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SYSTEMATIC REVIEW

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Efficacy of adjunctive measures in the non-surgical treatment of peri-implantitis: A systematic review

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Abstract

Aim: The aim of this systematic review was to evaluate the efficacy of patient-performed or administered adjunctive measures to non-surgical peri-implantitis therapy in terms of probing depth (PD) and/or bleeding on probing (BoP) reductions.

Materials and Methods: Randomized and controlled clinical trials with at least 6 months of follow-up were searched in three databases. Secondary outcomes included implant loss, disease resolution, recurrence of peri-implantitis, need of re-treatment, changes in marginal bone levels, patient-reported outcomes and adverse effects.

Results: Of 567 titles, 10 publications, reporting 9 investigations, were included. Three types of adjunctive measures were found (local/systemic antimicrobials and probiotics). Four studies evaluated the effects of local antimicrobials (i.e., minocycline microspheres, chlorhexidine chips or a metronidazole + amoxicillin gel), three studies evaluated systemic antimicrobials (either amoxicillin + metronidazole or metronidazole alone) and two studies evaluated probiotics (*Lactobacillus reuteri* strains). The addition of local antimicrobials led to modest improvements in PD reduction. Systemic antimicrobials showed significantly greater reductions in PD and BoP, especially at initially deep sites (PD > 6 mm). Due to the large heterogeneity among included studies, no meta-analyses were performed.

Conclusions: Different adjunctive measures in the non-surgical treatment of peri-implantitis have different impact in terms of PD and BoP reductions. Improved PD reductions result after the use of systemic antimicrobials, and to a lesser extent, after the use of local antimicrobials.

KEYWORDS
adjuncts, antimicrobials, non-surgical treatment, peri-implantitis, probiotics

Clinical Relevance

Scientific rationale for study: There is no consensus on the standard treatment of peri-implantitis, mainly because the predictability of different treatment approaches has proven to be limited or controversial. Therefore, it is important to know the potential beneficial role of different adjuncts to the non-surgical treatment of peri-implantitis.

Principal findings: The efficacy of different adjuncts seems to be disparate. While systemic antimicrobials may provide significant added benefits in terms of PD reductions even in the long term, the effect of local antimicrobials seems to be lower. Other adjuncts such as probiotics do not provide any added benefit. Home-use antiseptics, risk factor control interventions or other adjuncts have not been properly evaluated.

Practical implications: Systemic antimicrobials and, to a lesser extent, local antimicrobials may provide additional benefits in terms of PD reduction in the non-surgical treatment of peri-implantitis as compared with mechanical debridement alone. The added benefit seems to be more pronounced at initially deep sites (PD > 6 mm). Cost-effectiveness of these interventions has not been assessed.

1 | INTRODUCTION

Peri-implantitis is defined as a pathological condition affecting the peri-implant tissues and associated with dental biofilm accumulation. It is characterized by inflammation of the peri-implant mucosa and the subsequent progressive loss of bone (Berglundh et al., 2018). Although implant survival is higher than 90% after more than 10 years of follow-up (Howe et al., 2019), the prevalence of peri-implant diseases is also very significant when considering the case definition criteria proposed by the VIII European Workshop on Periodontology (Sanz et al., 2012). In fact, a recent systemic review reported a prevalence of 18.5% and 12.8% at the patient and implant levels, respectively (Dreyer et al., 2018).

There seems to be no consensus on treatment standards for the management of peri-implant diseases (Derks et al., 2022; Figuero et al., 2014; Renvert et al., 2013; Schwarz & Ramanauskaite, 2022). This is attributable to the high heterogeneity in the use of different therapeutic approaches, showing moderately successful treatment outcomes (Renvert & Polyzois, 2018). It has been shown that non-surgical treatment is effective in the management of peri-implant mucositis (Suarez-Lopez Del Amo et al., 2016). On the contrary, the non-surgical therapy of peri-implantitis may not be effective in a significant percentage of cases, especially in those with more advanced pathology and more complex peri-implant defect configuration (Renvert et al., 2008). With the aim of improving the outcome of non-surgical therapy, the adjunctive use of systemic/local antibiotics or probiotics has been evaluated, showing promising results in an important number of cases (Estefania-Fresco et al., 2019; Galofre et al., 2018; Linares et al., 2019; Machtei et al., 2012; Mombelli et al., 2001; Nart et al., 2020; Renvert et al., 2006).

However, when putting together all the studies, the efficacy of these and other adjunctive measures (e.g., risk factor control interventions, antimicrobial toothpastes/mouth rinses, and so on) to the non-surgical treatment of peri-implantitis remains unclear.

Thus, the objective of the present systematic review was to answer the following PICOS question: In patients diagnosed with peri-implantitis, which is the efficacy of patient-performed or administered adjunctive measures to non-surgical therapy as compared with no adjunct, in terms of probing depth (PD) and/or bleeding on probing (BoP) reductions, reported in randomized clinical trials (RCTs) or controlled clinical trials (CCTs) with at least 6 months of follow-up?

2 | MATERIALS AND METHODS

2.1 | Protocol development and focused question

The protocol of this systematic review followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Page et al., 2021). The review protocol was registered and allocated the identification number CRD42022325374 in the PROSPERO International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination, University of York, National Institute for Health Research (United Kingdom). The protocol aims at answering the following focused question (PICOS): 'In patients diagnosed with peri-implantitis (population), which is the efficacy of patient-performed or administered adjunctive measures to non-surgical therapy (intervention) as compared to no adjunct (comparison), in terms of PD and/or bleeding on probing reductions (primary outcomes), reported in RCTs or CCTs with at least 6 months of follow-up (study design)?'

2.1.1 | Eligibility criteria

Inclusion criteria (PICOS)

- *Population*: patients diagnosed with peri-implantitis, independently of the definition used in each investigation.
- *Intervention*: non-surgical supra-/sub-mucosal instrumentation with adjunctive measures (e.g., locally delivered antimicrobials with sustained release, systemic antimicrobials, probiotics, and so on) and any patient-performed or administered adjunctive measures by prescription (e.g., mouth rinses/toothpastes with antimicrobial agents, sub-marginal deposition or irrigation with antimicrobial agents, smoking cessation interventions, and so on).
- *Comparison*: non-surgical supra-/sub-mucosal instrumentation without those adjunctive measures (or with placebo or negative controls).
- Outcome: changes in PD and/or BoP.
- *Study design*: RCTs or CCTs with a minimum follow-up time of 6 months and a minimum of 10 patients per treatment arm.

Exclusion criteria

Studies focusing on patients with only peri-implant mucositis.

2.1.2 | Type of intervention and comparisons

Studies were selected when including any type of patient-performed or administered adjunctive measure to non-surgical treatment of peri-implantitis. These could include locally delivered antimicrobials with sustained release, systemic antimicrobials, probiotics, mouth rinses/toothpastes with antimicrobial agents, sub-marginal deposition or irrigation with antimicrobial agents, smoking cessation interventions, and so on.

2.1.3 | Type of outcomes

The primary outcome was PD reduction and/or BoP reduction.

The following secondary outcomes were considered:

- Implant survival/loss (%);
- Different composite outcomes to assess disease resolution (e.g., absence of PDs) > 6 mm, absence of BoP/suppuration and absence of further bone loss after treatment >0.5 mm (Carcuac et al., 2016);
- Changes in peri-implant outcomes, including:
  - Recurrence of peri-implantitis at patient and/or implant level (bone loss >1.0 mm, need of re-treatment [non-surgical or surgical]);
  - Changes in plaque indices (PIs);
  - Changes in marginal bone levels (MBLs).
- Side effects, aesthetic complications, patient-reported outcome measures (PROMs) and economic factors.

2.2 | Information sources and search

2.2.1 | Electronic search

Three electronic databases were used as sources in the search for studies satisfying the inclusion criteria: (1) PubMed; (2) Cochrane Library (including Cochrane Database for Systematic Reviews and Cochrane CENTRAL register for Clinical Trials); and (3) Scopus. These databases were searched for studies published up until March 2022. The search was limited to human subjects and to studies reported in English. No more languages were considered due to the limited time for the preparation of this systematic review.

2.2.2 | Manual search

All reference lists of the included studies and previously published systematic reviews were checked for cross-references. The following journals were hand-searched from 2012 to 2022: Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Implants Research, International Journal of Oral and Maxillofacial Implants, European Journal of Oral Implantology, Implant Dentistry, The International Journal of Periodontics and Restorative Dentistry, and Clinical Implant Dentistry and Related Research.

2.2.3 | Search strategy

Information on the search strategy can be accessed in Appendix S1.

2.3 | Screening methods

Two reviewers independently screened the titles and abstracts (Ana Molina and Juan Blanco). The same reviewers selected full manuscripts of studies meeting the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision. Any disagreement was solved by discussion with a third reviewer (Eduardo Montero). The inter-reviewer reliability (percentage of agreement and kappa correlation coefficient) for the titles/abstracts and for the full-text analysis was calculated

2.4 | Data extraction

Three different reviewers performed data extraction (Antonio Liñares, Ignacio Sanz-Sánchez and Eduardo Montero). When data were incomplete or missing, the authors of the studies were contacted for clarification. If agreement could not be reached, data were excluded until further clarification was available. When the results of a study were published more than once, the data were used upon necessity depending on the follow-up presented. If a study was comparing more than two arms, the data from the groups of interest were extracted.

2.5 | Quality assessment (risk of bias in individual studies)

Quality assessment of the included studies was performed by one reviewer (José Dopico). Cochrane recommendations for risk of bias assessment were followed. RoB 2 tool was used for risk of bias assessment in randomized controlled trials (Sterne et al., 2019).

2.6 | Risk of bias across studies

The publication bias was evaluated using a Funnel plot and the Egger's linear regression method for the primary outcome. A sensitivity analysis of the meta-analysis results was also performed for this outcome.

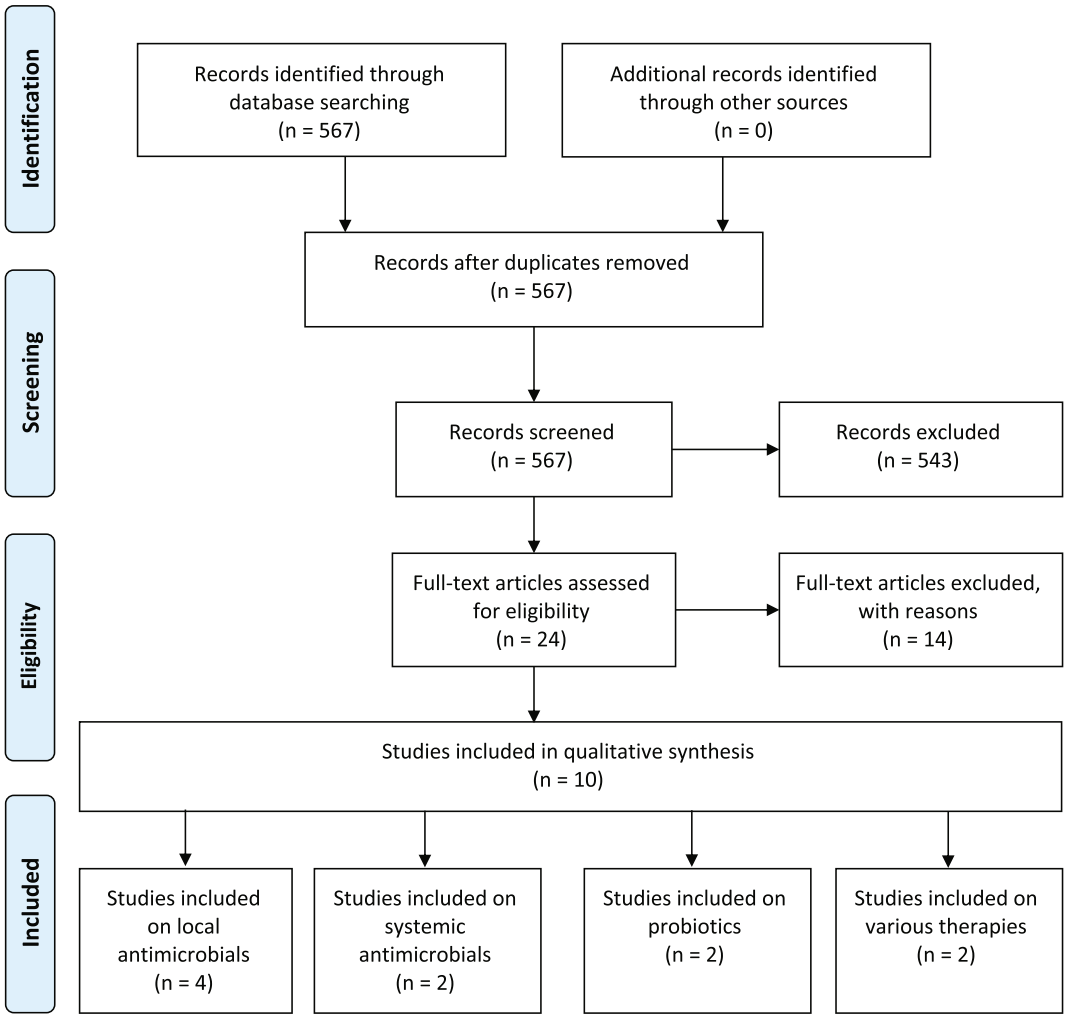

FIGURE 1 Flow chart depicting the article selection process.

2.7 | Data analyses

Means, standard deviations and 95% confidence intervals (CIs) were extracted and summarized in the Results section (Section 3). If possible, meta-analyses were performed (i.e., studies with similar designs, treatment methods and frequency, etc.). In these cases, the statistical heterogeneity among studies was assessed using the *Q* test based on chi-square statistics as well as the I^2 index (Higgins et al., 2003) in order to know the percentage of variation in the global estimate that was attributable to heterogeneity. To summarize and compare studies, mean values of primary and secondary outcomes were directly pooled and analysed with weighted mean differences (WMDs) and 95% CIs. Study-specific estimates were pooled with both the fixed- and random-effect models (DerSimonian & Laird, 2015). If a significant and high heterogeneity was found, then the random-effect model results were presented. STATA® (StataCorp LP, Lakeway Drive, College Station, Texas, USA) software was used to perform all analyses. Statistical significance was defined as a p value < .05.

3 | RESULTS

3.1 | Search

Figure 1 depicts the flow chart summarizing the results of the selection process. The search rendered 567 titles, which after evaluating their titles and abstracts, resulted in 17 articles for full-text analysis (agreement between reviewers 98.6%, kappa = 0.83; 95% CI [0.75; 0.94]). After full-text evaluation, 10 published articles were included for data extraction (agreement 92.0%; kappa = 0.85; 95% CI [0.77; 0.92]). Since two papers reported the results of a study at different time points (Bassetti et al., 2014; Schar et al., 2013), nine investigations were included at the end. Reasons for exclusion of the remaining studies are detailed in Table S1.

3.2 | Description of selected studies

Table 1 depicts the methodological characteristics of the selected studies. All the included investigations were RCTs with a parallel

TABLE 1 Methodological characteristics of the included studies.

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
Local antimicrobials						
Machtei et al. (2012)	Multi-centre RCT (parallel) 6 months University Israel Funding: Dexcel Pharma research grant.	Peri-implantitis: PD 6–10 mm + BoP and radiographic evidence of BLoss NR Years in function: NR	*Total*: $N = 60/56$ subjects; 77/73 implants • Tests: $N = 30/30$ subjects; 40 implants • Controls: $N = 30/26$ subjects; 37 implants *Age*: 59.2 (27–77) years old • Tests: 57.4 ± 10.5 years old • Controls: 61.0 ± 7.9 years old *Sex*: 58.3% females • Tests: 66.7% females • Controls: 50% females *Systemic condition*: all healthy *Tobacco smoking*: 16.7% smokers • Tests: 16.7% smokers • Controls: 16.7% smokers	*Test*: OHI + full-mouth supra-gingival scaling + sub-gingival debridement + sub-mucosal application of 2.5 mg chlorhexidine chips (up to four chips per pocket). Chlorhexidine chips were re-inserted in target sites presenting PD ≥ 6 mm at 2, 4, 6, 8 and 12 weeks. *Note*: use of toothpicks or interproximal hygiene was avoided for 10 days *Control*: OHI + full-mouth supra-gingival scaling + sub-gingival debridement + sub-mucosal application of placebo gelatine matrix chips.	Supra-gingival debridement: 12 weeks Follow-up visits: 2, 4, 6, 8, 12, 18 and 24 weeks	PD, CAL, Rec, BoP, PI, GI
Schar et al. (2013), Bassetti et al. (2014)	RCT (parallel) 12 months University Switzerland Funding: Bredent Medical GmbH & Co. KG, Geschäftsbereich HELBO, Walldorf, Germany	Initial peri-implantitis: PD 4–6 mm + BoP at ≥1 peri-implant site and radiographic BLoss 0.5–2.0 mm between prosthesis delivery and pre-screening appointment Straumann; sandblasted and acid-etched (SLA) Years in function: 7.4 (2.6–15) years • Tests: 7.3 (4–14.8) years • Controls: 7.2 (2.6–15) years	*Total*: $N = 40/38$ subjects • Tests: $N = 20/19$ subjects • Controls: $N = 20/19$ subjects *Age*: 58 (27–78) years old • Tests: 59 (29–78) years old • Controls: 57 (29–75) years old *Sex*: 50% females • Tests: 50% females	*Test*: OHI + mechanical debridement with titanium curettes and glycine-based powder for sub-gingival removal under local anaesthesia +3% H_2O_2 irrigation +1 mg minocycline hydrochloride microspheres *Note*: flossing was avoided 10 days after minocycline microspheres application *Control*: OHI + mechanical debridement with titanium	OH reinforcement: 1, 2, 4, and 8 weeks Follow-up visits: 3, 6, 9 and 12 months; in case of BoP recording at these visits, initial therapy was repeated	PD, CAL, Rec, BoP, mPI, disease resolution, microbiological outcomes, biomarkers in GCF

TABLE 1 (Continued)

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
			• Controls: 50% females *Systemic condition*: all healthy *Tobacco smoking*: 0% smokers • Tests: 0% smokers • Controls: 0% smokers	curettes and glycine-based powder for sub-gingival removal under local anaesthesia +2 sessions PDT with diode laser (baseline and 7 days later) + 3% H_2O_2 irrigation		
Machtei et al. (2021)	Multi-centre RCT (parallel) 6 months University and private practice Israel, USA, Germany, UK Funding: Dexcel Pharma research grant.	Peri-implantitis: implants in function for >2 years, with fixed restorations and PD 5–8 mm + BoP and/or suppuration and radiographic BLoss ≥3.0 mm from the implant shoulder with ≥2 mm residual bone support Various implant systems Years in function: >2 years	*Total*: $N = 290/290$ subjects; 386 implants • Tests: $N = 146/146$ subjects; 196 implants • Controls: $N = 144/144$ subjects; 189 implants *Age*: 62.5 (23.8–87.4) years old • Tests: 62.5 (25.5–86.9) years old • Controls: 62.6 (23.8–87.4) years old *Sex*: 59.3% females • Tests: 62.3% females • Controls: 53.3% females *Systemic condition*: all apparently healthy *Tobacco smoking*: 10% smokers • Tests: 10.3% smokers • Controls: 9.7% smokers	*Test*: OHI + full-mouth supra-gingival scaling + supra- and sub-gingival debridement + sub-mucosal application of chlorhexidine chips (up to two chips per pocket, depending on pocket width) every 2 weeks for 12 weeks *Control*: OHI + full-mouth supra- and sub-gingival scaling + supra-gingival debridement every 2 weeks for 12 weeks *Note*: patients were instructed to refrain from using chlorhexidine-based oral rinses throughout the study and toothpicks and floss for at least 24 h after treatment	OH reinforcement and sub-gingival debridement: 12 weeks Follow-up visits: 8, 12, 16 and 24 weeks	PD, Rec, BoP, PI, GI
Ahmed et al. (2020)	RCT (parallel) 6 months University Saudi Arabia	Peri-implantitis: PD ≥ 6 mm + BoP and/or suppuration at ≥1 peri-implant site +CAL ≤ 3 mm and radiographic BLoss ≥3 mm	*Total*: $N = 60/60$ subjects • Tests 1: $N = 20/20$ subjects	*Test 1*: OHI + full-mouth mechanical debridement with US under local anaesthesia + sub-gingival single topical application of	Follow-up visits: 3 and 6 months	PD, BoP, PI, radiographic outcomes and GCF biomarkers (IL-6 and TNF-α)

(Continues)

TABLE 1 (Continued)

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
	Funding: Deputyship for Research & Innovation, Ministry of Education, Saudi Arabia IFKSURG-1438-024	apical to the most coronal portion of the intraosseous part of the implant NR Years in function: NR	• Tests 2: $N = 20/20$ subjects • Controls: $N = 20/20$ subjects *Age*: • Tests 1: 51.4 ± 6.7 years old • Tests 2: 48.9 ± 4.5 years old • Controls: 50.7 ± 5.9 years old *Sex*: 0% females • Tests 1: 0% females • Tests 2: 0% females • Controls: 0% females *Systemic condition* T2DM patients (HbA1c levels ≥6.5%) *Tobacco smoking*: 0% smokers • Tests 1: 0% smokers • Tests 2: 0% smokers • Controls: 0% smokers	antibiotic gel (metronidazole 400 mg + amoxicillin 500 mg) + chlorhexidine 0.12% mouthwash twice per day *Test 2*: OHI + full-mouth mechanical debridement with US under local anaesthesia + single session of PDT with diode laser + chlorhexidine 0.12% mouthwash twice per day *Control*: OHI + full-mouth mechanical debridement with US under local anaesthesia		
Systemic antimicrobials						
Shibli et al. (2019)	RCT (parallel) 12 months University Brazil Funding: FAPESP (Sao Paulo Research Foundation) #05/01939-2 and 05/03557-0 grants	Peri-implantitis: implants in function for ≥5 years, with PD >5 mm + BoP and/or suppuration, and radiographic BLoss >4.0 mm with ≥50% residual bone support NR; machined surface, external hexagon Years in function: 5 years ±6.3 months • Tests: NR • Controls: NR	*Total*: $N = 40/40$ subjects/implants • Tests: $N = 20/20$ subjects/implants • Controls: $N = 20/20$ subjects/implants *Age*: 58.1 years old • Tests: NR • Controls: NR *Sex*: 72.5% females • Tests: NR • Controls: NR *Systemic condition* healthy	*Test*: OHI + full-mouth prophylaxis + non-surgical debridement with Teflon curettes + systemic antimicrobials (400 mg metronidazole +500 mg amoxicillin, three times per day, for 14 days) *Control*: OHI + full-mouth prophylaxis + non-surgical debridement with Teflon curettes + placebo pills	Periodontal supra-gingival maintenance therapy every 3 months Follow-up visits: 14 days, 3, 6 and 12 months	PD, CAL, BoP, Sup, PI, microbiological outcomes, radiographic outcomes, success (composite outcome: PD < 5 mm, no BoP, no BLoss between baseline and 1 year)

TABLE 1 (Continued)

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
			Tobacco smoking: 0% smokers • Tests: 0% smokers • Controls: 0% smokers			
Blanco et al. (2022)	RCT (parallel) 12 months University Spain Funding: Osteology Foundation (grant 16-070), Spanish Society of Periodontology SEPA (research scholarship 2018) Sponsoring: SUNSTAR IBERIA, S.L.U. (perio-implant diagnostic test and analysis)	BoP and/or suppuration, PD ≥ 6 mm and BLoss ≥3 mm after initial remodelling Various implant systems; rough surface Years in function: NR	*Total*: $N = 32/32$ subjects; 62/62 implants • Tests: $N = 16/16$ subjects; 28/28 implants • Controls: $N = 16/16$ subjects; 34/34 implants *Age*: • Tests: 58 (51–65) years old • Controls: 60 (55–65) years old *Sex*: 59% females • Tests: 44% females • Controls: 75% females *Systemic condition*: 12.5% systemic diseases • Tests: 19% systemic diseases • Controls: 6% systemic diseases *Tobacco smoking*: 28% smokers • Tests: 25% smokers • Controls: 31% smokers	*Test*: *Pre-treatment*: • Supra-gingival debridement • Elimination/reduction of plaque-retentive factors, including prosthesis modification (if needed) • OHI until FMPS ≤ 20% *Intervention*: • Sub-marginal instrumentation with US metal tips and simultaneous irrigation of 0.12% chlorhexidine digluconate • Curettage with steel curettes • 0.12% chlorhexidine digluconate irrigation of peri-implant pockets • Systemic metronidazole 500 mg ×3/7 days *Control*: *Pre-treatment*: • Supra-gingival debridement • Elimination/reduction of plaque-retentive factors, including prosthesis modification (if needed) • OHI until FMPS ≤ 20% *Intervention*:	OH reinforcement: 1 week, 3, 6, and 12 months Follow-up visits: 3, 6, and 12 months; all patients received supra-gingival debridement and sub-mucosal debridement with chlorhexidine digluconate irrigation only in sites with PD ≥ 5 mm	Implant loss, PD, Rec, BoP, PI, success criteria, MBL, PD reduction, MBL gain, microbiology testing (PCR, five species), adverse events

(Continues)

TABLE 1 (Continued)

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
				• Sub-marginal instrumentation with US metal tips and simultaneous irrigation of 0.12% chlorhexidine digluconate • Curettage with steel curettes • 0.12% chlorhexidine digluconate irrigation of peri-implant pockets • Systemic placebo ×3/7 days		
Almohareb et al. (2020)	RCT (parallel) 12 months University Saudi Arabia Funding: New faculty grants program (RAÀD), The Deanship of Scientific Research, King Saud University	Peri-implantitis: PD ≥ 6 mm + BoP and/or Sup at ≥1 peri-implant site plus CAL ≤ 3 mm and radiographic BLoss ≥3 mm apical to the most coronal portion of the intraosseous part of the implant NR Years in function: 13.8 years • Tests: 14.9 ± 4.2 years • Controls: 12.6 ± 3.5 years	*Total*: $N = 40/40$ subjects; 79 implants • Tests: $N = 20/20$ subjects; 36 implants • Controls: $N = 20/20$ subjects; 43 implants *Age*: 51.3 years old • Tests: 50.9 years old • Controls: 51.7 years old *Sex*: 15% females • Tests: 20% females • Controls: 10% females *Systemic condition*: all healthy *Tobacco smoking*: 0% smokers • Tests: 0% smokers • Controls: 0% smokers	*Test*: OHI + full-mouth mechanical debridement with US under local anaesthesia + systemic antimicrobials (400 mg metronidazole +500 mg amoxicillin, three times per day, for 7 days) + chlorhexidine 0.12% mouthwash twice per day *Control*: OHI + full-mouth mechanical debridement with US under local anaesthesia + single session of PDT with diode laser + chlorhexidine 0.12% mouthwash twice per day	Follow-up visits: 6 and 12 months	PD, CAL, BoP, PI, microbial outcomes, PROMs (pain rating scale)

TABLE 1 (Continued)

Authors/Year Study	Study design Follow-up Setting Location Funding	Case definition of peri-implantitis Implant characteristics (brand, surface) Years in function	Sample size (baseline/final) Age (mean ± SD or range) Sex (% females) Systemic condition Smoking status	Intervention	Supportive peri-implant Therapy	Outcome variables
Probiotics						
Tada et al. (2018)	Multi-centre RCT (parallel) 6 months University Japan Funding: NR Sponsoring: BioGaia AB Sweden (probiotic and placebo lozenges)	Peri-implantitis: PD 4–7 mm + BoP and BLoss >2 mm NR Years in function: • Tests: 8.3 ± 4.2 years • Controls: 6.0 ± 2.8 years	*Total*: $N = 30/30$ subjects • Tests: $N = 15/15$ subjects • Controls: $N = 15/15$ subjects *Age*: • Tests: 68.8 ± 7.5 years old • Controls: 65.9 ± 8.8 years old *Sex*: 73.3% females • Tests: 80% females • Controls: 66.7% females *Systemic condition*: all healthy *Tobacco smoking*: 0% smokers • Tests: 0% smokers • Controls: 0% smokers	*Test*: OHI + supra-gingival scaling + systemic antimicrobials (azithromycin 500 mg once per day, for 3 days) + 1 probiotic tablet per day, for 6 months (*Lactobacillus reuteri* DSM 17938 and *Lactobacillus reuteri* ATCC PTA 5289) *Control*: OHI + supra-gingival scaling + systemic antimicrobials (azithromycin 500 mg once per day, for 3 days) + 1 placebo tablet per day, for 6 months	Follow-up visits: 4, 12 and 24 weeks	PD, BoP, mPI, mBI and microbial outcomes
Laleman et al. (2020)	RCT (parallel) 6 months University Belgium Funding: BioGaia AB Sweden. KU Leuven (C24/17/086) and FWO (G091218N) grants.	Peri-implantitis: PD ≥ 4 mm + BoP and radiographic BLoss ≥1 mm between prosthesis delivery and screening appointment Initial peri-implantitis: peri-implantitis with a maximum PD = 6 mm and a maximum radiographic BLoss = 3 mm Rough surface implants: Nobel MKIII ($N = 18$) Astra OsseoSpeed ($N = 4$) Dentsply Ankylos ($N = 1$) Years in function: NR	*Total*: $N = 23/19$ subjects • Tests: $N = 11/9$ subjects • Controls: $N = 12/10$ subjects *Age*: • Tests: 64 years old • Controls: 69 years old *Sex*: 52% females • Tests: 44% females • Controls: 60% females *Systemic condition*: all apparently healthy *Tobacco smoking*: 0% smokers	*Test*: OHI + full-mouth prophylaxis + mechanical debridement with US plastic tips, titanium curettes and sub-gingival air-polishing under local anaesthesia + sub-gingival topical application of five drops with probiotics (*Lactobacillus reuteri* DSM 17938 and *Lactobacillus reuteri* ATCC PTA 5289) + 2 probiotic lozenges per day, for 10 days (*Lactobacillus reuteri* DSM 17938 and *Lactobacillus reuteri* ATCC PTA 5289)	Follow-up visits: 6, 12 and 24 weeks	BoP, mSBI, PD, PI, FMBS, FMPS, microbiological analysis (quantitative PCR for *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans*)

(Continues)

TABLE 1 (Continued)

Authors/Year	Study design	Case definition of peri-implantitis	Sample size (baseline/final)	Supportive peri-implant therapy	Outcome variables
Study	Follow-up		Age (mean ± SD or range)		
	Setting		Sex (% females)		
		Implant characteristics (brand, surface)			
	Location	Systemic condition			
	Funding	Years in function	Smoking status	Intervention	
			• Tests: 0% smokers • Controls: 0% smokers	*Control*: OHI + full-mouth prophylaxis + mechanical debridement with US plastic tips, titanium curettes and sub-gingival air-polishing under local anaesthesia + sub-gingival topical application of 5 placebo drops +2 placebo lozenges per day, for 10 days	

Abbreviations: BLoss, bone loss; BoP, bleeding on probing; CAL, clinical attachment level; FMPS, full-mouth plaque scores; GCF, gingival crevicular fluid; GI, gingival index; IL-6 interleukin 6; mBI, modified bleeding index; MBL, mean bone level; mPI, modified plaque index; mSBI, modified sulcus bleeding index; NR, not reported; OH, oral hygiene; OHI, oral hygiene instructions; PCR, polymerase chain reaction; PD, probing depth; PDT, photodynamic therapy; PI, plaque index; PROMs, patient-reported outcome measures; RCT, randomized clinical trial; Rec, recession; SD, standard deviation; Sup, suppuration; TNF-α, tumour necrosis factor alpha; UK, United Kingdom; US, ultrasonic; USA, United States of America.

group design. Eight out of nine investigations compared two different treatment arms and one study evaluated three treatment approaches (Ahmed et al., 2020). There were five publications evaluating local antimicrobials (Ahmed et al., 2020; Bassetti et al., 2014; Machtei et al., 2012, 2021; Schar et al., 2013), three evaluating systemic antimicrobials (Almohareb et al., 2020; Blanco et al., 2022; Shibli et al., 2019) and two using probiotics (Laleman et al., 2020; Tada et al., 2018). No other adjunctive measure was identified.

Among studies dealing with local antimicrobials, two evaluated chlorhexidine chips (Machtei et al., 2012, 2021), one minocycline hydrochloride microspheres (Bassetti et al., 2014; Schar et al., 2013) and one an antibiotic gel consisting of metronidazole 400 mg and amoxicillin 500 mg (Ahmed et al., 2020). Among studies evaluating systemic antimicrobials, one reported on the use of metronidazole 500 mg, three times per day for 7 days (Blanco et al., 2022), and two on the use of 400 mg metronidazole +500 mg amoxicillin, three times per day, for 7 days (Almohareb et al., 2020) or 14 days (Shibli et al., 2019). Both trials evaluating the role of probiotics used the same formula (*Lactobacillus reuteri* DSM 17938 and *L. reuteri* ATCC PTA 5289) but with different administration regimes, either one tablet per day for 6 months (Tada et al., 2018) or two tablets per day for 10 days after a sub-mucosal application of probiotic drops at the peri-implant sites (Laleman et al., 2020).

The resulting systematic review pooled data from 615 subjects and 797 implants at baseline. The follow-up ranged between 6 and 12 months. At the end of the follow-up period, 605 subjects and 787 implants were analysed.

Multiple definitions of peri-implantitis were reported, all of them including the presence of BoP plus radiographic evidence of bone loss as it was suggested in the World Workshop in Periodontology (Berglundh et al., 2018). However, different thresholds for bone loss from the most coronal portion of the implant shoulder in the absence of an initial radiograph were established, ranging from 0.5 to 4 mm. Similarly, in all the included studies, there was an inclusion criterion related with the PD component (ranging from ≥4 to ≥6 mm, with some upper limits in certain investigations), but no evidence of increased PD compared with previous examinations was available.

Most of the investigations performed supra- and sub-peri-implant mucosa debridement together with oral hygiene instructions as part of non-surgical therapy. There was just one study merely providing supra-mucosal debridement (Tada et al., 2018). Mechanical debridement was provided with ultrasounds and/or steel/plastic curettes. In one study (Blanco et al., 2022), minor soft tissue curettage of the pocket wall was performed. There were two studies also using air-polishing devices (Bassetti et al., 2014; Laleman et al., 2020; Schar et al., 2013). Three investigations included photodynamic therapy (PDT) with diode laser as part of the control treatment (Ahmed et al., 2020; Almohareb et al., 2020; Bassetti et al., 2014; Schar et al., 2013), and one of the studies evaluating probiotics prescribed a systemic antimicrobial in both treatment groups prior to the prescription of the probiotic/placebo tablets (Tada et al., 2018).

In five investigations, participants were included in a supportive periodontal care programme, consisting in most of the cases of oral

hygiene instructions plus supra- and/or sub-gingival debridement every 3 months. In the two investigations evaluating chlorhexidine chips, these were inserted in sites presenting PD ≥ 6 mm and re-inserted every 2 weeks for 12 weeks (Machtei et al., 2012, 2021). Some studies repeated initial therapy if BoP was present during the maintenance visit (Bassetti et al., 2014; Schar et al., 2013) or applied sub-mucosal irrigation with chlorhexidine in those sites with PD ≥ 5 mm (Blanco et al., 2022).

3.3 | Risk of bias in individual studies

RoB 2 tool was used to assess the risk of bias of the studies included in this review. Only one of the included studies was found to have an overall low risk of bias, while some concerns were present in the other nine included publications (Figure 2). The different sources of bias in the included studies are summarized in Figure S1.

3.4 | Risk of bias across studies

No significant publication bias was observed for the primary outcomes (Egger's linear regression test: $p = .695$ and $p = .394$, respectively; Figures S2 and S3). The sensitivity analyses showed that the exclusion of a single study did not substantially alter any estimate.

3.5 | Effects of interventions on primary outcomes by type of adjunctive measure

Due to the high heterogeneity of the adjunctive approaches used, even on the same category (i.e., systemic antimicrobials, local antimicrobials and probiotics), meta-analyses were not performed in most of the scenarios. Description of the main results of the included studies is displayed below taking into consideration the type of adjunctive measure.

3.5.1 | Systemic antimicrobials

PD reduction

PD reduction at patient level was reported in the three included studies (Table 2). Shibli et al. (2019) showed PD reduction of 3.1 ± 1.2 mm in the test group and 1.8 ± 0.2 mm in the control ($p < .001$). Blanco et al. (2022) reported a PD reduction of 2.53 ± 0.59 mm in the test and 1.02 ± 0.49 mm in the control group ($p < .001$). One study did not show differences between test and control groups (Almohareb et al., 2020). However, baseline PD in this study was lower (≈5 mm) in comparison to the other two. Analysis of the behaviour of treatment at the deepest sites was reported in Shibli et al. (2019) and Blanco et al. (2022) studies. Shibli et al. showed a PD reduction of 4.8 and 3.8 mm in the test and control groups, respectively. Blanco et al. (2022) showed a PD reduction of 3.29 mm in the test and 1.52 mm in the control group.

Bleeding on probing reduction

Two studies (Almohareb et al., 2020; Shibli et al., 2019) reported BoP reduction at the implant level, whereas the study by Blanco et al. (2022) reported full-mouth bleeding index score (FMBS). Shibli et al. (2019) showed a reduction on BoP of 50% and 45% at test and control sites, respectively. Almohareb et al. (2020) showed a reduction of BoP of 20% and 27% at test and control sites, respectively. In both studies, this reduction was statistically significant within each group, but not when comparing test and control interventions. The study from Blanco et al. (2022) reported a decrease in FMBS of ≈20% in both groups.

3.5.2 | Local antimicrobials

PD reduction

Table 3 depicts the results of the included studies in terms of PD reduction ($n = 5$). Three publications (Ahmed et al., 2020; Bassetti et al., 2014; Schar et al., 2013) reported data at patient level and two

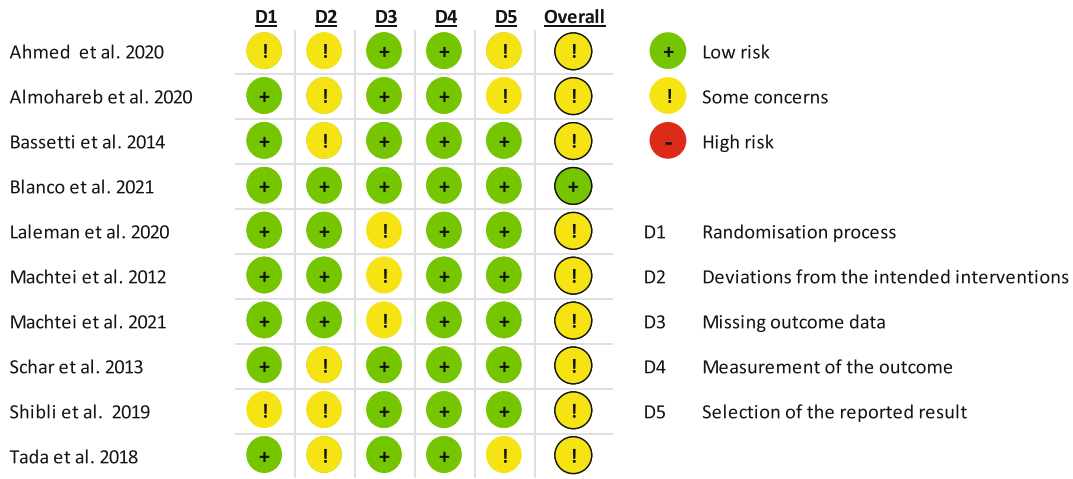

FIGURE 2 Individual assessment of risk of bias for included studies using the robvis tool.

TABLE 2 Clinical and radiographic outcomes of the included studies on non-surgical peri-implantitis therapy with systemic antimicrobials as adjuncts to mechanical debridement on patient-level data.

		Systemic antimicrobials					
		Shibli et al. (2019) 500 mg amoxicillin and 400 mg metronidazole ×3/14 days		Blanco et al. (2022) 500 mg metronidazole ×3/7 days		Almohareb et al. (2020) 500 mg amoxicillin and 400 mg metronidazole ×3/7 days	
		Mean	SD	Mean	SD	Mean	SD
Initial PPD (mm)	Test	7.0	2.6	6.9	1.8	5.4	2.1
	Control	5.5	1.3	5.9	1.2	5.2	2.0
PPD reduction at 6 months (mm)	Test	3.1	2.6	2.4	1.8	0.7	1.8
	Control	2.1	1.2	0.9	0.8	0.8	1.7
PPD reduction at 12 months (mm)	Test	3.1	1.2	2.5	1.9	1.3	1.8
	Control	1.8	0.2	1.0	1.7	1.4	1.7
Initial CAL (mm)	Test	7.2	2.6	7.3	1.8	NR	NR
	Control	5.9	1.3	6.1	1.2	NR	NR
CAL gain at 6 months (mm)	Test	3.0	2.3	2.2	2.0	NR	NR
	Control	2.1	1.2	0.5	0.8	NR	NR
CAL gain at 12 months (mm)	Test	2.6	2.3	2.1	1.9	NR	NR
	Control	1.4	1.4	0.5	1.6	NR	NR
Initial BoP (%)	Test	86.6	32.2	NR	NR	43.8	13.9
	Control	85.0	18.3	NR	NR	45.3	14.8
BoP reduction at 6 months (%)	Test	40.4	34.5	NR	NR	29.7	13.2
	Control	36.6	25.8	NR	NR	27.2	13.3
BoP reduction at 12 months (%)	Test	35.6	26.2	NR	NR	25.7	8.1
	Control	40.3	30.3	NR	NR	18.6	7.9
Initial MBL (mm)	Test	NR	NR	6.3	6.3	NR	NR
	Control	NR	NR	5.5	5.5	NR	NR
MBL change at 6 months (mm)	Test	NR	NR	1.7	1.1	NR	NR
	Control	NR	NR	0.8	0.9	NR	NR
MBL change at 12 months (mm)	Test	0.4	0.4	2.3	1.3	NR	NR
	Control	0.5	0.3	1.1	1.5	NR	NR

Abbreviations: BoP, bleeding on probing; CAL, clinical attachment level; MBL, marginal bone levels; PPD, probing pocket depth; SD, standard deviation.

at implant level (Machtei et al., 2012, 2021). One study (Ahmed et al., 2020) reported a reduction in PD of 2.7 mm in the test and 2.2 mm in the control group at 6 months after a single application of a gel containing metronidazole 400 mg and amoxicillin 500 mg. The other two publications belong to the same investigation reporting outcomes at 6 (Schar et al., 2013) and 12 months (Bassetti et al., 2014). PD reduction was of 0.56 mm for the use of local antibiotic (minocycline microspheres) and 0.11 mm for the adjunctive application of PDT. At implant level, two studies analysed the adjunctive use of chlorhexidine chips (Machtei et al., 2012, 2021). In the first study, PD reduction at 6 months was 2.19 mm in the test and 1.59 mm in the control group, this difference being statistically not significant (Machtei et al., 2012). In the second study, PD reduction was 1.76 mm in the test and 1.54 mm in the control group at 6 months, this difference being statistically significant (Machtei et al., 2021). The meta-analysis performed after pooling the data from both studies revealed a significantly greater PD reduction after the use of chlorhexidine chips ($n = 2$; WMD = 0.2 mm; 95% CI [0.0; 0.5]; $p = .031$; $I^2 = 0.0\%$; $p = .570$).

Bleeding on probing reduction

Table 3 shows the results of the included studies comparing BoP reductions between test and control groups ($n = 5$). Again, three studies (Ahmed et al., 2020; Bassetti et al., 2014; Schar et al., 2013) showed data at patient level and two at implant level (Machtei et al., 2012, 2021).

At patient level, the reduction in BoP-positive sites after 6 months was 52% in the control and 63% in the test group, this difference being statistically not significant (Schar et al., 2013). At 12 months follow-up, this difference remained not significant (65% in the test and 57% in the control) (Bassetti et al., 2014). Ahmed et al. (2020) reported a reduction of BoP sites of 40.2% in the test and 26.8% in the control group. The two studies evaluating chlorhexidine

TABLE 3 Clinical and radiographic outcomes of the included studies on non-surgical peri-implantitis therapy with local antimicrobials as adjuncts to mechanical debridement.

		Local antimicrobials									
		Machtei et al. (2012) CHX chips		Schar et al. (2013) Minocycline microspheres		Bassetti et al. (2014) Minocycline microspheres		Machtei et al. (2021) CHX chips		Ahmed et al. (2020) Metronidazole and amoxicillin gel	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Initial PPD (mm)	Test	7.6	NR	4.2	0.6	4.2	0.6	6.2	1.0	NR	NR
	Control	7.2	NR	4.4	0.8	4.4	0.8	6.1	0.9	NR	NR
PPD reduction at 6 months (mm)	Test	2.1	1.4	0.4	0.6	NR	NR	1.8	1.1	NR	NR
	Control	1.7	1.2	0.5	0.8	NR	NR	1.5	1.1	NR	NR
PPD reduction at 12 months (mm)	Test	NR	NR	NR	NR	0.1	0.7	NR	NR	NR	NR
	Control	NR	NR	NR	NR	0.6	0.8	NR	NR	NR	NR
Initial CAL (mm)	Test	7.9	NR	2.7	0.7	2.7	0.7	6.7	NR	NR	NR
	Control	7.6	NR	2.7	0.7	2.7	0.7	6.3	NR	NR	NR
CAL gain at 6 months (mm)	Test	2.2	1.4	0.2	0.8	NR	NR	1.5	1.4	NR	NR
	Control	1.7	1.2	0.2	0.7	NR	NR	1.4	1.2	NR	NR
CAL gain at 12 months (mm)	Test	NR	NR	NR	NR	0.1	0.9	NR	NR	NR	NR
	Control	NR	NR	NR	NR	0.3	0.7	NR	NR	NR	NR
Initial BoP (%)	Test	100	NR	67.2	27.7	67.2	27.7	100	NR	NR	NR
	Control	100	NR	73.5	25.2	73.5	25.2	100	NR	NR	NR
BoP reduction at 6 months (%)	Test	57.5	50.1	25.2	23.5	NR	NR	50.0	NR	NR	NR
	Control	45.5	50.6	35.0	25.8	NR	NR	55.0	NR	NR	NR
BoP reduction at 12 months (%)	Test	NR	NR	NR	NR	29.0	22.8	NR	NR	NR	NR
	Control	NR	NR	NR	NR	25.8	21.0	NR	NR	NR	NR
Initial MBL (mm)	Test	NR	NR	NR	NR	NR	NR	NR	NR	2.0	0.6
	Control	NR	NR	NR	NR	NR	NR	NR	NR	1.8	0.5
MBL change at 6 months (mm)	Test	NR	NR	NR	NR	NR	NR	NR	NR	1.2	0.5
	Control	NR	NR	NR	NR	NR	NR	NR	NR	0.6	0.6

Abbreviations: BoP, bleeding on probing; CAL, clinical attachment level; CHX, chlorhexidine; MBL, marginal bone levels; PPD, probing pocket depth; SD, standard deviation.

chips (Machtei et al., 2012, 2021) reported a reduction in the percentage of sites with BoP of ≈50%, both in the test and control groups, with no statistically significant differences.

3.5.3 | Probiotics

PD reduction

Table 4 depicts PD reduction in the two included studies comparing non-surgical therapy + probiotics and non-surgical therapy alone. In one study, all patients received a course of systemic azithromycin 500 mg, once a day for 3 days before allocating them to the intervention group (Tada et al., 2018). In this investigation, PD reduction was only statistically significant in the test (0.43 mm vs. 0.06 mm). In the study by Laleman et al. (2020), both groups showed a statistically significant PD reduction, without differences when comparing the adjunctive use of probiotics and non-surgical therapy alone (1.02 and 1.27 mm, respectively).

Bleeding on probing reduction

Table 4 depicts the percentage of BoP reductions in the two included studies using probiotics. In one study, no statistically significant differences were observed within or between groups in terms of BoP reduction (Tada et al., 2018). In the investigation by Laleman et al. (2020), both groups showed a statistically significant reduction in BoP (28% in the test and 34% in the control group), but without significant differences when comparing them.

3.6 | Effects of interventions: Secondary outcomes

3.6.1 | Implant loss, disease resolution, recurrence of peri-implantitis and need for surgery

Implant loss was reported in four publications, all of them showing 100% implant survival in both groups (Blanco et al., 2022; Laleman

TABLE 4 Clinical outcomes of the included studies on non-surgical peri-implantitis therapy with probiotics as adjuncts to mechanical debridement.

		Probiotics			
		Tada et al. (2018) *Lactobacillus reuteri* strains DSM 17938 and ATCC PTA 5289		Laleman et al. (2020) *Lactobacillus reuteri* strains DSM 17938 and ATCC PTA 5289	
		Mean	SD	Mean	SD
Initial PPD (mm)	Test	3.6	0.8	5.2	0.9
	Control	3.5	1.0	5.5	1.2
PPD reduction at 6 months (mm)	Test	0.4	0.8	1.0	0.7
	Control	0.1	1.0	1.3	1.0
Initial BoP (%)	Test	38.8	28.5	87.0	23.0
	Control	45.5	29.2	87.0	22.0
BoP reduction at 6 months (%)	Test	25.5	23.5	59.0	23.0
	Control	38.8	32.5	53.0	27.0

Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth; SD, standard deviation.

et al., 2020; Schar et al., 2013; Shibli et al., 2019). Five investigations reported on disease resolution, using four different definitions (Bassetti et al., 2014; Blanco et al., 2022; Laleman et al., 2020; Machtei et al., 2012; Schar et al., 2013; Shibli et al., 2019). Two investigations considered the resolution of peri-implant mucosal inflammation (i.e., no sites with BoP) as success criteria (Bassetti et al., 2014; Laleman et al., 2020; Schar et al., 2013), one investigation merely considered the absence of sites with PD≥6 mm (Machtei et al., 2012), while the remaining two studies used different composite outcomes considering different PD thresholds as clinical end point, together with the absence of BoP and no further bone loss (Blanco et al., 2022; Shibli et al., 2019). The percentage of success ranged between 0% and 65% in the test groups and between 15% and 55% in the control groups. Due to the important differences in the definition of disease resolution, no meta-analysis was performed.

Recurrence of peri-implantitis was not assessed in any investigation and just one study reported the need for surgical treatment after study completion (three subjects in the test and two subjects in the control group) (Bassetti et al., 2014).

3.6.2 | Peri-implant clinical parameters

PIs were evaluated in 8 out of 10 included studies, either as the percentage of sites harbouring plaque (Ahmed et al., 2020; Almohareb et al., 2020; Blanco et al., 2022; Laleman et al., 2020; Shibli et al., 2019) or as the modified plaque index by Mombelli et al. (1987) (Bassetti et al., 2014; Schar et al., 2013; Tada et al., 2018). No effect of the adjuncts was observed for the PI (%) at 6- or 12-month follow-ups.

Clinical attachment levels were assessed in five investigations (Bassetti et al., 2014; Blanco et al., 2022; Machtei et al., 2012, 2021; Schar et al., 2013; Shibli et al., 2019). When stratifying by adjunctive group, systemic antibiotics showed a significantly greater CAL gain at 6 months ($n = 2$; WMD = 1.4 mm; 95% CI [1.2; 1.5]; $p < .001$; $I^2 = 0.0\%$; $p = .426$) and 12 months ($n = 2$; WMD = 1.2 mm; 95% CI [1.1; 1.4]; $p < .001$; $I^2 = 0.0\%$; $p = .960$).

Recession was registered in three investigations (Bassetti et al., 2014; Blanco et al., 2022; Machtei et al., 2021; Schar et al., 2013). According to these studies, adjunct measures may contribute to a higher, but minor (0.1–0.2 mm), mucosal recession as a consequence of the resolution of peri-implant soft tissue inflammation.

3.6.3 | Marginal bone levels

MBLs in peri-apical x-rays were evaluated in three studies (Ahmed et al., 2020; Blanco et al., 2022; Shibli et al., 2019). In the study by Ahmed et al. (2020), MBLs improved in both groups. In the test group, MBLs were reduced by 1.2 mm, while in the control group, they were reduced by 0.6 mm; this difference was statistically significant. Shibli et al. (2019) showed a modest improvement in MBLs at 12 months in both groups with no difference between them (0.41 and 0.47 mm in the test and control groups, respectively). The study from Blanco et al. (2022) reported data at patient and implant levels, with a follow-up of 6 and 12 months. At patient level, 6 months after therapy, the test group showed a radiographic bone gain of 1.65 mm, while in the control group, it was of 0.82 mm. At the 12-month examination, MBLs presented further improvement, with a radiographic bone gain of 2.33 mm in the test group and 1.13 in the control group. Both intra- and inter-group comparisons were statistically significant at 6 and 12 months.

3.6.4 | Microbiological and immunological outcomes

Six investigations evaluated microbiological outcomes (Almohareb et al., 2020; Bassetti et al., 2014; Blanco et al., 2022; Laleman

et al., 2020; Shibli et al., 2019; Tada et al., 2018). Samples were taken in all studies at baseline from the deepest pocket of the affected implant. Five investigations used quantitative polymerase chain reaction (qPCR) for the analyses of different bacteria, while just one investigation used the checkerboard DNA–DNA hybridization technique (Shibli et al., 2019). The two studies evaluating a probiotic formula did not find any significant inter- or intra-group difference throughout the study (Laleman et al., 2020; Tada et al., 2018). Two other investigations did not observe any significant inter-group difference among the counts of target bacteria when using minocycline microspheres (Bassetti et al., 2014) or systemic metronidazole + amoxicillin (Almohareb et al., 2020). However, the two studies evaluating systemic antimicrobials found significant microbiological differences between groups for red complex species (Shibli et al., 2019) or for the counts of *Porphyromonas gingivalis* and *Tannerella forsythia*, specifically (Blanco et al., 2022).

Samples were obtained from the peri-implant sulcus in two investigations to evaluate the levels of pro-inflammatory markers (e.g., interleukin (IL)-1β, TNF-α, IL-6, IL-8, IL-10, matrix-metalloproteinase [MMP]-1 and [MMP]-8 by means of enzyme-linked immunosorbent assays [ELISA]) (Ahmed et al., 2020; Bassetti et al., 2014). No significant differences between treatment groups were observed at the last appointment.

3.6.5 | Side effects, aesthetic complications, PROMs and economic factors

None of the included studies addressed aesthetic complications or economic factors. The study by Blanco et al. was the only one reporting side effects, with six subjects (38%) in the test group (systemic metronidazole) and five (31%) in the control group (placebo) reporting either gastrointestinal disorders, headaches or metallic taste, without significant differences among groups (Blanco et al., 2022). Just one investigation evaluated the pain experienced after the procedures using a numeric pain rating scale, reporting an improvement when compared with baseline in both groups without differences among them (Almohareb et al., 2020).

4 | DISCUSSION

The present systematic review was able to identify nine RCTs (reported in 10 publications) assessing patient-performed or administered adjunctive measures to the non-surgical treatment of peri-implantitis with the primary goal of obtaining better clinical outcomes in order to diminish the need of further treatment. In summary, the included studies show that the adjunctive use of systemic antimicrobials improves the clinical outcomes of the non-surgical treatment of peri-implantitis in terms of PD reductions. These differences in favour of systemic antimicrobials seem to be greater at the deepest sites. Local antimicrobials in general and chlorhexidine chips in particular have shown a modest added value in terms of PD reduction. The studies evaluating probiotics did not show clinical improvement when used as adjuncts to the non-surgical treatment of peri-implantitis.

Although the primary outcome in the treatment of peri-implantitis should be disease resolution, only five investigations reported on this outcome, using four different definitions. It should be acknowledged that including more parameters makes it more difficult to achieve treatment success, especially when trying to completely eliminate BoP. This parameter has shown a considerable false-positive rate to diagnose peri-implantitis, probably attributed to the fragility of healthy peri-implant tissues (Hashim et al., 2018). The use of non-dichotomic scales, such as the modified sulcus bleeding index (Mombelli et al., 1987), may improve the accuracy of the assessment of the inflammatory condition, at least on research environments.

The results from the present systematic review have shown that the adjunctive protocols used were very heterogeneous. Therefore, it is pertinent to consider the effects of these agents separately.

4.1 | Systemic antimicrobials

In relation to systemic antimicrobials, two out of the three studies included in the present systematic review showed a clear improvement when using them in terms of PD reduction after 6 and 12 months (Blanco et al., 2022; Shibli et al., 2019). In contrast, the study by Almohareb et al. (2020) reported no differences between groups. This discrepancy may be explained by the fact that in the study by Almohareb et al. the control group received adjunctive PDT, so it did not consist of mechanical debridement alone. Moreover, baseline PD values in this study were lower than in the other two. It has been shown that the added value of systemic antimicrobials seems to be more evident at deep sites. Specifically, in the study by Blanco et al., initially, deep sites (i.e., >6 mm) were reduced below the cut-off of 6 mm at the end of the trial only in the test group, which may have an impact on further treatment needs (e.g., surgical therapy). These results are in line with the results of Shibli et al., indicating that the impact of systemic antimicrobials in the non-surgical treatment of peri-implantitis may depend on the severity of peri-implantitis. The observed PD reductions and rates of disease resolution (≈60%) are also comparable to those reported in other case series in which different antibiotic regimens were used (Estefania-Fresco et al., 2019; Linares et al., 2019; Mombelli & Lang, 1992; Nart et al., 2020).

The two antibiotic regimes used in the studies included in this systematic review were systemic metronidazole 500 mg, three times per day for 7 days (Blanco et al., 2022), and the prescription of 400 mg metronidazole +500 mg amoxicillin, three times per day, for 7 days (Almohareb et al., 2020) or 14 days (Shibli et al., 2019). The rationale behind the use of metronidazole is based on the high prevalence of anaerobic pathogens in peri-implantitis lesions (Charalampakis & Belibasakis, 2015) and on the efficacy shown in reducing PD and attaining clinical attachment gain in moderately deep and deep sites around teeth, and thus reducing the need of periodontal surgeries (Teughels et al., 2020). On the other hand, the rationale

for the use of amoxicillin plus metronidazole has also been extrapolated from the field of periodontal therapy, in order to eliminate *Aggregatibacter actinomycetemcomitans* (van Winkelhoff et al., 1992). However, the studies included in the present systematic review that analysed the presence of *A.a* could not detect this bacteria at the baseline examination, which confirms the disparate prevalence of *A.a* in different populations (Minguez et al., 2014; Minguez et al., 2016): a finding that could influence the selection of the systemic antimicrobial, especially in light of the emergence of multi-drug-resistant bacteria associated with the excessive use of wide-spectrum antibiotics (e.g., amoxicillin).

Regarding MBLs, the present systematic review has shown that (i) radiographic bone levels can be maintained and even improved with non-surgical therapy; and (ii) adjunctive measures to non-surgical approaches may improve MBLs at 6 and 12 months. This finding was more evident when systemic antimicrobials were used. However, the impact of systemic antibiotics was clearly based on implant surface roughness. Whereas in one study, a mean radiographic bone gain of 2.33 mm was achieved in the test group at 12 months when treating moderate rough implants (Blanco et al., 2022), in the other investigation, this amount was reduced to 0.4 mm in both groups when treating machined implants (Shibli et al., 2019). Moreover, MBLs improved from 6 to 12 months in the study by Blanco et al., from 1.68 to 2.33 mm in the test group and from 0.8 to 1.1 in the control group. This finding should be considered when establishing the follow-up of studies that analyse radiographic outcomes after non-surgical peri-implant therapy. The impact of systemic antimicrobials on peri-implantitis in implants with moderately rough surfaces is in line with one study that showed that the addition of systemic antibiotics together with resective therapy of peri-implantitis had a positive effect on disease resolution only when treating implants with a modified surface (Carcuac et al., 2016). Peri-implantitis lesions at rough implant surfaces are more aggressive and extend more apically to the bone than in machined surfaces (Carcuac et al., 2013), which could explain why the adjunctive use of systemic antibiotics may have an impact when treating rough implant surfaces. Indeed, the radiographic bone gain observed after the addition of systemic metronidazole to the non-surgical therapy protocol was similar to the one reported in a recent systematic review (≈1.9 mm) comparing the reconstructive surgical therapy of peri-implantitis to access flaps (Tomasi et al., 2019). Still, further investigations are needed to test other systemic antimicrobials, shorter intake periods and the role of peri-implant defect configuration, as it has shown to play an important role in clinical and radiographic outcomes of peri-implantitis therapy (Schwarz et al., 2010).

4.2 | Local antimicrobials

The local application of antimicrobials as adjuncts to mechanical decontamination methods has been proposed in the treatment of peri-implantitis, seeking to avoid the undesirable effects of systemic antibiotics (i.e., antimicrobial susceptibility/resistance). However, only four studies (five publications) dealing with local antimicrobials could be included in the present systematic review, two evaluating chlorhexidine chips, one minocycline hydrochloride microspheres and one an antibiotic gel consisting of metronidazole 400 mg and amoxicillin 500 mg. In general, these studies showed some clinical improvements in terms of PD and BoP reductions, although the results are modest from a clinical perspective (≈0.5 mm greater PD reduction and ≈10% greater BoP reduction). However, as in the field of periodontitis, the use of these products should be balanced with their cost–benefit and their availability in some countries before making any possible clinical recommendation for their use (Henke et al., 2001).

4.3 | Probiotics

The added effect of probiotics in the non-surgical therapy of peri-implantitis has also been evaluated from clinical and microbiological standpoints. The present systematic review was able to identify only two RCTs evaluating the role of probiotics, and one systemic azithromycin was prescribed before the administration of the probiotic both in the test and control groups (Tada et al., 2018). The study by Laleman et al. (2020), dealing with 'initial' peri-implantitis (i.e., maximum mean PD of 6 mm and bone loss ≤3 mm), was not able to find any additional benefit after the use of *L. reuteri* drops and tablets (Laleman et al., 2020). Similarly to what it occurs in the treatment of periodontitis, it remains unclear which is the most suitable probiotic formulation, dosage or administration vehicle (Donos et al., 2020; Sanz et al., 2020). Therefore, more studies on different populations evaluating different micro-organisms and preparations are needed before drawing any conclusion on the effectiveness of probiotics as adjuncts to non-surgical treatment of peri-implantitis.

Finally, the present systematic review was not able to find any adjunctive measure as part of the daily patient's care, such as the use of chemical or mechanical plaque control products, or different interventions for risk factors control (e.g., smoking cessation programmes).

4.4 | Limitations and conclusions

Some limitations related to this systematic review should be acknowledged. First, few studies with small sample sizes and mostly with an unclear risk of bias could be included. Moreover, the high heterogeneity found between the type of adjunctive protocols prevents to obtain robust conclusions and limits the possibility to conduct meta-analyses. Finally, the severity of peri-implantitis in terms of PD and bone loss was very different among studies, which could limit the benefit of adjunctive measures in less severe cases.

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

- Different adjunctive measures in the non-surgical treatment of peri-implantitis had different impact in terms of PD and BoP reductions;

- Improved PD reductions were observed after the use of systemic antimicrobials, especially in initially deep pockets, and, to a lesser extent, after the use of local antimicrobials;
- Further studies are needed to evaluate the real impact of these procedures on disease resolution and their effect in the long term.

AUTHOR CONTRIBUTIONS

Antonio Liñares designed the study, extracted data and drafted the manuscript. Ignacio Sanz-Sánchez designed the study, extracted data and critically reviewed the manuscript. José Dopico performed the electronic and manual search as well as the risk of bias analyses. Ana Molina performed the electronic search. Juan Blanco designed the study and critically reviewed the manuscript. Eduardo Montero designed the study, extracted data, performed the statistical analysis and drafted the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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