (κ = .891, 95% CI [0.797; 0.984]; Appendix S3). At the end, 34 articles were included in this systematic review reporting on 28 different studies with data from 66 test or placebo study arms. In four studies, data came from two papers each [(Preus, Gjermo, & Baelum, 2017; Preus, Gunleiksrud, Sandvik, Gjermo, & Baelum, 2013); (Cosgarea et al., 2017, 2016); (Mestnik et al., 2010, 2012); (Griffiths et al., 2011; Guerrero et al., 2005)] and in one study from three papers [(Heller et al., 2011; Silva-Senem et al., 2013; Varela et al., 2011)]. When reporting these studies, only the original papers were quoted (Cosgarea et al., 2016; Guerrero et al., 2005; Heller et al., 2011; Mestnik et al., 2010; Preus et al., 2013). For 13 studies, additional data were obtained after contacting the authors (Aimetti, Romano, Guzzi, & Carnevale, 2012; Andere et al., 2017; Casarin et al., 2012; Cosgarea et al., 2016; Feres et al., 2012; Guerrero et al., 2005; Haas et al., 2008; Harks et al., 2015; Heller et al., 2011; Mestnik et al., 2010; Morales et al., 2018; Oteo et al., 2010; Sampaio et al., 2011).

TABLE 2 Treatment groups, outcome variable assessment and sample characteristics for studies on systemic antimicrobials

References	Recording	Number of sites	Intervention before SRP	None study-related interventions during study	Treatment	Anaesthesia	Number of operators
Aimetti et al. (2012)	FM	6	OHI, proph.	CS: CHX HC: CHX for 60 days	FMSRP	Yes	1
Al-Joburi et al. (1989)	PM: 2 sites with deepest interproximal PPD with adjacent tooth	1	No	OHI	FMSRP	NR	NR
Andere et al. (2017)	FM	6	OHI, proph.	No	FMSRP	Yes	1
Ardila et al. (2015)	FM	6	No	OHI	FMSRP	Yes	1
Bain et al. (1994)	PM: 2 sites with deepest interproximal PPD with adjacent tooth	1	No	OHI	SSRP	NR	NR
Basegmez et al. (2011)	FM	6	No	OHI	SSRP	Yes	1
Berglundh et al. (1998)	PM: half of the upper jaw and half of the lower jaw got SRP	4	OHI, proph.	OHI if indicated	SSRP	Yes	NR
Borges et al. (2017)	FM	6	OHI, proph.	OHI, periodontal maintenance	SSRP	Yes, pockets with PPD ≥ 5 mm	2
Casarin et al. (2012)	PM: PPD & CAL: deepest site of teeth with PPD ≥ 5mm without furcation involvement FM: BOP	1 6	OHI, proph.	No	FMSRP	NR	NR
Cionca et al. (2009)	PM: teeth with PPD > 4mm at baseline	6	OHI, proph.	0.1% CHX subgingival, 0.2% CHX rinse 2/day for 10 days, OHI, supragingival proph.	FMSRP	Yes	1
Cosgarea et al. (2016)	FM	6	OHI, proph. until FMPS ≤ 25%	CS: 0.12% CHX subgingival, HC: 0.2% CHX rinse 2/day 2 min + 0.2% CHX tooth paste for 14 days	FMSRP	Yes	1
Emingil et al. (2012)	FM	6	No	No	SSRP	Yes	1
Feres et al. (2012)	FM	6	No	OHI, periodontal maintenance at each visit, half of the groups used CHX 0.12% for 2 months but had no significant effect	SSRP	Yes	2
Guerrero et al. (2005)	FM	6	No	OHI, HC: 0.2% CHX 2/day for 14 days	FMSRP	As needed	1

Operator	Debridement time (hr)	Timing antibiotics	Groups	Single dose (mg)	Frequency	Duration	Average age ± *SD*	% of females	% of smokers	Number of patients
Dental hygienist	No limit	After 1st SRP	PLAC				35.7 ± 2.8	50.0%	No	20
			MET + AMOX	500/500	3	7	36.3 ± 3.2	58.0%	No	19
NR	2 × 3 hr	After 1st session FMSRP	PLAC				NR	NR	NR	24
			TET	250	4	14	NR	NR	NR	27
			SPIR	500	2	14	NR	NR	NR	28
Periodontist	Max 1 hr	After SRP	PLAC				31.2 ± 4.6	95.0%	No	20
			CLAR	500	2	3	31.4 ± 3.7	95.0%	No	20
Experienced clinician	2.5 hr	After SRP	PLAC				26.4 ± 1.1	52.2%	No	20
			MOX	400	1	7	28.7 ± 0.9	47.8%	No	20
NR	3–5 hr	After 1st session SSRP	PLAC				48.5 ± 1.2	NR	NR	97
			SPIR	500	2	14	47.3 ± 1.0	NR	NR	97
NR	NR	After 1st session scaling	PLAC				42.1 ± 9.0	NR	No	20
			MINO	100	1	14	39.8 ± 5.8	NR	No	20
NR	NR	After 1st session SSRP	PLAC				NR	NR	NR	8
			MET + AMOX	250/375	3/2	14	NR	NR	NR	8
Periodontists	NR	After 1st session SSRP	PLAC				45.6 ± 8.0	59.0%	No	22
			MET + AMOX 1	250/500	3	7	46.6 ± 8.9	64.0%	No	22
			MET + AMOX 2	400/500	3	7	45.9 ± 7.8	54.0%	No	22
			MET + AMOX 3	250/500	3	14	47.0 ± 8.6	52.0%	No	21
			MET + AMOX 4	400/500	3	14	48.5 ± 7.4	54.0%	No	22
NR	1 × 0.75 hr	After 1st SRP	PLAC				28.3 ± 5.9	58.3%	No	12
			MET + AMOX	250/375	3	7	28.8 ± 6.2	75.0%	No	13
Periodontist	NR	After FMSRP	PLAC				50.5 ± 13.6	58.0%	29%	23
			MET + AMOX	500/375	3	7	50.6 ± 8.6	70.0%	39%	24
Periodontist	NR	After FMSRP	PLAC				41.8 ± 10.0	61.5%	8%	30
			MET + AMOX 1	500/500	3	3	42.4 ± 9.9	62.5%	8%	30
			MET + AMOX 2	500/500	3	7	43.6 ± 9.5	56.0%	6%	31
NR	NR	After SRP	PLAC				29.5 ± 5.9	50.0%	38.5	16
			AZI	500	3	3	28.7 ± 4.4	44.0%	43.8	16
Periodontists	4–6 × 1 hr	After 1st session SSRP	PLAC				45.8 ± 8.5	70.0%	No	40
			MET	400	3	14	43.4 ± 8.3	61.5%	No	39
			MET + AMOX	400/500	3	14	46.3 ± 8.6	56.4%	No	39
Periodontist	2 × 2 hr	Before SRP	PLAC				31.7 ± 5.2	57.0%	19%	21
			MET + AMOX	500/500	3	7	31.3 ± 5.2	80.0%	25%	20

(Continues)

TABLE 2 (Continued)

References	Recording	Number of sites	Intervention before SRP	None study-related interventions during study	Treatment	Anaesthesia	Number of operators
Haas et al. (2008)	FM	6	OHI, proph.	No	SSRP	Yes	1
Han et al. (2012)	FM	6	No	OHI + proph.	SSRP	Yes	1
Harks et al. (2015)	FM	6	No	OHI + proph.	FMSRP	NR	NR
Heller et al. (2011)	FM	6	OHI (<20% plaque on surfaces)	CS: 0.2% CHX gel subgingival, HC: 2/day for 45 days 0.12% CHX rinse + tongue brushing	FMSRP	Yes	1
Martande et al. (2016)	FM	6	OHI, proph.	at each visit OHI	SSRP	Yes	1
Mestnik et al. (2010)	FM	6	OHI	HC: 0.12% CHX 2/day for 60 days	SSRP	Yes	1
Morales et al. (2018)	FM	6	OHI, proph.	Periodontal supportive therapy	SSRP	NR	2
Oteo et al. (2010)	FM	6	OHI	OHI, CHX 0.12% + CPC 0.05% rinse 2/day 15 days	FMSRP	Yes	1
Pradeep et al. (2012)	PM: 4 teeth with most severe breakdown	6	proph., OHI, 0.2% CHX rinse 2/day for 1 week	At each visit OHI	FMSRP	Yes	1
Pradeep and Kathariya (2011)	FM	6	No	OHI	SSRP	NR	1
Preus et al. (2013)	FM	4	proph., OHI (<15% sites with plaque)	CS: air polishing/pumice paste after scaling, 1% CHX gel subgingival, approximal sites flossed, every 6 months OHI, proph. HC: tongue brushing w/ brush + 1% CHX gel 1/day 1 min, 0.2% CHX rinse 1/day 7 days	FMSRP SSRP	Yes Yes	1 1
Rooney et al. (2002)	FM	4	OHI, proph.	OHI, 0.2% CHX 2/day till 1 week after SRP	SSRP	Yes	2
Sampaio et al. (2011)	FM	6	OHI	No	SSRP	Yes	2
Taiete et al. (2016)	PM: Teeth with PPD > 4 mm without furcation involvement	NR	OHI (<30% plaque on surfaces)	No	NR	NR	NR

Abbreviations: AMOX, amoxicillin; AZI, azithromycin; BOP, bleeding on probing; CAL, clinical attachment level; CHX; CLAR, clarithromycin; CS, chairside; FM, full mouth; FMSRP, full-mouth scaling and root planing; hr, hour; HC, home care; MET, metronidazole; MINO, minocycline; MOX, moxifloxacin; NR, not reported; OHI, oral hygiene instruction; ORD, ornidazole; PLAC, placebo; PM, partial mouth; PPD, probing pocket depth; proph., prophylaxis; *SD*, standard deviation; SPIR, spiramycin; SRP, scaling and root planing; SSRP, sectional scaling and root planing; TET, tetracycline

Operator	Debridement time (hr)	Timing antibiotics	Groups	Single dose (mg)	Frequency	Duration	Average age ± *SD*	% of females	% of smokers	Number of patients
Periodontist	NR	After 1st SRP	PLAC				20.1 ± 3.6	NR	17%	12
			AZI	500	1	3	22.5 ± 3.6	NR	25%	12
Periodontist	NR	After SSRP	PLAC				44.8 ± 5.0	43.0%	42.8%	14
			AZI	500	1	3	46.8 ± 5.1	28.6%	50%	14
Dentists, dental hygienists	NR	After FMSRP	PLAC				52.3 ± 10.8	49.7%	25.1%	200
			MET + AMOX	400/500	3	7	53.5 ± 10.1	50.0%	28.8%	206
Periodontist	2 × 1 hr	After SRP	PLAC				32.4 ± 1.0	57.0%	11.7%	17
			MET + AMOX	250/500	3	10	33.5 ± 1.1	86.7%	11.1%	18
Dentist	3–5 × 1–2 hr	After SSRP	PLAC				33.3 ± 7.3	40.0%	No	35
			AZI	500	1	3	32.6 ± 5.4	46.0%	No	35
Periodontist	6 × 1 hr	After 1st SRP	PLAC				27.6 ± 3.5	73.3%	No	15
			MET + AMOX	400/500	3	14	26.8 ± 3.9	60.0%	No	15
Periodontists	NR	After SSRP	PLAC				52.8 ± 7.5	47.0%	40.0%	15
			AZI	500	1	5	49.0 ± 7.9	37.5%	18.7%	16
Dentist, postgraduate student	2 × 1.5 hr	After FMSRP	PLAC				47.1 (range: 36–65)	38.5%	46.2%	13
			AZI	500	1	3	46.6 (range: 38–62)	53.0%	53.3%	15
NR	NR	After FMSRP	PLAC				48.5 ± 11.5	55.0%	No	25
			ORD	500	2	7	49.3 ± 12.5	45.0%	No	25
NR	NR	After SSRP	PLAC				37.3 ± 5.7	53.0%	No	19
			CLAR	500	2	3	35.2 ± 6.0	50.0%	No	18
Hygienist	2 × 1 hr	1 day before FMSRP	PLAC 1				55.1 ± 7.9	62.2%	53.3%	45
			MET 1	400	3	10	53.7 ± 7.6	43.5%	47.8%	46
Hygienist	2 × 1 hr	1 day before 2nd session SSRP (d20)	PLAC 2				54.9 ± 8.5	51.1%	57.5%	47
			MET 2	400	3	10	56.8 ± 8.3	43.5%	63.0%	46
Periodontists	0.75 hr	After SSRP	PLAC				NR	NR	NR	15
			MET	200	3	7	NR	NR	NR	15
			AMOX	250	3	7	NR	NR	NR	16
			MET + AMOX	200/250	3	7	NR	NR	NR	15
Periodontists	4–6 × 2 hr	After SSRP	PLAC				43.5 ± 5.9	45.0%	25%	20
			AZI	500	1	5	44.4 ± 7.4	35.0%	25%	20
NR	NR	NR	PLAC				27.5 ± 5.5	67.0%	No	18
			MET + AMOX	250/375	3	7	28.5 ± 5.1	72.0%	No	21

3.2 | Study characteristics

3.2.1 | Study design

The study settings (country, number and type of centre), duration and target populations are described in Table 1. All studies were double-blind, placebo-controlled and had a parallel design.

3.2.2 | Disease definition

The studies were divided into those on aggressive periodontitis patients (n = 10) and on chronic periodontitis patients (n = 17; Table 1). In two studies, additional microbial criteria were used as inclusion criteria (Martande et al., 2016; Oteo et al., 2010). One study included chronic and aggressive periodontitis patients (Harks et al., 2015). Since the majority of these patients were chronic periodontitis patients, the study was included as chronic periodontitis for the meta-analysis.

3.2.3 | Selected samples

The characteristics of the populations recruited in the different studies are shown in Table 2. The number of patients ranged from 8 to 206. The mean age of the patients ranged from 20.1 to 56.8 years. Four studies did not report the smoking status of the patients, and 12 studies did not include smokers. If smokers were included, their proportion ranged from 6% to 63%.

3.2.4 | Outcome assessment

The majority of the studies reported on full-mouth data and used 6 sites per tooth (range 1–6), and seven studies reported partial-mouth data (Table 2).

3.3 | Types of interventions

The studies varied in regard to the interventions applied before the SRP therapy (Table 2). In some studies, there was no intervention before SRP (n = 10), whereas in others, oral hygiene instructions were given to the patient (n = 18) and prophylaxis was performed (n = 13) or patients were instructed to use a chlorhexidine (CHX) mouth rinse (n = 1). In addition, different SRP approaches were used, including full-mouth SRP (FMSRP, SRP executed within 1 week) and staged SRP (SSRP, SRP executed in multiple sessions). In addition, two studies used mechanical debridement by means of ultrasonic device only. The duration of the mechanical treatment, which was performed in one or in multiple sessions, ranged from 45 min to 12 hr.

Volunteers started antibiotic or placebo intake either prior to SRP (n = 2), after the first SRP session (n = 11) or after completion of SRP (n = 15). The studies also differed regarding the treatments applied after completion of the SRP treatment. Some studies performed an additional chairside disinfection of the pockets with CHX (n = 5), while in other studies, patients were instructed to rinse CHX mouth rinse (n = 10).

In most studies, local anaesthesia was given to the patient and the clinical procedure was executed by one or two dental hygienists (n = 3), periodontists (n = 13), dentists (n = 3), postgraduate students (n = 1) or experienced clinicians (n = 1). Sometimes, it was not mentioned who performed the SRP. Studies included one (n = 22), two (n = 4), three (n = 1) or four (n = 1) test groups. The antibiotics used were as follows: ornidazole (ORD, n = 1) 500 mg, 2/day for 7 days; tetracycline (TET, n = 1) 250 mg, 4/day for 14 days; minocycline (MINO, n = 1) 100 mg, 1/day for 14 days; moxifloxacin (MOX, n = 1) 400 mg, 1/day for 7 days; clarithromycin (CLAR, n = 2) 500 mg, 2/day for 3 days, spiramycin (SPIR, n = 2) 500 mg, 2/day for 14 days; azithromycin (AZI, n = 7) 500 mg, 1–3/day for 3–5 days; amoxicillin (AMOX, n = 1) 250 mg, 3/day for 7 days; metronidazole (MET, n = 4), with dosages ranging from 200 to 400 mg, 3/day for a duration of 7–14 days; or the combination of metronidazole and amoxicillin (MET + AMOX, n = 17), with metronidazole at a dosage of 200–500 mg and amoxicillin at a dosage of 250–500 mg, both 3 times a day for 3–14 days.

3.4 | Risk of bias in individual studies

Risk of bias of the individual studies was assessed according to Cochrane recommendations (Table A4.1 in Appendix S4). Twenty studies were considered to have an overall low risk of bias, and seven studies, a high risk of bias. For one study, the risk of bias was considered low for the first article reporting on 12-month data (Preus et al., 2013) but high for the subsequent article reporting on data upon 60 months (Preus et al., 2017).

3.5 | Synthesis of the results

Studies not reporting data on the primary outcome or reporting only partial-mouth data were excluded from the analysis (Al-Joburi et al., 1989; Bain et al., 1994; Cionca, Giannopoulou, Ugolotti, & Mombelli, 2009; Pradeep et al., 2012), but those providing data for deep sites were included (Berglundh et al., 1998; Casarin et al., 2012; Taiete et al., 2016).

3.5.1 | *Probing pocket depth*—All sites (full-mouth data, primary outcome variable)

At 6 months, a statistically significant difference (WMD = 0.448, 95% CI [0.324; 0.573]) in favour of systemic antimicrobials was observed with significant heterogeneity (I2 = 74.10%; Table 3). PI was −0.10 to 0.99 (A5.a.19 in Appendix S5). Only MET + AMOX

(WMD = 0.433, 95% CI [0.358; 0.508]) and MOX (WMD = 0.350, 95% CI [0.051; 0.649]) showed significant WMDs when compared to the control group. Only one study was available for MOX. For chronic periodontitis, the adjunctive use of MET + AMOX (WMD = 0.409, 95% CI [0.322; 0.496]) and CLAR (WMD = 1.000, 95% CI [0.783; 1.217]) resulted in a statistically significant additional PPD reduction. Only one study was available for CLAR. In aggressive periodontitis patients, this benefit was observed with adjunctive MET + AMOX (WMD = 0.505, 95% CI [0.356; 0.654]) and MOX (WMD = 0.350, 95% CI [0.051; 0.649]). Only one study was available for MOX.

At 12 months, an overall statistically significant difference (WMD = 0.485, 95% CI [0.322; 0.648]) in favour of the adjunctive use of a systemic antibiotics was still observed, with significant heterogeneity (I2 = 72.40%). PI was −0.11 to 1.08 (A5.a.19 in Appendix S5). The use of MET + AMOX (WMD = 0.536, 95% CI [0.335; 0.737]) and MET (WMD = 0.259, 95% CI [0.132; 0.385]) resulted in a significant benefit. In chronic periodontitis patients, the use of MET + AMOX (WMD = 0.546, 95% CI [0.307; 0.785] or MET (WMD = 0.259, 95% CI [0.132; 0.385]) resulted in statistically significant additional PPD reductions, and in aggressive periodontitis patients, this benefit was observed only with the use of MET + AMOX (WMD = 0.519 (95% CI [0.230; 0.807]).

3.5.2 | *Probing pocket depth*—Initially moderately deep pockets

For initially moderately deep pockets, systemic antimicrobials resulted in a statistically significant additional PPD reduction at 6 (WMD = 0.417, 95% CI [0.306; 0.528]) and 12 months post-treatment (WMD = 0.557, 95% CI [0.428; 0.686]) with significant heterogeneity at both time points (I2 = 70.8% and I2 = 66.30%, respectively). PIs were −0.03 to 0.87, and 0.12 to 0.99, respectively (A5.a.20 in Appendix S5). The use of MET + AMOX and MET resulted in statistically significant benefits (WMD = 0.534, 95% CI [0.465; 0.602] and WMD = 0.300, 95% CI [0.056; 0.544], respectively) at 6 months, and also at 12 months (WMD = 0.594, 95% CI [0.470; 0.718], and WMD = 0.400, 95% CI [0.179; 0.621], respectively). MET + AMOX showed statistically significant benefits in reducing PPD in chronic and aggressive periodontitis patients, while MET led to a significant benefit in chronic periodontitis patients at 6 and 12 months. AZI also resulted in a statistically significant reduction in PPD in aggressive periodontitis at 12 months and CLAR at 6 months. Only one study was available for MET, AZI and CLAR.

3.5.3 | *Probing pocket depth*—Initially deep pockets

For initially deep pockets, systemic antimicrobials resulted in a statistically significant additional PPD reduction at 6 (WMD = 0.969, 95% CI [0.755; 1.183]) and 12 months (WMD = 1.049, 95% CI [0.784; 1.314]) with significant heterogeneity at both time points (I2 = 66.9% and, I2 = 58.6%, respectively). The PIs were 0.12–1.81, and 0.21–1.89, respectively (A5.a.21 in Appendix S5). The use of MET + AMOX, MET and AZI resulted in statistically significant benefits at 6 months (WMD = 1.211, 95% CI [1.013; 1.409]; WMD = 0.700, 95% CI [0.189; 1.211]; WMD = 0.310, 95% CI [0.063; 0.556], respectively) and at 12 months (WMD = 1.191, 95% CI [0.888; 1.495]; WMD = 0.800, 95% CI [0.282; 1.318]; WMD = 0.543, 95% CI [0.077; 1.009]; respectively). MET + AMOX showed statistically significant benefits in reducing PPD in chronic and aggressive periodontitis patients, while MET led to a significant benefit in chronic periodontitis patients at 6 and 12 months. AZI also resulted in a statistically significant reduction in PPD in aggressive periodontitis at 6 and 12 months. Only one study was available for MET and AZI at 12 months.

3.5.4 | Pocket closure

The adjunctive use of systemic antimicrobials resulted in an additional percentage of pocket closure at 6 (WMD = −14.477, 95% CI [−17.846; −11.107]) and 12 months (WMD = −12.08, 95% CI [−16.8; −7.359]; Table A4.2 in Appendix S4). When the antimicrobials were evaluated individually, only MET + AMOX and MET resulted in a statistically significant additional percentage of pocket closure at both time points, when all patients were considered together. MET + AMOX had a positive impact on percentage of pocket closure in patients with chronic and aggressive periodontitis at 6 and 12 months, whereas MET had a positive impact on percentage of pocket closure in patients with chronic periodontitis at 6 and 12 months. Only one study was available for MET at 12 months.

3.5.5 | Frequency of residual pockets

The use of systemic antimicrobials had a statistically significant impact, both at 6 and at 12 months on the frequency of pockets of ≥4, ≥5, ≥6 and ≥7 mm (Table A4.3 in Appendix S4). Of all antimicrobials, the combination MET + AMOX was the only protocol that significantly lowered at, respectively, 6 and 12 months, the frequency of residual pockets of ≥4 mm (WMD: 15.734, 95% CI [10.622; 20.847] and WMD: 16.515, 95% CI [9.747; 23.284]), ≥5 mm (WMD: 7.092, 95% CI [5.496; 8.688] and WMD: 9.913, 95% CI [6.524; 13.301]), ≥6 mm (WMD: 6.654, 95% CI [4.615; 8.693] and WMD: 5.978, 95% CI [3.701; 8.133]), and ≥7 mm (WMD: 3.925, 95% CI [2.311; 5.539] and WMD: 3.453, 95% CI [1.841; 5.066]). When compared to the placebo treatment, these magnitudes of WMDs corresponded to additional reductions of 36.66% (standard deviation, *SD* = 15.83] of sites with PPD ≥ 4 mm, 60.56% (*SD* = 17.63)] with PPD ≥ 5 mm, 60.29% (*SD* = 20.96)] with PPD ≥ 6 and 63.56% (*SD* = 15.44)] with PPD ≥ 7 mm, at 12 months post-treatment. Also, MET lowered significantly at, respectively, 6 and 12 months, the frequency of

residual pockets of ≥4 mm (WMD: 7.028, 95% CI [0.403; 13.653]; WMD: 12.97, 95% CI [4.687; 21.253]).

MET + AMOX was the only protocol that lowered the frequency of residual pockets of ≥4, ≥5, ≥6 and ≥7 mm in chronic and aggressive periodontitis patients at 6 and 12 months. Additionally, MET significantly lowered the frequency of residual pockets of ≥4 mm at 6 and at 12 months, and AZI at 6 months, in patients with chronic periodontitis.

3.5.6 | Clinical attachment level

A statistically significant effect in favour of systemic antimicrobials for improving CAL was observed at 6 months (WMD = 0.389, 95% CI [0.267; 0.511]) with significant heterogeneity (I2 = 67.0%) and 12 months (WMD = 0.285, 95% CI [0.202; 0.367]) without significant heterogeneity (Table 4). The 6-month PI ranged from −0.09 to 0.87 (A5.d.19 in Appendix S5). MET + AMOX showed significant benefits in improving CAL when compared to the control group, at the full-mouth analysis and at moderately deep and deep sites, at 6 and 12 months for chronic and aggressive patients. Further details for the impact of antimicrobials in moderately deep and deep sites in subjects with chronic and aggressive periodontitis are described in Table 4.

3.5.7 | Bleeding on probing

A statistically significant effect in favour of systemic antimicrobials for reducing the percentage of sites with BOP was observed at 6 (WMD = 6.64, 95% CI [4.201; 9.078]) and 12 months (WMD = 9.727, 95% CI [6.731; 12.722]), with significant heterogeneity (I2 = 49.30 and I2 = 89.3, respectively; Table 5), and a PI from −2.12 to 15.41 and −0.56 to 20.20, respectively (A5.e.7 in Appendix S5). MET + AMOX showed significant benefits in reducing BOP when compared to the control group, in chronic and aggressive patients at 6 and 12 months. MET also showed this effect when all patients were evaluated together and in patients with chronic periodontitis at 6 and 12 months. Only one study was available for MET at 12 months. AZI showed this same benefit when all patients were evaluated together and in chronic periodontitis at 6 months. Further details for the impact of antibiotics in reducing BOP are described in Table 5.

3.5.8 | Meta-regressions

Meta-regressions were performed and did not show statistically significant differences between 6 and 12 months for all patients together (coefficient = .351; p = .351), for chronic periodontitis (coefficient = .293, p = .481) or aggressive periodontitis (coefficient = .274, p = .805) for the parameters of PPD, pocket closure, frequency of residual sites, CAL and BOP (A5.f in Appendix S5).

3.5.9 | Patient-reported outcome measures and adverse events

Patient-reported outcome measures were retrieved from 25 studies, whereas in two studies, they were not recorded (Table A4.4 in Appendix S4). In five studies, "no adverse events" were observed. In 21 studies, PROMs were identified and described as "nausea/stomach upset/vomiting," "diarrhea/gastro-intestinal disturbance," "metallic taste," "oral ulceration," "dizziness," "fever," "headache," "periodontal abscess," "general unwellness (e.g. irritability)" and "allergic reactions." In general, these PROMs were more frequently reported in the antimicrobial (ranging from 0% to 36.36%) than in the placebo groups (ranging from 0% to 20%). No allergic reactions were reported in the placebo groups, whereas in the antimicrobial group, one study reported one anaphylactic shock (Harks et al., 2015). However, "oral ulceration," "fever" and "periodontal abscess" were more frequently reported in the placebo groups. When reported, "fever" ranged from 6.67% to 16.67% in the placebo groups, whereas the range in the antimicrobial groups was from 0% to 9.52%. "Periodontal abscesses" were also reported more frequently in the placebo groups with a range between 8.70% and 9.52%, when reported. No "periodontal abscesses" were reported in the antimicrobial groups. The highest frequency of side effects was always reported for MET + AMOX, although they were not always present.

3.6 | Risk of bias across studies (publication bias) and sensitivity analyses

No publication bias was detected in the main outcome variable (p = .515; Egger´s test for changes in PPD; Figure A4.1 in Appendix S4). The sensitivity analyses detected the influence of particular studies in the overall heterogeneity, but as the global estimator did not change significantly after omitting each of the contributing studies, it was decided to keep all selected studies (Figure A4.2 in Appendix S4).

4 | DISCUSSION

4.1 | Summary of evidence

This systematic review identified 28 RCTs (reported in 34 publications), assessing the use of systemically administered antimicrobials as adjuncts to SRP or subgingival mechanical debridement, for up to 6 months and 1-year post-treatment. The results of the meta-analysis, including 24 RCTs, showed that the adjunctive use of systemic antimicrobials in the active phase of periodontal treatment led to a statistically significant additional full-mouth PPD reduction (WMD = 0.448 mm, primary outcome variable) and CAL gain (WMD = 0.389 mm) at 6 months, when compared to the control groups. These beneficial effects of the systemic antimicrobials remained stable for at least 1 year (PPD: WMD = 0.485 mm; CAL: WMD = 0.285 mm, p < .05), although this analysis was hampered by the fact that the follow-up period for most of the studies was 6 months. Similar benefits were observed for all the other

TABLE 3 Systemic antimicrobials: meta-analyses for probing pocket depth (PPD) changes in 6- and 12-month studies, in all initial PPD categories, in moderately deep sites or in severe sites, for all types of periodontitis (ALL), chronic periodontitis (CH) or aggressive periodontitis (AG)

				Weighted mean difference (WMD)					Heterogeneity		
		Number of			95% CI						
Perio	Test	Studies	Patients	WMD	Lower	Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
PPD (all sites)—6 months											
ALL	All	19	1,316	0.448	0.324	0.573	.000	Random	74.10	.000	A5.a.1
	AZI	7	253	0.344	−0.034	0.723	>.05	Random	82.60	.000	
	CLAR	2	77	0.572	−0.271	1.415	>.05	Random	96.20	.000	
	MET	1	79	0.190	−0.070	0.450	>.05	Random			
	MET + AMOX	8	867	0.433	0.358	0.508	.000	Fixed	27.00	.179	
	MINO	1	40	0.100	−0.269	0.469	>.05	Random			
	MOX	1	40	0.350	0.051	0.649	.022	Random			
CH	All	11	1,036	0.486	0.307	0.665	.000	Random	80.90	.000	A5.a.2
	AZI	5	197	0.397	−0.151	0.945	>.05	Random	87.90	.000	
	CLAR	1	37	1.000	0.783	1.217	.000	Random			
	MET	1	79	0.190	−0.070	0.450	>.05	Random			
	MET + AMOX	4	723	0.409	0.322	0.496	.000	Fixed	44.10	.085	
	MINO	1	40	0.100	−0.269	0.469	>.05	Random			
AG	All	8	280	0.372	0.264	0.481	.000	Fixed	23.40	.243	A5.a.3
	AZI	2	56	0.219	−0.061	0.500	>.05	Fixed	0.00	.655	
	CLAR	1	40	0.140	−0.108	0.388	>.05	Random			
	MET + AMOX	4	144	0.505	0.356	0.654	.000	Fixed	0.00	.716	
	MOX	1	40	0.350	0.051	0.649	.022	Random			
PPD (all sites)—12 months											
ALL	All	11	1,117	0.485	0.322	0.648	.000	Random	72.40	.000	A5.a.4
	AZI	3	134	0.496	−0.510	1.501	>.05	Random	88.50	.000	
	MET	2	259	0.259	0.132	0.385	.000	Fixed	0.00	.381	
	MET + AMOX	7	764	0.536	0.335	0.737	.000	Random	65.80	.001	
CH	All	8	1,028	0.501	0.314	0.689	.000	Random	76.30	.000	A5.a.5
	AZI	2	110	0.592	−1.127	2.311	>.05	Random	88.60	.003	
	MET	2	259	0.259	0.132	0.385	.000	Fixed	0.00	.381	
	MET + AMOX	5	699	0.546	0.307	0.785	.000	Random	70.10	.001	

(Continues)

TABLE 3 (Continued)

				Weighted mean difference (WMD)					Heterogeneity		
		Number of			95% CI						
Perio	Test	Studies	Patients	WMD	Lower	Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
AG	All	3	89	0.438	0.191	0.695	.000	Fixed	29.40	.243	A5.a.6
	MET + AMOX	2	65	0.519	0.230	0.807	.000	Fixed	42.10	.189	
	AZI	1	24	0.220	−0.255	0.695	>.05	Random			
PPD (moderately deep)—6 months											
ALL	All	16	1,161	0.417	0.306	0.528	.000	Random	70.80	.000	A5.a.7
	AZI	5	152	0.128	−0.092	0.348	>.05	Random	69.70	.010	
	CLAR	1	40	0.140	−0.176	0.456	>.05	Random			
	MET	1	79	0.300	0.056	0.544	.016	Random			
	MET + AMOX	10	930	0.534	0.465	0.602	.000	Fixed	4.10	.406	
CH	All	7	858	0.426	0.286	0.566	.000	Random	74.80	.000	A5.a.8
	AZI	3	96	0.036	−0.116	0.189	>.05	Fixed	29.40	.243	
	MET	1	79	0.300	0.056	0.544	.016	Random			
	MET + AMOX	4	723	0.529	0.451	0.607	.000	Fixed	11.60	.340	
AG	All	9	303	0.401	0.205	0.597	.000	Random	67.40	.002	A5.a.9
	AZI	2	56	0.290	−0.200	0.779	>.05	Random	87.20	.005	
	CLAR	1	40	0.140	−0.176	0.456	.000	Random			
	MET + AMOX	6	207	0.549	0.406	0.692	.000	Fixed	10.40	.349	
PPD (moderately deep)—12 months											
ALL	All	8	851	0.557	0.428	0.686	.000	Random	66.30	.000	A5.a.10
	AZI	2	64	0.113	−1.208	1.434	>.05	Random	92.50	.000	
	MET	1	79	0.400	0.179	0.621	.000	Random			
	MET + AMOX	6	748	0.594	0.470	0.718	.000	Random	55.50	.017	
CH	All	5	762	0.515	0.374	0.656	.000	Random	65.80	.002	A5.a.11
	AZI	1	40	−0.600	−1.277	0.077	>.05	Random			
	MET	1	79	0.400	0.179	0.621	.000	Random			
	MET + AMOX	4	683	0.571	0.445	0.696	.000	Random	51.10	.046	
AG	All	3	89	0.749	0.574	0.924	.000	Fixed	41.40	.181	A5.a.12
	AZI	1	24	0.750	0.489	0.965	.000	Random			
	MET + AMOX	2	65	0.748	0.513	0.984	.000	Fixed	70.70	.065	

(Continues)

TABLE 3 (Continued)

Perio	Test	Number of Studies	Patients	Weighted mean difference (WMD)					Heterogeneity		
				WMD	95% CI Lower	95% CI Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
PPD (deep)—6 months											
ALL	All	16	1,161	0.969	0.755	1.183	.000	Random	66.90	.000	A5.a.13
	AZI	5	152	0.310	0.063	0.556	.014	Fixed	8.70	.357	
	CLAR	1	40	0.930	−0.008	1.868	>.05	Random			
	MET	1	79	0.700	0.189	1.211	.007	Random			
	MET + AMOX	10	930	1.211	1.013	1.409	.000	Random	43.80	.040	
CH	All	7	858	1.039	0.749	1.329	.000	Random	71.00	.000	A5.a.14
	AZI	3	96	0.261	−0.132	0.654	>.05	Fixed	0.00	.694	
	MET	1	79	0.700	0.189	1.211	.007	Random			
	MET + AMOX	4	723	1.316	1.016	1.615	.000	Random	63.70	.007	
AG	All	9	303	0.861	0.536	1.186	.000	Random	60.20	.010	A5.a.15
	AZI	2	56	0.341	0.025	0.658	.035	Fixed	71.90	.059	
	CLAR	1	40	0.930	−0.008	1.868	>.05	Random			
	MET + AMOX	6	207	1.073	0.828	1.317	.000	Fixed	0.00	.607	
PPD (deep)—12 months											
ALL	All	8	851	1.049	0.784	1.314	.000	Random	59.60	.003	A5.a.16
	AZI	2	64	0.543	0.077	1.009	.022	Fixed	67.20	.081	
	MET	1	79	0.800	0.282	1.318	.002	Random			
	MET + AMOX	6	748	1.191	0.888	1.495	.000	Random	60.10	.007	
CH	All	5	762	1.091	0.767	1.415	.000	Random	67.40	.001	A5.a.17
	AZI	1	40	−0.380	−1.516	0.756	>.05	Random			
	MET	1	79	0.800	0.282	1.318	.002	Random			
	MET + AMOX	4	683	1.226	0.878	1.573	.000	Random	67.10	.003	
AG	All	3	89	0.849	0.457	1.241	.000	Fixed	0.00	.416	A5.a.18
	AZI	1	24	0.730	0.219	1.241	.005	Random	19.70	.265	
	MET + AMOX	2	65	1.020	0.408	1.633	.000	Fixed	19.70	.265	

Abbreviations: All, all test groups combined; AMOX, amoxicillin; AZI, azithromycin; CI, confidence interval; CLAR, clarithromycin; Figure, refers to the figure number for forest plots in Appendix S5; MET, metronidazole; MET + AMOX, metronidazole + amoxicillin; MINO, minocycline; MOX, moxifloxacin; ORD, ornidazole; Perio, type of periodontitis; PLAC, placebo; SPIR, spiramycin; TET, tetracycline.

TABLE 4 Systemic antimicrobials: meta-analyses for clinical attachment level (CAL) changes in 6- and 12-month studies, in all initial PPD categories, in moderately deep PPD or in deep PPD, for all types of periodontitis (ALL), chronic periodontitis (CH) or aggressive periodontitis (AG)

				Weighted mean difference (WMD)					Heterogeneity		
		Number of			95% CI						
Perio	Test	Studies	Patients	WMD	Lower	Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
CAL (all sites)—6 months											
ALL	All	19	1,316	0.389	0.267	0.511	.000	Random	67.00	.000	A5.d.1
	AZI	7	253	0.315	0.120	0.511	.002	Fixed	44.80	.093	
	CLAR	2	77	0.564	−0.200	1.328	>.05	Random	95.70	.000	
	MET	1	79	0.130	−0.244	0.504	>.05	Random			
	MET + AMOX	8	867	0.358	0.284	0.432	.000	Fixed	44.80	.784	
	MINO	1	40	−0.030	−0.269	0.209	>.05	Random			
	MOX	1	40	0.620	0.321	0.919	.000	Random			
CH	All	11	1,036	0.399	0.219	0.579	.000	Random	76.00	.000	A5.d.2
	AZI	5	197	0.328	−0.062	0.718	>.05	Random	61.90	.033	
	CLAR	1	37	0.950	0.754	1.146	.000	Random			
	MET	1	79	0.130	−0.244	0.504	>.05	Random			
	MET + AMOX	4	723	0.356	0.268	0.444	.000	Fixed	0.00	.522	
	MINO	1	40	−0.030	−0.269	0.209	>.05	Random			
AG	All	8	280	0.349	0.242	0.457	.000	Fixed	0.00	.461	A5.d.3
	AZI	2	56	0.202	−0.282	0.752	>.05	Fixed	0.00	.800	
	CLAR	1	40	0.170	−0.078	0.418	>.05	Random			
	MET + AMOX	4	144	0.361	0.225	0.497	.000	Fixed	0.00	.794	
	MOX	1	40	0.620	0.321	0.919	.000	Random			
CAL (all sites)—12 months											
ALL	All	11	1,117	0.285	0.202	0.367	.000	Fixed	0.90	.442	A5.d.4
	AZI	3	134	0.614	0.177	1.051	.006	Fixed	52.90	.120	
	MET	2	259	0.223	0.009	0.437	.042	Fixed	0.00	.926	
	MET + AMOX	7	764	0.280	0.188	0.371	.000	Fixed	1.40	.425	
CH	All	8	1,028	0.263	0.175	0.352	.000	Fixed	0.00	.544	
	AZI	2	110	0.753	0.255	1.252	.030	Fixed	66.10	.086	A5.d.5
	MET	2	259	0.223	0.009	0.437	.042	Fixed	0.00	.926	
	MET + AMOX	5	699	0.253	0.153	0.352	.000	Fixed	0.00	.779	

(Continues)

TABLE 4 (Continued)

Perio	Test	Number of Studies	Patients	Weighted mean difference (WMD)					Heterogeneity		
				WMD	95% CI Lower	95% CI Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
AG	All	3	89	0.412	0.195	0.630	.000	Fixed	28.80	.245	A5.d.6
	AZI	1	24	0.150	−0.760	1,060	>.05	Random			
	MET + AMOX	2	65	0.428	0.204	0.652	.000	Fixed	59.50	.116	
CAL (moderately deep)—6 months											
ALL	All	15	1,129	0.361	0.267	0.455	.000	Random	49.00	.007	A5.d.7
	AZI	4	120	0.073	−0.067	0.213	>.05	Fixed	0.00	.637	
	CLAR	1	40	0.210	−0.106	0.526	>.05	Random			
	MET	1	79	0.300	0.100	0.500	.003	Random			
	MET + AMOX	10	930	0.470	0.397	0.544	.000	Fixed	0.00	.721	
CH	All	7	858	0.355	0.240	0.469	.000	Random	58.90	.005	A5.d.8
	AZI	3	96	0.070	−0.076	0.216	>.05	Fixed	0.00	.433	
	MET	1	79	0.300	0.100	0.500	.003	Random			
	MET + AMOX	4	723	0.466	0.383	0.549	.000	Fixed	0.00	.850	
AG	All	8	271	0.407	0.272	0.543	.000	Fixed	30.80	.182	A5.d.9
	AZI	1	24	0.110	−0.384	0.604	>.05	Random			
	CLAR	1	40	0.210	−0.106	0.526	>.05	Random			
	MET + AMOX	6	207	0.487	0.329	0.644	.000	Fixed	20.00	.283	
CAL (moderately deep)—12 months											
ALL	All	9	867	0.393	0.268	0.518	.000	Random	58.90	.003	A5.d.10
	AZI	2	64	0.321	−0.105	0.748	>.05	Fixed	3.80	.308	
	MET	1	79	0.200	−0.021	0.421	>.05	Random			
	MET + AMOX	7	764	0.424	0.280	0.567	.000	Random	64.30	.002	
CH	All	6	778	0.359	0.274	0.444	.000	Random	60.20	.005	A5.d.11
	AZI	1	40	−0.010	−0.777	0.757	>.05	Random			
	MET	1	79	0.200	−0.021	0.421	>.05	Random			
	MET + AMOX	5	699	0.401	0.247	0.554	.000	Random	63.80	.005	
AG	All	3	89	0.483	0.267	0.689	.000	Fixed	60.80	.078	A5.d.12
	AZI	1	24	0.470	−0.043	0.983	>.05	Random			
	MET + AMOX	2	65	0.557	0.020	1,095	.000	Random	80.40	.024	

(Continues)

TABLE 4 (Continued)

Perio	Test	Number of Studies	Patients	Weighted mean difference (WMD)				Model	Heterogeneity		Figure
				WMD	95% CI Lower	95% CI Upper	*p*-Value		I2 (%)	*p*-Value	
CAL (deep)—6 months											
ALL	All	15	1,129	0.789	0.586	0.992	.000	Random	57.80	.001	A5.d.13
	AZI	4	120	0.367	−0.077	0.812	>.05	Fixed	17.00	.306	
	CLAR	1	40	0.520	−0.412	1.452	>.05	Random			
	MET	1	79	0.600	0.157	1.043	.008	Random			
	MET + AMOX	10	930	0.880	0.646	1.114	.000	Random	62.70	.001	
CH	All	7	858	0.822	0.541	1.103	.000	Random	66.50	.001	A5.d.14
	AZI	3	96	0.299	−0.241	0.839	>.05	Fixed	41.60	.180	
	MET	1	79	0.600	0.157	1.043	.008	Random			
	MET + AMOX	4	723	0.941	0.609	1.272	.000	Random	71.20	.001	
AG	All	8	271	0.865	0.671	1.059	.000	Fixed	41.80	.100	A5.d.15
	AZI	1	24	0.510	−0.272	1,292	>.05	Random			
	CLAR	1	40	0.520	−0.412	1.452	>.05	Random			
	MET + AMOX	6	207	0.906	0.701	1.112	.000	Fixed	52.60	.061	
CAL (deep)—12 months											
ALL	All	9	867	0.805	0.587	1.023	.000	Random	47.70	.024	A5.d.16
	AZI	2	64	0.546	−0.084	1.176	>.05	Fixed	0.00	.626	
	MET	1	79	0.500	−0.007	1.007	>.05	Random			
	MET + AMOX	7	764	0.876	0.617	1.136	.000	Random	57.00	.010	
CH	All	6	778	0.828	0.571	1.085	.000	Random	58.40	.007	A5.d.17
	AZI	1	40	0.330	−0.742	1,402	>.05	Random			
	MET	1	79	0.500	−0.007	1.007	>.05	Random			
	MET + AMOX	5	699	0.900	0.606	1.195	.000	Random	64.40	.004	
AG	All	3	89	0.725	0.255	1.196	.003	Fixed	0.00	.665	A5.d.18
	AZI	1	24	0.660	−0.119	1.439	>.05	Random			
	MET + AMOX	2	65	0.763	0.172	1.353	.000	Fixed	0.00	.379	

Abbreviations: All, all test groups combined; AMOX, amoxicillin; AZI, azithromycin; CI, confidence interval; CLAR, clarithromycin; Figure, refers to the figure number for forest plots in Appendix S5; MET, metronidazole; MET + AMOX, metronidazole + amoxicillin; MINO, minocycline; MOX, moxifloxacin; ORD, ornidazole; Perio, type of periodontitis; PLAC, placebo; SPIR, spiramycin; TET, tetracycline.

outcomes evaluated. These data are in line with observations from previous systematic reviews (Haffajee et al., 2003; Herrera et al., 2012, 2002; Keestra, Grosjean, Coucke, Quirynen, & Teughels, 2015a, 2015b; Rabelo et al., 2015; Sgolastra, Gatto, et al., 2012; Sgolastra, Petrucci, et al., 2012; Sgolastra et al., 2014; Zandbergen et al., 2013, 2016).

4.2 | Level of evidence

The level of evidence varied substantially among the different antimicrobials studied; therefore, the effects of these agents should be considered separately. In general, data showed that MET + AMOX was the most relevant approach, in terms of significance and magnitude of the effects. The quality of the body of evidence for the benefits obtained with MET + AMOX was assessed as high, based on the results of 11 RCTs, 10 of them with low risk of bias and 7 providing data up to 1 year of follow-up. Adjunctive MET + AMOX led to statistically significant benefits over those obtained with SRP only in all clinical outcomes evaluated, including PPD reduction and CAL gain in the full mouth and in initially moderately deep and deep pockets, percentage of pocket closure (from PPD ≥ 4 to PPD ≤ 3 mm) and frequency of pockets ≥ 4, 5, 6 and 7 mm, as well as of sites showing BOP.

The level of evidence for the benefits brought about by the adjunctive use of MET and AZI was assessed as moderate, but the results for MET were more consistent. Although only two studies, both with low risk of bias, evaluated MET, the results were consistent in showing benefits of this antimicrobial in reducing mean PPD in the full mouth (at 1 year), in moderately deep and deep sites (at 6 months and 1 year), and in improving the percentage of pocket closure at 6 months and 1 year of follow-up. On the other hand, the findings of the seven studies (6 with low risk of bias) that assessed AZI were somewhat controversial. At 6 months, for example, the overall clinical effect showed a statistically significant gain in full-mouth CAL in favour of AZI; however, the results of the individual studies differed substantially for this parameter. While three studies showed benefits for the adjunctive agent (Emingil et al., 2012; Martande et al., 2016; Oteo et al., 2010), another four studies described none or minor benefits for this parameter (Haas et al., 2008; Han et al., 2012; Morales et al., 2018; Sampaio et al., 2011). At 1 year, the overall clinical effect on full-mouth CAL was maintained, together with a statistically significant benefit of AZI in reducing PPD in initially deep pockets. However, the few studies presenting data at 1 year were conflicting. Among the three studies with data available for full-mouth CAL, for example, two described minor or no benefit for this antibiotic (−0.02 and 0.15, respectively), and the major effect came from a single study (1.0), which was considered of high risk of bias (Martande et al., 2016).

The level of evidence for CLAR, MINO and MOX was considered low. Two RCTs assessed the effects of CLAR (Andere et al., 2017; Pradeep & Kathariya, 2011) and one of MINO (Basegmez, Berber, & Yalcin, 2011). No additional benefits from the use of these agents were observed at 6 months of follow-up, and 12-month data were not available for these antibiotics. The only RCT assessing MOX showed full-mouth greater reduction in mean PPD reduction and CAL gain, in comparison with the control group, with the use of this agent after 6 months.

4.3 | Comparison with other studies and reviews

The validity of the data set was ascertained by analysing the performance of the placebo treatment arms. At 6 months, the average PPD reduction of the placebo treatment arms was 1.58 mm (*SD* = 0.42) and 2.82 mm (*SD* = 1.10) for initially moderate and deep sites, respectively. This is in line with the WMDs (1.6 and 2.6 mm, respectively) reported by Suvan et al. (2020) and slightly higher than the reported mean PPD reductions of 1.07 mm (standard error, *SE* = .16) and 1.97 mm (*SE* = .19), respectively, by Hung and Douglass (2002). Also at 12 months, the average PPD reductions of 1.46 mm (*SD* = 0.22) and 2.91 mm (*SD* = 0.53) for initially moderate and deep sites, respectively, were slightly higher than the reported mean PPD reductions of 1.16 mm (*SE* = .10) and 2.20 mm (*SE* = .14; Hung & Douglass, 2002). These data ascertain that the obtained significant WMDs for the different systemic antimicrobials do not originate from a suboptimal performance of the control arms in these studies.

The data of the present study corroborate and extend the findings of previous meta-analysis on the effectiveness of certain systemic antimicrobial protocols, more specifically of MET + AMOX in the treatment of chronic and aggressive periodontitis (Assem et al., 2017; Chambrone et al., 2016; Feres et al., 2015; Haffajee et al., 2003; Keestra, Grosjean, Coucke, Quirynen, & Teughels, 2015a, 2015b; Rabelo et al., 2015; Sgolastra, Gatto, et al., 2012; Sgolastra, Petrucci, et al., 2012; Sgolastra et al., 2014; Zandbergen et al., 2013, 2016; Zhang, Zheng, & Bian, 2016). There is a general idea that systemic antimicrobials would provide larger benefits for subjects with aggressive periodontitis, but this was not confirmed in this study. Although small differences on the benefits of the antimicrobials were observed between chronic and aggressive periodontitis patients, these differences did not seem to be statistically significant and clinically relevant. This is in line with previous systematic reviews, showing that the effects of systemic antimicrobials on chronic and aggressive periodontitis patients were comparable (Keestra, Grosjean, Coucke, Quirynen, & Teughels, 2015a, 2015b). However, the observation made by Keestra et al. (2015b) that the benefits of MET + AMOX in aggressive periodontitis patients were more profound than those observed for chronic periodontitis at 6 and 12 months was not confirmed in the present study.

The lack of differences on the impact of systemic antimicrobials between aggressive and chronic periodontitis may be related to the fact that these conditions do not show major differences in the subgingival microbiota, or in the host response mechanisms to this microbiota (Duarte et al., 2015; Mombelli, Casagni, & Madianos, 2002). In fact, these concepts have been extensively discussed recently (Tonetti, Greenwell, & Kornman, 2018) and gave rise to a new classification system that recognized periodontitis as a single disease (Papapanou et al., 2018), and will help to personalize treatment according to the different categories established. Different protocols

of treatment would vary according to severity, complexity and distribution of the disease (stages) and the risk of progression (grades, e.g. percentage of bone loss/age and associated risk factors). According to the inclusion criteria and clinical profile of the study populations included in this review, apparently, the vast majority of studies recruited patients with periodontitis stages III and IV, and grades B and C. Thus, actually most of the current evidence regarding the benefits of systemic antimicrobials in periodontal treatment refers to these categories of disease. This is also in accord with the consensus statement of the 6th European Workshop, when it was posed that the use of systemic antimicrobials in periodontitis patients should be restricted to certain patients and certain periodontal conditions such as in severe and progressing forms of periodontitis (Sanz & Teughels, 2008).

It should be highlighted that the current review tried to overcome some drawbacks of previous reviews, by incorporating only placebo-controlled, parallel, double-blind studies with at least 6 months of follow-up and by analysing different antimicrobials separately. Additionally, most previously published systematic reviews have only analysed mean changes in full-mouth PPD, CAL and BOP,

TABLE 5 Systemic antimicrobials: meta-analyses for bleeding on probing (BOP) changes in 6- and 12-month studies, for all types of periodontitis (ALL), chronic periodontitis (CH) or aggressive periodontitis (AG)

				Weighted mean difference (WMD)					Heterogeneity		
		Number of			95% CI						
Perio	Test	Studies	Patients	WMD	Lower	Upper	*p*-Value	Model	I2 (%)	*p*-Value	Figure
BOP—6 months											
ALL	All	19	1,324	6.640	4.201	9.078	.000	Random	49.30	.003	A5.e.1
	AMOX	1	31	7.200	−5.466	19.866	>.05	Random			
	AZI	7	253	3.258	0.151	6.366	.040	Fixed	0.00	.614	
	CLAR	1	40	−4.300	−14.380	5.780	>.05	Random			
	MET	2	109	9.131	1.117	17.146	.026	Fixed	0.00	.903	
	MET + AMOX	10	921	10.014	6.846	13.182	.000	Random	46.20	.030	
	MOX	1	40	−2.200	−8.051	3.651	>.05	Random			
CH	All	10	1,020	7.441	5.474	9.408	.000	Fixed	20.20	.218	A5.e.2
	AMOX	1	31	7.200	−5.466	19.866	>.05	Random			
	AZI	5	185	3.681	0.263	7.100	.035	Fixed	0.00	.506	
	MET	2	109	9.131	1.117	17.146	.026	Fixed	0.00	.903	
	MET + AMOX	5	753	9.407	6.833	11.980	.000	Fixed	17.20	.290	
AG	All	9	304	5.519	0.630	10.460	.002	Random	67.40	.002	A5.e.3
	AZI	2	56	1.246	−6.210	8.702	>.05	Fixed	0.00	.368	
	CLAR	1	40	−4.300	−14.380	5.780	>.05	Random			
	MET + AMOX	5	168	11.187	4.313	18.062	.000	Random	69.10	.012	
	MOX	1	40	−2.200	−8.051	3.651	>.05	Random			
BOP—12 months											
ALL	All	10	937	9.727	6.731	12.722	.000	Random	89.30	.000	A5.e.4
	AZI	3	134	1.307	−2.581	5.195	>.05	Fixed	60.10	.081	
	MET	1	79	10.700	0.662	20.738	.037	Random			
	MET + AMOX	7	764	12.544	9.668	15.419	.000	Random	87.50	.000	
CH	All	7	848	10.021	6.884	13.159	.000	Random	91.00	.000	A5.e.5
	AZI	2	110	−0.627	−10.917	9.664	>.05	Random	76.30	.040	
	MET	1	79	10.700	0.662	20.738	.037	Random			
	MET + AMOX	5	699	12.503	9.475	15.530	.000	Random	89.80	.000	
AG	All	3	89	8.269	0.979	15.559	.000	Fixed	66.50	.051	A5.e.6
	AZI	1	24	−4.940	−19.161	9.281	>.05	Random			
	MET + AMOX	2	65	12.978	4.487	21.469	.003	Fixed	32.10	.225	

Abbreviations: All, all test groups combined; AMOX, amoxicillin; AZI, azithromycin; CI, confidence interval; CLAR, clarithromycin; Figure, refers to the figure number for forest plots in Appendix S5; MET, metronidazole; MET + AMOX, metronidazole + amoxicillin; MINO, minocycline; MOX, moxifloxacin; ORD, ornidazole; Perio, type of periodontitis; PLAC, placebo; SPIR, spiramycin; TET, tetracycline.

which may mask the most clinically relevant effects of systemic antimicrobials occurring in deeper sites. Full-mouth PPD, CAL and BOP often lead to small magnitudes of differences, which many times hampers the use of the results of the reviews for decision-making in clinical practice (Sgolastra et al., 2014). In an attempt to minimize this problem, the current systematic review presented data for full-mouth PPD reduction and CAL gain, as well as in initially moderately deep and deep pockets, percentage of pocket closure and frequency of residual pockets. For the latter two outcome measures, no previous systematic reviews and meta-analyses are available so far, hampering a more direct comparison with the data presented here.

MET + AMOX was the only antimicrobial protocol more effective than SRP in improving all the outcomes evaluated, including an important effect in reducing the number of residual pockets and in the percentage of sites with BOP. These results have direct clinical implications, since previous comprehensive risk assessment studies have showed that the presence of residual pockets after treatment is an important risk indicator for disease recurrence (Matuliene et al., 2008, 2010). Other authors have also discussed the association between the presence of residual pockets, with and/or without BOP and the lack of periodontal stability (Borges et al., 2017; Cionca et al., 2009; Feres et al., 2012; Lang & Tonetti, 2003). Thus, these clinical benefits of MET + AMOX in reducing residual sites and BOP can impact the long-term clinical stability of treated periodontitis patients together with the advantage of reducing the need of periodontal surgeries. Although not as evident as MET + AMOX, MET also had an effect, over those obtained with SRP, in reducing PPD and gaining CAL in initially moderately deep and deep sites. The benefits of MET in the periodontal treatment has also been suggested in a previous systematic review with meta-analysis (Sgolastra et al., 2014). On the other hand, the only observed benefit of AZI in residual sites was in improving PPD of deep pockets at 1 year. The fact that AZI had a lower efficacy than MET or MET + AMOX is in contradiction with the conclusions of a previous review (Zhang et al., 2016), probably because of differences in the inclusion criteria between both systematic reviews. No conclusion can be made for the other types of antimicrobials due to the low number of studies available.

Another point that should be considered is that, although no meta-analysis could be performed for the PROMs, the overall data suggested that MET + AMOX were associated with more side effects than the other antimicrobial protocols. Although these side effects were not always present and were also observed in the control groups, one serious event was reported with one patient from Harks et al. (2015), out of over 800 patients evaluated in the MET + AMOX studies.

4.4 | Limitations

The main limitation of this systematic review was the considerable differences observed in the treatment protocols of the included studies, such as (a) previous treatments of volunteers prior to SRP; (b) differences in how SRP was executed (e.g. duration, use of anaesthetics, additional use of antiseptics, full-mouth or staged SRP, mechanical debridement); (c) dosage and duration of antimicrobials; and (d) volunteers included (e.g. severity of the disease, sample size, percentage of smokers). However, none of these variables were taken into consideration in the meta-analyses because of the limited number of studies available. On the other hand, due to the inclusion of only placebo-controlled studies, the risk of bias was reduced, with only 7 out of the 28 studies having a high risk of bias.

One limitation related to the available evidence for the use of systemic antimicrobials is that the analysis was restricted to 12 months of follow-up. At the moment, there are only two studies available with a follow-up time of 2 years (Berglundh et al., 1998; Harks et al., 2015). Berglundh et al. (1998) did not perform an inter-group analysis. Harks et al. (2015) showed significant differences between placebo and MET + AMOX for PPD, CAL, BOP and percentage of moderately deep and deep sites at 2 years. There is only one study available with a follow-up time of 5 years, which did not show significant differences between placebo and MET at 5 years post-treatment (Preus et al., 2017). Unfortunately, with the exception of CAL, that study does not provide outcome data that allows a proper evaluation of the 5-year follow-up period. Additionally, one has to consider that the patients in this study had low severity of disease that may not represent the clinical profile that benefits the most from adjunctive antimicrobials. Therefore, there is currently no conclusive long-term evidence (over 2 years) for the benefits of systemic antimicrobials as adjuncts to SRP.

The wide variety in antimicrobial prescriptions leads to another critical limitation, since no consistent evidence is available to decide dosages and duration. For example, for MET + AMOX, different durations have been compared (Borges et al., 2017; Cosgarea et al., 2017, 2016). In one study (Cosgarea et al., 2017, 2016), it was shown that 3 and 7 days of antimicrobial intake was both more effective than the control group receiving SRP, while another study (Borges et al., 2017) concluded that 14 days of MET + AMOX was more effective than 7 days, in a population with very advanced disease. The dosage of MET was also tested (Borges et al., 2017), and no important differences were observed between 250 and 400 mg of the agent.

It remains debatable to which extent the observed statistically significant WMDs are clinically relevant. There is currently no consensus from which point on an effect size is clinically relevant. When considering effect size, however, for all systemic antimicrobials combined, the full-mouth WMDs at 6 (0.448 mm) and 12 months (0.485 mm) represent an additional full-mouth average PPD reduction of 45.93% (*SD* = 34.86) and 43.71% (*SD* = 30.85), respectively, when compared to placebo. For MET + AMOX, the full-mouth WMD for PPD reduction at 12 months (0.536 mm) represents an additional full-mouth average PPD reduction of 49.11% (*SD* = 25.05); the reduction for moderately deep sites was 0.594 mm (45.57%, *SD* = 19.45) and for deep sites 1.191 mm (52.36%, *SD* = 28.02). Additionally, these changes corresponded to an additional reduction of 60.56% (*SD* = 17.63) of residual

sites with PPD ≥ 5 mm at 12 months post-treatment. For the percentage of pocket closure, the WMDs at 6 months (15.74%) and 12 months (13.72%) corresponded to an additional reduction of 43.84% (*SD* = 31.13) and 27.29% (*SD* = 18.75%), respectively, when compared to placebo.

Other unanswered questions regarding the use of systemic antimicrobials in periodontal treatment include whether these agents should be administered during the initial phase of treatment or after the healing phase (e.g. at 3 months post-SRP) and the effects of these drugs in changing the microbiome.

One final limitation is that, despite favourable clinical effects, excessive and incorrect use of systemic antimicrobials contributes to the emergence specific-drug-resistant and multi-drug-resistant bacterial species (Elias et al., 2017; World Health Organization, 2014a, 2014b). A single course of systemic antimicrobial administration can result in an increase, albeit transient, in the percentage of resistant oral bacterial species (Feres et al., 2002; Zaura et al., 2015). However, at least one study also showed a concomitant long-lasting impact of such a single course of systemic antimicrobials on the faecal microbiome, including an increase in genes associated with antimicrobial resistance (Zaura et al., 2015). In terms of frequency of exposure to systemic antimicrobials, it should be noted that the antimicrobial resistance profiles of periodontopathogens are higher in a population with a higher frequency of exposure to systemic antimicrobials (van Winkelhoff, Herrera, Oteo, & Sanz, 2005). This should warn us for an unrestricted use of systemic antimicrobials since antimicrobial drug resistance is globally a serious socio-economic and health problem. A recent study estimated over 600,000 infections with antibiotic-resistant bacteria yearly in the European Union and in the European Economic Area. These infections accounted for an estimated 33,000 attributable deaths and 870,000 disability-adjusted life-years (Cassini et al., 2019). Relevant institutions to control the global emergence of bacterial resistance, such as the World Health Organization (World Health Organization, 2014a, 2014b) and the European Centre for Disease Prevention and Control (European Centre for Disease Prevention & Control, 2017), have suggested a rationale and prudent use of systemic antimicrobials. Thus, their use should be restricted as much as possible to patients where the systemic antimicrobial makes a clinically relevant difference. Although some recent evidence (Eickholz et al., 2019) suggested that certain specific patient profiles may benefit more from systemic antimicrobial therapy, the precise effect of these agents in different stages and grades of periodontitis is yet to be determined.

5 | CONCLUSIONS

Within the limitations of this systematic review, it can be concluded that:

- The use of systemic antimicrobials as an adjunct to SRP, specifically MET + AMOX, results in statistically significant greater PPD reduction, higher percentage of pocket closure, reduction in frequency of pockets of ≥4, ≥5, ≥6 and ≥7 mm, CAL gain and BOP reduction.
- The additional PPD reduction and CAL gain elicited by MET + AMOX, and to a lesser extent by MET and AZI, are more pronounced in initially deep than in initially moderately deep pockets.
- These clinical effects are maintained up to 12 months after their use.
- There is currently no evidence above 2 years of follow-up for the benefits of systemic antimicrobials as adjuncts to SRP.
- There are no indications that the effect of systemic antimicrobials is different between aggressive and chronic periodontitis patients.
- Among the different types of systemic antimicrobials, the use of MET + AMOX is associated with the largest frequency of side effects.
- MET and AZI have a significant impact on some outcome measures, but smaller than MET + AMOX in terms of magnitude.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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