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Research Article

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Efficacy of adjunctive systemic or local antibiotics therapy in peri-implantitis: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract: Objective: This systematic review and meta-analysis considered the results of randomized controlled clinical trials (RCTs) to evaluate the efficacy of systemic or local antibiotics therapy on peri-implantitis. Methods: Two independent reviewers screened publications from three electronic databases to include randomized controlled clinical trials meeting all the inclusion and exclusion criteria. A meta-analysis was performed to evaluate the weighted mean differences in survival rate (SR), changes in pocket probing depth (PPD), bone level (BL), and clinical attachment level (CAL). The study cohorts were defined as antibiotics and control groups with subgroups for analysis. Main results: Seven studies including 309 patients and 390 implants were considered. Within the limitations of this review, patients in the antibiotic groups exhibited significant improvements in PPD. Subgroup analysis indicated that the administration of systemic antibiotics or the use of antibiotics in nonsurgical treatments did not result in a significant alteration in BL. Conclusions: Within the limitations of this review, it was established that the addition of antibiotics can ameliorate PPD and SR in the treatment of peri-implantitis, whether through surgical or non-surgical approaches, and also show moderate performance regarding BL and CAL. Considering the lack of application of new technologies in control groups and the hardship of assessing the potential risks of antibiotics, careful clinical judgment is still necessary.

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Key words: Peri-implantitis, Dental implant, Oral medicine, Microbiology, Disease management, Clinical study/trial

1 Introduction

Peri-implantitis is characterized by the inflammation and progressive loss of supporting bone tissue surrounding a functioning dental implant, leading to irreversible damage (Zitzmann et al. 2001). In recent studies, the prevalence of peri-implantitis has been found to be 19% and 11.2% among patients and implants, respectively (Zhang et al. 2018). This condition is associated with

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progressive bone loss, bone resorption, impaired osseointegration, increased pocket formation, and the presence of purulent discharge (Smeets et al. 2014; Lee et al. 2017). In addition, a notable positive association has been established between the occurrence of peri-implantitis and the length of implant function (Derks and Tomasi 2015). Currently, peri-implantitis treatment methods can reach a high implant survival rate, with around three-quarters of implants treated for peri-implantitis still present after five years; however, disease recurrence, bone loss progression, and implant loss still occur (Heitz-Mayfield et al. 2018), demonstrating that there is still room for improvement.

According to a recent evaluation, the risk factors associated with peri-implantitis development include poor plaque control, smoking, infrequent periodontal treatment, a history of periodontitis, excess cement, insufficient keratinized mucosa, diabetes, and other systemic diseases (Darby 2022). Similar to that in periodontitis (Zhao et al. 2023), all of the aforementioned conditions impair the dental plaque removal capacity, which is still thought to be the primary etiological agent of peri-implantitis (Berglundh et al. 2018; Agrawal et al. 2023). As a result, therapeutical techniques aiming at plaque management are critical for treating peri-implantitis.

A range of therapies have been applied, including non-surgical and surgical treatment, with the former being successful for peri-mucositis but inconclusive for peri-implantitis (Khoshkam et al. 2013; Chan et al. 2014). According to research, it is difficult to reduce bacterial loads to the threshold level for disease transmission using simply mechanical measures (Renvert et al. 2007; Heitz-Mayfield and Mombelli 2014; Figuero et al. 2014). As a result, monotherapy may not be effective for disease control, prompting the consideration of surgical therapy and adjuvant devices.

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The utility of antibiotics as adjunctive therapy has been demonstrated in controlling intra-oral biofilm, managing clinical symptoms, and promoting radiographic bone regeneration (Keestra et al. 2015; Cha et al. 2019). According to one study, the use of systemic antibiotics could be crucial in managing conditions primarily attributed to bacterial plaque (Graziani et al. 2017). Extensive evidence supports its efficacy in both non-surgical and surgical interventions for periodontitis under specific circumstances (Santos et al. 2016; Rovai et al. 2016). Moreover, it is posited that adjunctive antibiotic therapy should be considered for the treatment of peri-implantitis owing to the etiological commonalities (Mombelli and Lang 1992; Smeets et al. 2014; Carcuac et al. 2016); numerous clinical studies were conducted to assess the effective of this approach.

In contrast, antibiotics can lead to adverse effects like resistance and dysbiosis, among other undesirable outcomes (Singh et al. 2014). Reviews on the efficacy of antibiotics have indicated that additional randomized controlled clinical trials (RCTs) are required to validate their usage (Klinge et al. 2002; Grusovin et al. 2022). In specific instances, the administration of adjunctive pharmacotherapy did not confer additional enhancement in clinical or microbiological outcomes compared to mechanical debridement or surgical intervention as monotherapies (Santos et al. 2016; Carcuac et al. 2017). Therefore, researchers are exploring alternative treatments such as laser therapy, antimicrobial photodynamic therapy, and antibacterial medicines (Li et al. 2022; Yong et al. 2023). However, whether these treatment modalities can replace antibiotics still

requires further investigations in academic research. Currently, some scholars have conducted meta-analyses on the efficacy of adjunctive antibiotic therapy in treating peri-implantitis; however, most of these have been limited to interventions in surgical or nonsurgical treatment settings (Grusovin et al. 2022; Baus-Domínguez et al. 2023; Keestra et al. 2015; Rovai et al. 2016; Teughels et al. 2023). In a review encompassing both surgical and nonsurgical treatments (Wang et al. 2022), subgroup analyses were performed only on local or systemic antibiotic administration, with the conflation of peri-implantitis and mucositis in the analysis. Furthermore, the outcome measures in current meta-analyses are far from comprehensive.

This study investigated the outcomes of implants treated for peri-implantitis by surgical or nonsurgical methods, comparing the results with or without supplementary antibiotics through a meta-analysis. The objective was to assess whether antibiotics demonstrate superior efficacy in treatment for peri-implantitis. A systematic umbrella review concerning this topic has been conducted (Boccia et al. 2023); however, a detailed analysis pertinent to the subject is lacking. Our study exclusively included randomized controlled clinical trials to acquire higher-quality outcomes. Probing pocket depth (PPD), bone level (BL), clinical attachment level (CAL) changes, and implant survival rate (SR) were evaluated.

Registration: This review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered with PROSPERO (reference no: CRD42023391623).

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2 Methods

2.1 Focused question: PICO

The PICO approach was adopted to ask the focused question: "Can adjunctive antibiotics demonstrate superior efficacy, compared to other adjuvant approaches, in the treatment of peri-implantitis?"

The PICOS elements included:

Population (P): Based on available evidence, patients affected by peri-implantitis.

Intervention (I): Systematic or local antibiotic treatment as an adjunct

Comparison (C): Treatment with other alternative options or no adjunctive treatment.

Outcome (O): The evaluation of outcomes was methodically conducted by measuring alterations in probing pocket depth (PPD), bone level (BL), and clinical attachment level (CAL), in addition to survival rate (SR).

Study (S): Randomized controlled clinical trials.

2.2 Eligibility criteria

The inclusion criteria for articles were established as follows:

1. At least three months of follow-up for adults in good general health.

2. Identification of peri-implantitis with precision through research.

3. Antibiotics are evaluated in peri-implantitis research against other adjuvant treatments.

4. Changes in clinical parameters are compared at the implant level to determine effectiveness, including PPD decreases, CAL gains and BL gains.

5. The study is written in English language.

The following exclusion criteria were applied to evaluate pre-selected studies:

1. Peri-implantitis lacking a clear clinical definition.

2. Medication type or dosage is not described in sufficient detail.

3. Duplicate studies.

4. Systematic reviews, in vitro studies, cross-over studies, commentaries, case reports, unpublished articles, and letters to the editor.

5. If data are given only at the patient and not the implant level.

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2.3 Information source

All relevant articles were collected from PubMed, EMBASE and COCHRANE CENTRAL by the researchers. The search included English language publications up until 1 July 2023. Additionally, to ensure comprehensive coverage, the reference lists of chosen articles were independently examined to identify potential studies that could have been missed during the initial search.

Two reviewers (namely LY and BS) independently conducted the data extraction. Discrepancies were resolved either until consensus was reached via discussion or by seeking input from a third author.

Initially, the eligibility criteria were applied to exclude articles by evaluating their titles or abstracts. Afterwards, a more refined selection was achieved by screening the full texts.

The essential features of each study were outlined, encompassing details such as the primary author, publication year, research methodology, enrollment size of patients or implants, groups, interventions, diagnostic standards, outcome assessments, and durations of follow-up. In cases where information was missing, efforts were undertaken through email communication to reach out to the corresponding author with the intention of acquiring comprehensive data. In the

absence of a response, an identical email was forwarded to the co-authors. Should there be no reply, the study was excluded from the analysis.

2.4 Search strategy

The searching strategy was as follows: ((“drug delivery” OR “drug implants” OR “drug compounding” OR “drug release” OR “local drug treatment” OR “medication” OR “drug treatment” OR “antibacterial agents” OR “local drug administration” OR “anti-microbial” OR “bactericides” OR “anti-infective agents” OR “antibiotics” OR “systemic antibiotics” OR “antibiotic prophylaxis”) AND (“peri-implantitis” OR “periimplantitis” OR “peri-implant disease*” OR “peri-implant infection” OR “peri-implantitides” OR “peri-implant bone loss” OR “periimplant mucositis” OR “periimplant” OR “peri-implant mucositis” OR “dental implant inflammation” OR “peri-implant”) AND “randomized controlled trial”)

2.5 Effect measures and synthesis methods

The mean±standard deviation effect measures were used to record all outcomes. In the case where there were a minimum of two studies featuring similar interventions and observation times could be compared, Review Manager (RevMan, version 5.3 for Mac) was utilized to perform a meta-analysis, merging the data for each outcome measurement. To assess heterogeneity among the studies, I^2 statistics were employed. I^2 values falling within the range of 25-50% suggested low heterogeneity, while values within 50-75% indicated medium heterogeneity. Values exceeding 75% denoted high heterogeneity (Higgins et al. 2003). Significant heterogeneity was deemed present when the I^2 statistic surpassed 50%. In instances of non-significant heterogeneity ($I^2 \leq 50\%$), fixed-effects models were employed. Conversely, random-effects models were used in cases of significant heterogeneity ($I^2 > 50\%$) (Higgins et al. 2003). The criterion for statistical significance was set at $P < 0.05$. The findings of the analysis were presented using forest plots, displaying the weighted mean differences (WMD) along with a 95% confidence interval (CI). All outcomes were calculated at the implant level.

The studies were categorized into two subgroups for analysis: (1) patients who received surgical or nonsurgical treatment, and (2) patients who used systemic or local antibiotics.

2.6 Reporting bias assessment

The screened human clinical articles were evaluated for bias risk using the Cochrane Collaboration Tool (Higgins, J.P.T. et al. 2011). This assessment considers various factors such as detection bias, selection bias, performance bias, and other sources of bias. Each item was classified as having a low, high or unclear risk of bias. An overall estimation of bias risk was determined for each study based on a cumulative score. The study was regarded as having a low risk of bias if all the items were evaluated as such. In contrast, when any item was deemed to have

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an uncertain or elevated risk of bias, that study was evaluated as one with an uncertain or significant risk of bias.

3 Results

3.1 Study selection

The flowchart of the screening process is presented in Fig. 1. Seven studies were included in the systematic review, featuring a total of 309 patients (390 implants).

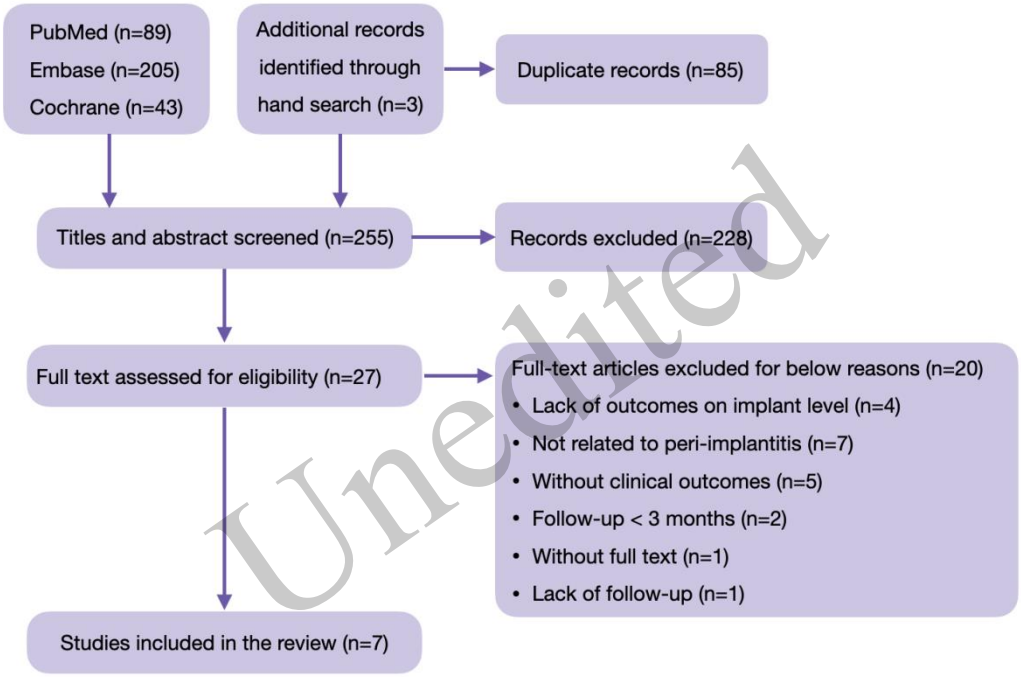

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Fig. 1 Flowchart of the process of literature search and selection

3.2 Study characteristics

The included studies were summarized in Table S1-S2, providing an overview of the research. Across these studies, the average age of patients varied between 58.31 and 66.3 years, and the follow-up periods ranged from 3 months to 12 months. All studies provided information on smoking habits, with four of them specifically focusing on nonsmokers (Shibli et al. 2019; Cha et al. 2019; Emanuel et al. 2020) or light smokers (Park et al. 2021). Four studies recorded the history of periodontal disease (Carcuac et al. 2016; Cha et al. 2019; Blanco et al. 2022; Polymeri et al. 2022), and the groups were comparable at the beginning of the research. Four

studies described the type of implant used: one study mentioned only the brand of the implant (Polymeri et al. 2022), another study only specified the implant surface (Park et al. 2021), and the remaining two studies included multiple types of implants, providing details on both brand and surface (Carcuac et al. 2016; Cha et al. 2019).

Detailed treatment information in the included studies was listed in Table S3. The protocols for debridement and ultrasonic instruments implemented in the non-surgical treatment included Teflon curettes (Shibli et al. 2019), Polyether Ether Ketone (PEEK), fiber tip with carbon fiber reinforced plastic hand instruments (Polymeri et al. 2022), and ultrasonic steel scaling inserts (Park et al. 2021; Blanco et al. 2022). Despite variations among studies, the maintenance protocols were outlined in all of them. Chlorhexidine 0.12% was used in two studies, which instructed patients to rinse it off after treatment (Polymeri et al. 2022) and another used it before, during and after the debridement (Blanco et al. 2022). In studies using surgical treatment, subgingival scaling/debridement with the open-flap technique was applied. The use of local anesthesia was reported in all three studies (Carcuac et al. 2016). Adjunctive antibiotics were administered either locally (Cha et al. 2019; Emanuel et al. 2020; Park et al. 2021) or systemically (Carcuac et al. 2017; Shibli et al. 2019; Blanco et al. 2022; Polymeri et al. 2022).

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3.3 Risk of bias across studies

Fig. 2 presents an overview of the risk of bias assessment. Not all studies provided detailed descriptions of blinding and randomized allocation methods. None of the studies were classified as having a low risk of bias, five studies were categorized as having an unclear risk of bias (Carcuac et al. 2016; Shibli et al. 2019; Cha et al. 2019; Park et al. 2021; Polymeri et al. 2022), and the remaining studies were deemed to have a high risk of bias.

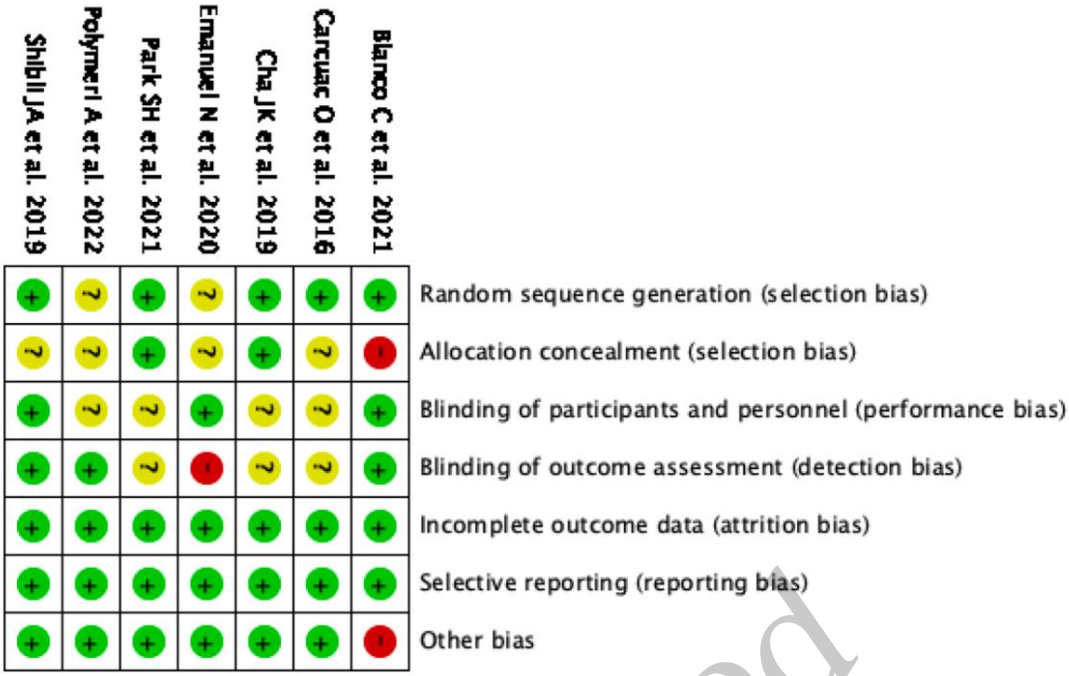

Fig. 2 Risk of bias summary

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3.4 Meta-analysis

3.4.1 Synthesis of the results for changes in PPD

In general, the utilization of adjunctive antibiotics demonstrated marked improvement in probing depth reduction compared to controls (WMD = 1.21; 95% CI, 1.00 to 1.42, P = .00; Fig. 3). Moreover, the beneficial effect of both surgical and nonsurgical treatment, in combination with local or systemic antibiotics, was also evident in the subgroup analysis. Fortunately, heterogeneity in the subgroups was considered relatively low (the number of I^2 in surgical, systemic antibiotics and local antibiotics subgroups all equaled 0%), except for slightly higher heterogeneity in the nonsurgical subgroup (I^2 = 58%).

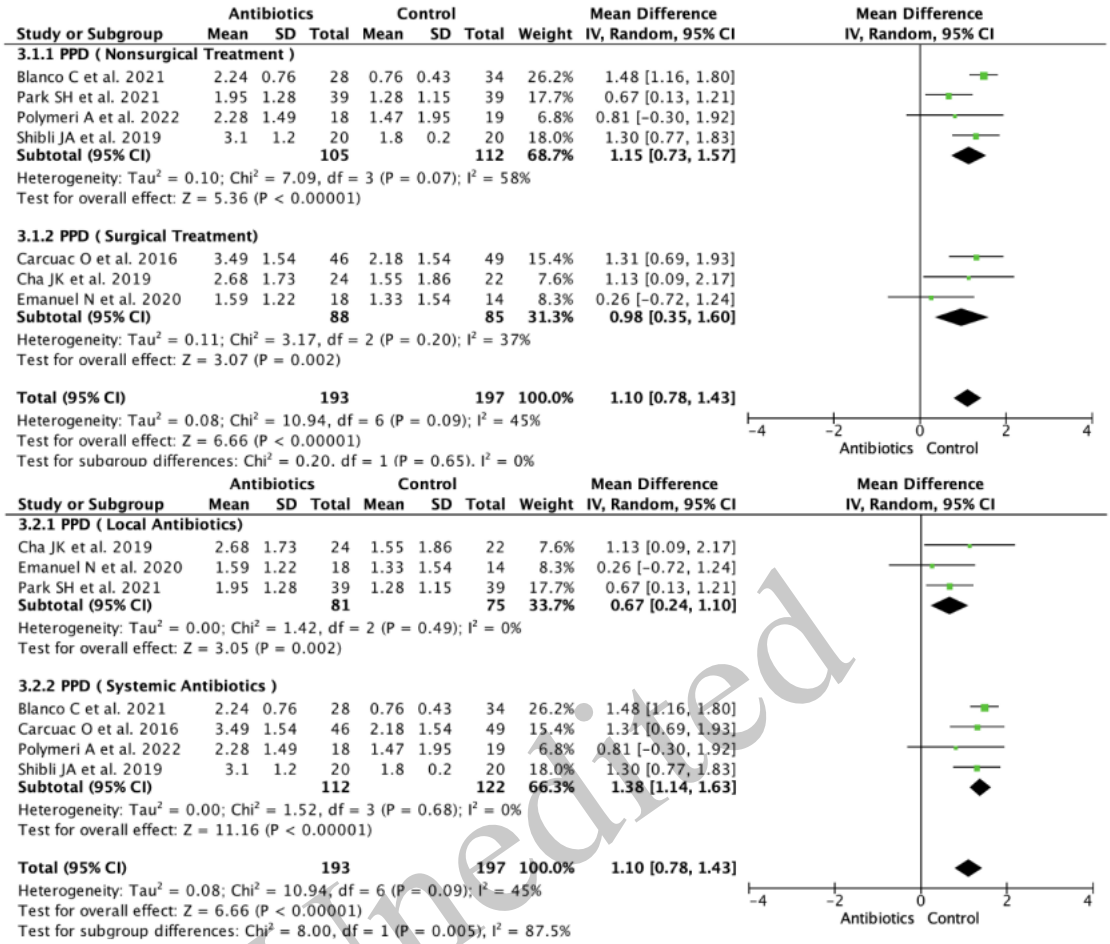

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Fig. 3 Forest plot of PPD and meta-analyses for the comparison of pocket probing depth changes

3.4.2 Synthesis of results for SR

Six studies provided comparisons of success rate between adjunctive antibiotics and control groups. Consistency in defining treatment success was observed in six studies. The antibiotics group demonstrated enhanced treatment efficacy compared to the control group (weighted pooled odds ratios = 2.37; 95% CI, 1.53 to 3.65, P = .00; Fig. 4). Similar results were found in subgroups (Fig. 4), and the heterogeneity test results were satisfactory ($I^2 \leq 20\%$).

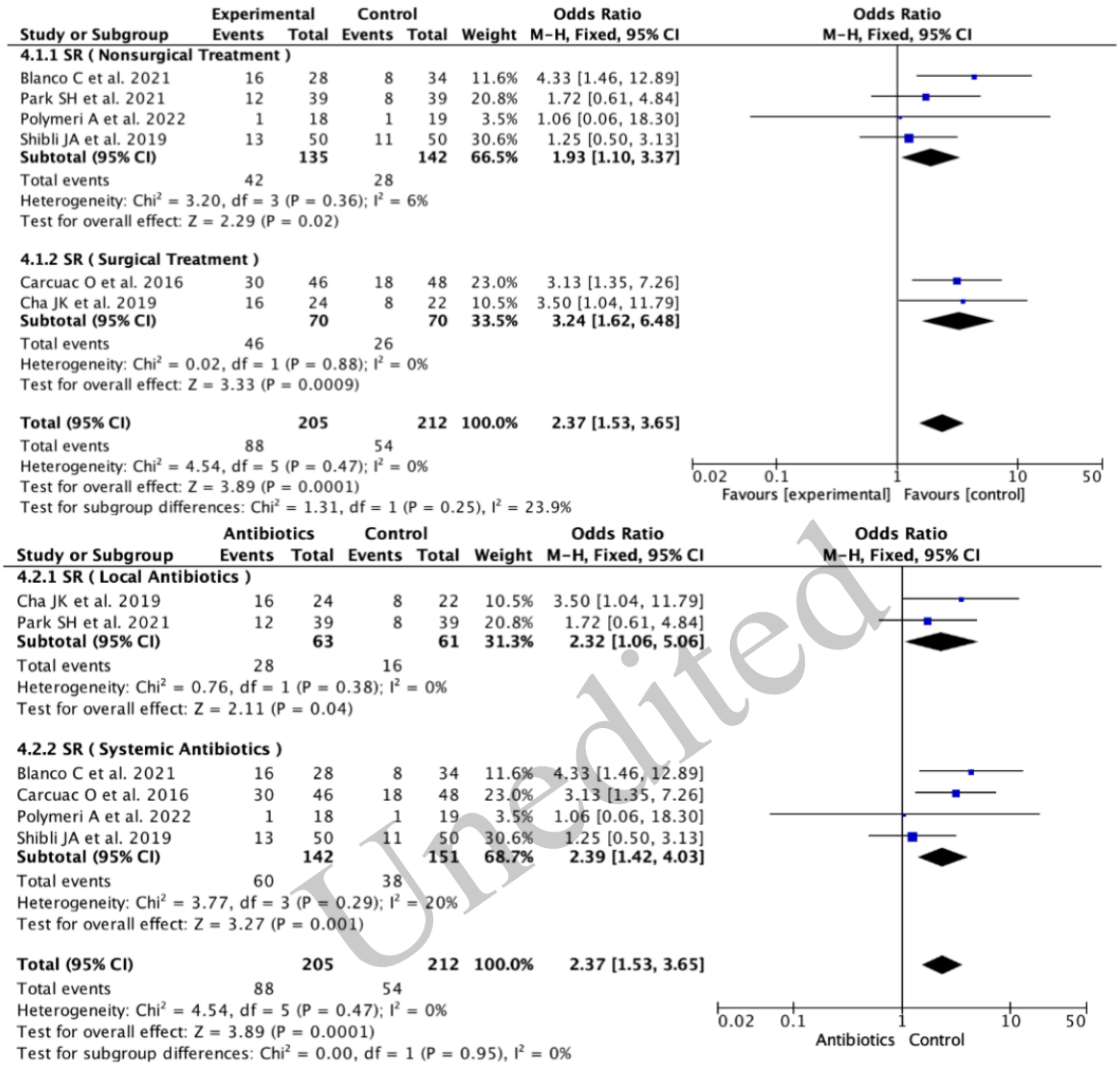

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Fig. 4 Forest plot of SR and meta-analyses for the comparison of survival rate

3.4.3 Synthesis of results for changes in CAL

Only three studies assessed the changes in clinical attachment level over a 12-month period. Significantly reduced attachment loss was observed in the groups receiving antibiotics as compared to the control group, according to the meta-analysis (weighted mean difference = 1.28; 95% CI, 1.00 to 1.55 P = .40; Fig. 5). The result was merely the same when only considering the condition only using nonsurgical treatment plus adjunctive systemic antibiotics (weighted mean difference = WMD = 1.34; 95% CI, 1.05 to 1.62 P = .00; Fig. 5) with low heterogeneity ($I^2 = 0$).

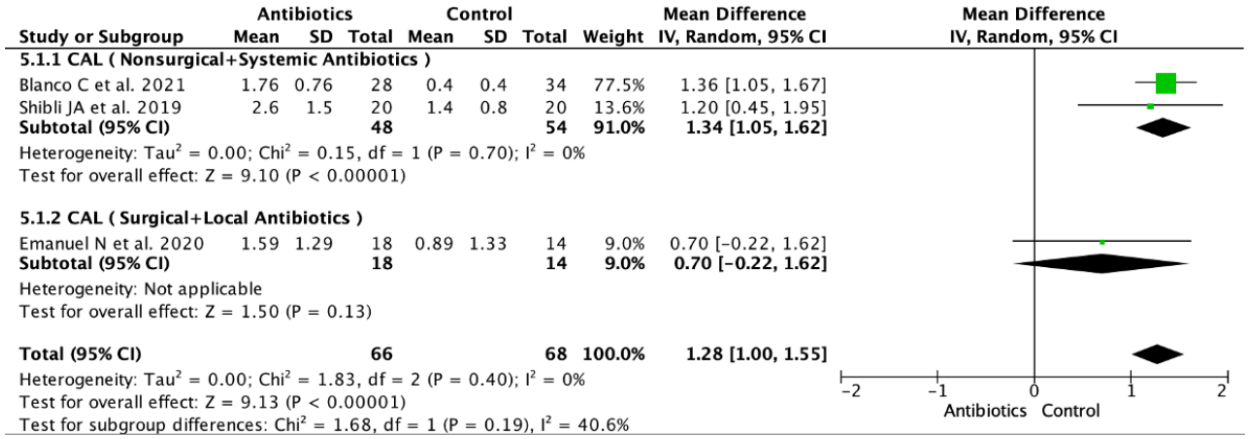

Fig. 5 Forest plot of CAL and meta-analyses for the comparison of clinical attachment level

3.4.4 Synthesis of results for changes in BL

Changes in the bone level for five researches differed significantly between the two groups (WMD = 0.80; 95% CI, 0.25 to 1.34 P = .004; Fig. 6). In addition, a great amount of heterogeneity was found (χ^2 = 49.47, I^2 = 92%, P =.00). When barrowing the results to subgroups, those taking surgical method or local antibiotics showed remarkable higher bone level in antibiotics group (Fig. 6) but the amounts of heterogeneity were both high (I^2 = 81%; I^2 = 75%, respectively).

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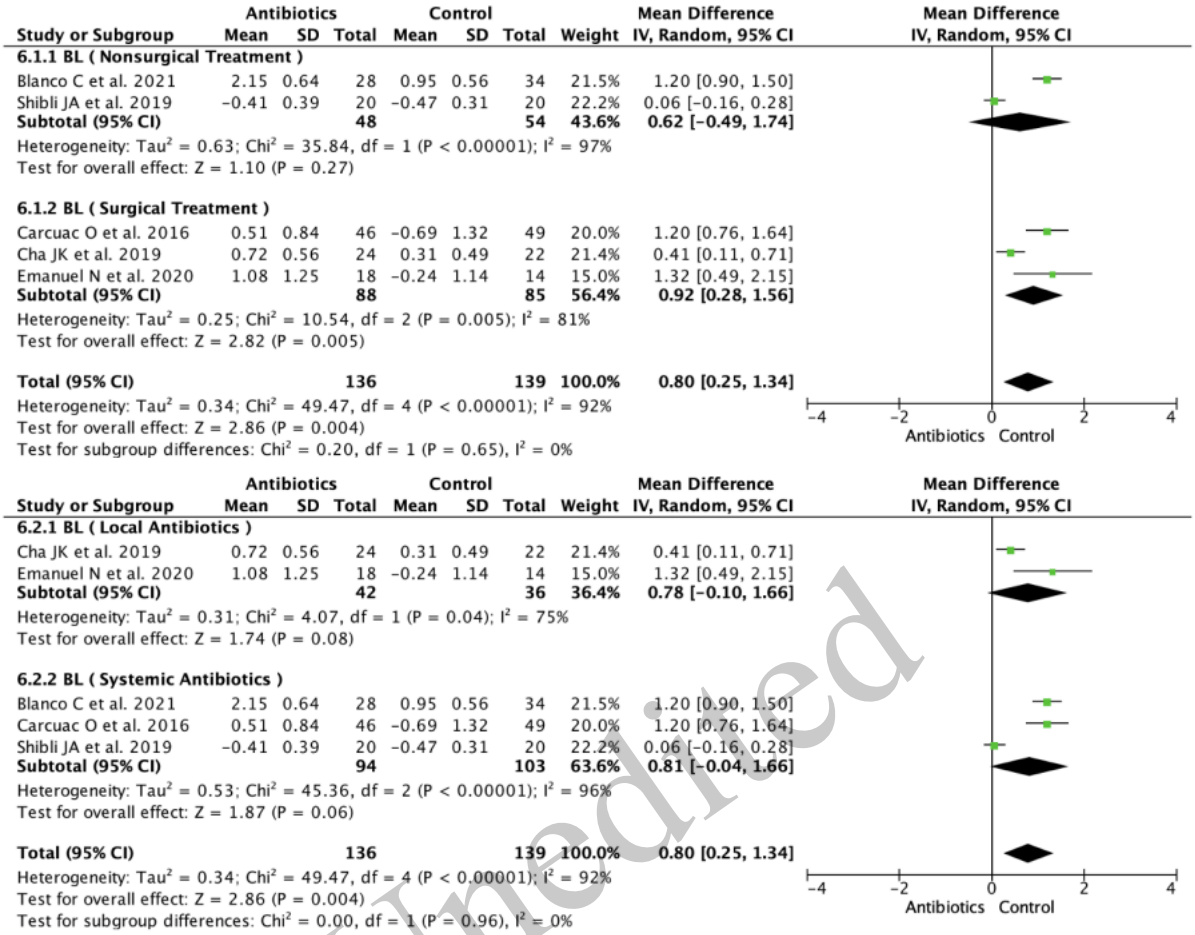

Fig. 6 Forest plot of BL and meta-analyses for the comparison of bone level

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4 Discussion

Overall, notable clinical benefits were observed when treating peri-implantitis with the inclusion of supplementary antibiotics. These benefits included a significant reduction in probing depth, improved bone level, enhanced clinical attachment level, and overall treatment success. When subgroup analysis was conducted, it was observed that the benefits of antibiotics were particularly pronounced in terms of probing depth reduction and treatment success across all treatment methods. In addition, antibiotics in conjunction with surgical therapy or local antibiotics resulted in reduced bone loss compared to control groups. It is noteworthy that, for the subgroup receiving nonsurgical treatment combined with systemic antibiotics, a significant improvement was reported at the clinical attachment level, which was not observed in other subgroups.

4.1 Local and systemic antibiotics

The substantial variability identified in the studies reporting BL values (I^2 = 92%) (Fig. 6) can be explained by the varied measurements employed in the different researches and whether they were performed by more than one individual. For example, Shibli et al. 2019 measured the distance between the level of the abutment and the top of the alveolar ridge with intraoral radiographs, whereas Emanuel et al. 2020 evaluated this parameter with standardized periapical radiographs relating to the reference point of implant; additionally, Carcuac et al. 2016 measured the mean values separately by two investigators, which was not mentioned in other studies.

In the studies concerned by this review, the use of antibiotics as systemic adjuvant could significantly ameliorate peri-implant inflammation in the short term, which was also proved in other meta-analyses (Feres et al. 2023). However, other reviewers doubted the effect of systemically-delivered antibiotics in combination with nonsurgical or surgical treatments (Boccia et al. 2023; Baus-Domínguez et al. 2023), especially in the long term (Teughels et al. 2023). Besides, the side effects of antibiotics can also make peri-implantitis more challenging to control. A recent systematic review (Verdugo et al. 2016) expressed concerns regarding the possibility of recurrent peri-implant opportunistic bacterial, viral and yeast infections in immunocompetent patients, in which several researches advocated drug sensitivity testing prior to systemic antibiotic use, although this was not performed in these studies.

The advantages of local antibiotic administration encompass the option to attain high concentrations at the targeted site, coupled with a lower risk of adverse effects and antibiotic resistance. Similarly, repeated and regular dosing is more conducive to antibiotic efficacy, and the patient's compliance does not affect the clinical advantages. The major drawbacks include significant cost and the need for experienced dentists to administer the treatment. The meta-analysis indicated substantial improvements in PPD (WMD = 0.67 (95% CI 0.13-1.21), I^2 = 0%), SR (WMD = 2.23 (95% CI 1.06-5.06), I^2 = 0%), and BL (WMD = 0.78 (95% CI -0.10-1.66), I^2 = 75%) in the antibiotics group (WMD = 0.78 (95% CI -0.10-1.66), I^2 = 75%). These findings align with the comprehensive review and meta-analysis conducted by Rovai et al. 2016, examining the supplementary impact of localized antibiotic therapy in treating peri-implantitis. Furthermore, a recent analysis confirmed the promising performance of localized antibiotics in surgical interventions (Baus-Domínguez et al. 2023). However, due to a paucity of data, it was difficult to interpret the results in terms of CAL and BL. What is more, Emanuel et al. 2020 found significantly higher bone growth in antibiotic groups than control groups after 6 months (-1.08±1.25 vs. 0.24±1.14, P = 0.005 < 0.01) and 12 months follow-up (-0.88±1.23 vs. -0.33±1.00, P = 0.006 < 0.01), and also significantly higher CAL in the antibiotic group after 12 months of follow-up (-2.21±1.27 vs. -0.42±1.38, P = 0.001<0.01), suggesting that local antibiotics may also have a beneficial effect on the bone and attachment levels. In addition, the observation time of relevant studies on topical antibiotics was shorter and longer observation is required, which is consistent with Passarelli et al. 2021.

4.2 Surgical and nonsurgical treatment

The adjunctive use of antibiotics in surgical treatment significantly improved PPD (WMD = 1.04 (95% CI 0.57-1.50), I^2 = 37%), SR (WMD = 3.24 (95% CI 1.62-6.48), I^2 = 0%) and BL (WMD = 0.92 (95% CI 0.28-1.56), I^2 = 81%). Except for BL, the heterogeneity for those values were modest, making the results more plausible. However, due to the lack of CAL data, me-

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ta-analysis could not be performed. Another meta-analysis of adjuvant antibiotic in non-surgical treatment (Grusovin et al. 2022) found similar results for PPD and concluded that adjuvant antibiotics can be used when mechanical debridement does not reach the therapeutic objectives. On the other hand, following a network meta-analysis investigating the impact of non-augmentative techniques in surgical interventions for peri-implantitis treatment, the adjuvant use of systemic antibiotics did not improve additional PPD or BL in peri-implantitis treatment. This included studies that did not directly compare antibiotics with other forms of adjuvant treatment, which may explain the disparity in the conclusions.

Notably, remarkable enhancements in PPD (WMD = 1.15 (95% CI 0.73-1.57), I^2 = 58%), SR (WMD = 1.93 (95% CI 1.10-3.37), I^2 = 6%), and CAL (WMD = 0.62 (95% CI 1.05-1.62), I^2=0%) were observed in the meta-analysis of adjuvant antibiotics in nonsurgical treatment. The current findings are partially consistent with prior researches, which indicated that supplemental antibiotics in non-surgical treatment for peri-implantitis improve PPD and SR (Grusovin et al. 2022). There was no significant difference in BL (WMD = 0.62 (95% CI -0.49-1.74), I2 = 97%), and given the substantial overlap of data within the meta-analysis between the non-surgical treatment and systemic antibiotics subgroups, attributing the observed effect specifically to the adjunctive use of antibiotics in non-surgical therapy remains challenging. It merits attention that, within a prospective case series analysis employing systemic antibiotics, the authors posited that the efficacy of non-surgical treatment modalities is questionable (Vilarrasa et al. 2023), which inspires us to conduct further investigation.

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4.3 The treatment method used in the control groups

In this review, the control groups in two trials (Emanuel et al. 2020; Park et al. 2021) received no extra therapy, while they received placebo in three other studies (Shibli et al. 2019; Cha et al. 2019; Blanco et al. 2022). In the remaining two articles (Carcuac et al. 2016; Polymeri et al. 2022), patients in control groups were rinsed with chlorhexidine, which was applied in both groups in one of them (Carcuac et al. 2016). In a way, these "control groups" did not use the updated techniques, such as laser therapy, photodynamic therapy, etc., even if the calculations showed that the effect of adjuvant use of antibiotics was superior to other adjuvant approaches. Thus, we cannot conclude that "adjunctive antibiotics are still the best adjuvant therapy for the treatment of peri-implantitis." Rather, the utilization of adjunctive antibiotics demonstrates enhanced effectiveness in addressing peri-implantitis when compared to adjuvant chlorhexidine rinsing or no additional therapy in terms of reducing periodontal pocket depth, controlling bone resorption and attachment loss, and improving implant survival rate. Additionally, in another meta-analysis published in 2021, our research team observed no substantial disparity in the impact of supplementary photodynamic therapy and supplemental

antibiotics in the treatment of peri-implant inflammation (Zhao et al. 2021). In fact, some other systematic reviews have found different impacts for different adjunctive measures, where antimicrobials could reduce PPD via a local or systemic method (Liñares et al. 2023). Because only RCTs were included in this review, and there are currently no relevant RCTs to validate the new technologies, we need more updated and higher-quality research on the adjuvant treatment of peri-implantitis to help clinicians make more informed decisions.

4.4 Sulcus bleeding index and microbiological results

The gingival sulcus bleeding index can detect early peri-implant mucosal inflammation (Lu et al. 2018). Due to the common occurrence of bacterial biofilms, peri-implant disease often arises, and alterations in the microbiome can be used to predict treatment effectiveness (Alves et al. 2022).

Changes in the gingival bleeding index were assessed in five articles, and only one of them showed greater changes in data for control groups than for antibiotics groups, with no statistically significant difference. It is important to note that the control group received chlorhexidine therapy. Control groups in the other trials were administered placebo or no adjuvant treatment, and only two of these trials revealed significant differences between the groups. Due to the diverse display techniques of bleeding on probing (BOP) scores, such as dichotomous and continuous approaches, no further data processing was performed in this work. In a previous meta-analysis review, no distinction was observed between the two groups regarding the impact of adjunctive antimicrobial photodynamic therapy and antibiotics implemented in the treatment of peri-implantitis (Zhao et al. 2021), which can be regarded as a reference for the effect of adjunctive antibiotics on the BOP indicator.

Microbiome results were also highlighted in five researches, all of which discovered a substantial drop in oral microbiome following therapy. Two papers indicated microbiome regeneration after three months, and the microbiota in the antibiotic groups exhibited a significant decrease throughout the entire study period. The abundance of P. gingivalis in the control group at the follow-up exhibited a significant reduction compared to the initial levels, according to Park et al. 2021. In other studies that did not report the number rebound, groups without antibiotic treatment exhibited a substantial decrease in bacterial count. This implies that only surgical/nonsurgical treatment may be "sufficient" in microflora control. Certainly, the employment of contemporary methodologies, such as the now widespread sequencing analysis technologies, is imperative to facilitate further research (Chen et al.2023).

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The varying conclusions across studies could be attributed to variations in the sampling methods used for microbiological analysis. For example, one study utilized DNA-DNA checkers hybridization, but the majority of the listed studies employed CFU to determine the number of bacteria.

4.5 Strengths and Limitations

The key weaknesses of this review are the inclusion of papers with a high-quality bias and the absence of pertinent randomized controlled clinical trials. It is important to highlight that different trials may have variations in treatment techniques, materials, prosthesis management, and dosage administration, which can potentially introduce bias in the results. Furthermore, the previously mentioned treatment limitations in the control group also contribute to potential bias. In one study (Cha et al. 2019), all patients took systemic antibiotics after therapy, which could have skewed the results. To minimize the impact of different data selection methods and observation times on the results, we selected the average value of multiple site data at the implant level as the analysis data, and considered data recorded as much as possible beyond the follow-up period of 6 months. Moreover, only data from two investigations (Emanuel et al. 2020; Blanco et al. 2022) were evaluated with numerous indicators, which also reduced the representativeness of data. Finally, due to the lack of pertinent reports, it is challenging to interpret the findings of these studies regarding the harmful effects of antibiotics.

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5 Conclusion

The administration of adjunctive antibiotics in the management of peri-implantitis can achieve a beneficial impact on short-term treatment outcomes, whereas possible side effects, such as drug resistance, still need to be considered. There is a lack of research comparing antibiotics to other emerging adjunctive technologies for peri-implantitis management, highlighting the need for further investigations. In general, the adjunctive use of antibiotics in the treatment of peri-implantitis still needs to be undertaken with caution.

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Author contributions

Yi-fan LU, Qian-ming CHEN, and Mi-si SI contributed to conception and design. Yi-fan LU, Si-qi BAO, and Hong-ke LUO performed the data acquisition, interpretation and statistical analysis. The first draft of the manuscript was written by Yi-fan LU, and all authors critically reviewed the manuscript.

Compliance with ethics guidelines

Yi-fan LU, Si-qi BAO, Hong-ke LUO, Qian-ming CHEN and Mi-si SI declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Agrawal R, Kumar A, Mohammed, et al. 2023. Biomaterial types, properties, medical applications, and other factors: a recent review [J]. J Zhejiang Univ Sci A, 24(5): 373-386.
https://doi.org/10.1631/jzus.A2200403

Alves CH, Russi KL, Rocha NC, et al., 2022. Host-microbiome interactions regarding peri-implantitis and dental implant loss. J Transl Med. 20(1):425.
https://doi.org/10.1186/s12967-022-03636-9

Baus-Domínguez M, Bakkali S, Hermida-Cabrera P, et al., 2023. A Systematic Review and Meta-Analysis of Systemic and Local Antibiotic Therapy in the Surgical Treatment of Peri-Implantitis. Antibiot Basel Switz. 12(7):1223.
https://doi.org/10.3390/antibiotics12071223

Berglundh T, Armitage G, Araujo MG, et al., 2018. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 45 Suppl 20:S286–S291.
https://doi.org/10.1111/jcpe.12957

Blanco C, Pico A, Dopico J, et al., 2022. Adjunctive benefits of systemic metronidazole on non‐surgical treatment of peri‐implantitis. A randomized placebo‐controlled clinical trial. J Clin Periodontol. 49(1):15–27.
https://doi.org/10.1111/jcpe.13564

Boccia G, Di Spirito F, D'Ambrosio F, et al., 2023. Local and Systemic Antibiotics in Peri-Implantitis Management: An Umbrella Review. Antibiot Basel Switz. 12(1):114.
https://doi.org/10.3390/antibiotics12010114

Carcuac O, Derks J, Abrahamsson I, et al., 2017. Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical trial. J Clin Periodontol. 44(12):1294–1303.
https://doi.org/10.1111/jcpe.12813

Carcuac O, Derks J, Charalampakis G, et al., 2016. Adjunctive Systemic and Local Antimicrobial Therapy in the Surgical Treatment of Peri-implantitis: A Randomized Controlled Clinical Trial. J Dent Res. 95(1):50–57.
https://doi.org/10.1177/0022034515601961

Cha JK, Lee JS, Kim CS. 2019. Surgical Therapy of Peri-Implantitis with Local Minocycline: A 6-Month Randomized Controlled Clinical Trial. J Dent Res. 98(3):288–295.
https://doi.org/10.1177/0022034518818479

Chan H-L, Lin G-H, Suarez F, et al., 2014. Surgical management of peri-implantitis: a systematic review and meta-analysis of treatment outcomes. J Periodontol. 85(8):1027–1041.
https://doi.org/10.1902/jop.2013.130563

Chen QM, Wang YH, Shuai J. 2023. Current status and future prospects of stomatology research. J Zhejiang Univ Sci B. 24(10):853-867.
https://doi.org/10.1631/jzus.B2200702

Claffey N, Clarke E, Polyzois I, et al., 2008. Surgical treatment of peri-implantitis. J Clin Periodontol. 35(8 Suppl):316–332.
https://doi.org/10.1111/j.1600-051X.2008.01277.x

Darby I. 2022. Risk factors for periodontitis & peri-implantitis. Periodontol 2000. 90(1):9–12.
https://doi.org/10.1111/prd.12447

Derks J, Tomasi C. 2015. Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol. 42 Suppl 16: S158-171.
https://doi.org/10.1111/jcpe.12334

Emanuel N, Machtei, Reichart M, Shapira L. 2020. D-PLEX500: a local biodegradable prolonged release doxycycline-formulated bone graft for the treatment for peri-implantitis. A randomized controlled clinical study. Quintessence Int. 51(7):546–553.
https://doi.org/10.3290/j.qi.a44629

Feres M, Martins R, Souza JGS, et al., 2023. Unraveling the effectiveness of antibiotics for peri-implantitis treatment: A scoping review. Clin Implant Dent Relat Res. 25(4):767–781.
https://doi.org/10.1111/cid.13239

Figuero E, Graziani F, Sanz I, et al., 2014. Management of peri-implant mucositis and peri-implantitis. Periodontol 2000. 66(1):255–273.
https://doi.org/10.1111/prd.12049

Graziani F, Karapetsa D, Alonso B, et al., 2017. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? Periodontol 2000. 75(1):152–188.
https://doi.org/10.1111/prd.12201

Grusovin MG, Pispero A, Del Fabbro M, et al., 2022. Antibiotics as Adjunctive Therapy in the Non-Surgical Treatment of Peri-Implantitis: A Systematic Review and Meta-Analysis. Antibiotics. 11(12):1766.
https://doi.org/10.3390/antibiotics11121766

Heitz-Mayfield LJ, Aaboe M, Araujo M, et al., 2018. Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry. Clin Oral Implants Res. 29 Suppl 16:351–358.
https://doi.org/10.1111/clr.13307

Heitz-Mayfield LJA, Mombelli A. 2014. The therapy of peri-implantitis: a systematic review. Int J Oral Maxillofac Implants. 29 Suppl:325–345.
https://doi.org/10.11607/jomi.2014suppl.g5.3

Unedited

Higgins, J.P.T.; Altman, D.G.; Gøtzsche, P.C., et al., 2011. The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials. BMJ. 343, d5928.
https://doi.org/10.1136/bmj.d5928

Higgins JPT, Thompson SG, Deeks JJ, et al., 2003. Measuring inconsistency in meta-analyses. BMJ. 327(7414):557–560.
https://doi.org/10.1136/bmj.327.7414.557

Keestra J a. J, Grosjean I, Coucke W, Quirynen, et al., 2015. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. J Periodontal Res. 50(3):294–314.
https://doi.org/10.1111/jre.12221

Khoshkam V, Chan HL, Lin GH, et al., 2013. Reconstructive procedures for treating peri-implantitis: a systematic review. J Dent Res. 92(12 Suppl):131S–8S.
https://doi.org/10.1177/0022034513509279

Klinge B, Gustafsson A, Berglundh T. 2002. A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. J Clin Periodontol. 29 Suppl 3:213–225; discussion 232-233.
https://doi.org/10.1034/j.1600-051x.29.s3.13.x

Lee C-T, Huang Y-W, Zhu L, et al., 2017. Prevalences of peri-implantitis and peri-implant mucositis: systematic review and meta-analysis. J Dent. 62:1–12.
https://doi.org/10.1016/j.jdent.2017.04.011

Li Z-B, Li K, Ding T, et al., 2022. The Effect of Nonaugmentative Approaches in the Surgical Treatment of Peri-implantitis: A Systematic Review and Network Meta-analysis. Int J Oral Maxillofac Implants. 37(2):270–282.
https://doi.org/10.11607/jomi.9211

Liñares A, Sanz-Sánchez I, Dopico J, et al., 2023. Efficacy of adjunctive measures in the non-surgical treatment of peri-implantitis: A systematic review. J Clin Periodontol. 50 Suppl 26:224–243.
https://doi.org/10.1111/jcpe.13821

Lu H, Tang H, Zhou T, Kang N. 2018. Assessment of the periodontal health status in patients undergoing orthodontic treatment with fixed appliances and Invisalign system: A meta-analysis. Medicine (Baltimore). 97(13):e0248.
https://doi.org/10.1097/MD.0000000000010248

Mombelli A, Lang NP. 1992. Antimicrobial treatment of peri-implant infections. Clin Oral Implants Res. 3(4):162–168.
https://doi.org/10.1034/j.1600-0501.1992.030402.x

Park S, Song YW, Cha J, et al., 2021. Adjunctive use of metronidazole‐minocycline ointment in the nonsurgical treatment of peri‐implantitis: A multicenter randomized controlled trial. Clin Implant Dent Relat Res. 23(4):543–554.
https://doi.org/10.1111/cid.13006

Polymeri A, van der Horst J, Anssari Moin D, et al., 2022. Non‐surgical peri‐implantitis treatment with or without systemic antibiotics: a randomized controlled clinical trial. Clin Oral Implants Res. 33(5):548‐557.
https://doi.org/10.1111/clr.13914

Renvert S, Roos-Jansåker A-M, Lindahl C, et al., 2007. Infection at titanium implants with or without a clinical diagnosis of inflammation. Clin Oral Implants Res. 18(4):509–516.
https://doi.org/10.1111/j.1600-0501.2007.01378.x

Rovai ES, Souto MLS, Ganhito JA, et al., 2016. Efficacy of Local Antimicrobials in the Non-Surgical Treatment of Patients With Periodontitis and Diabetes: A Systematic Review. J Periodontol. 87(12):1406–1417.
https://doi.org/10.1902/jop.2016.160214

Santos RS, Macedo RF, Souza EA, et al., 2016. The use of systemic antibiotics in the treatment of refractory periodontitis: A systematic review. J Am Dent Assoc 1939. 147(7):577–585.
https://doi.org/10.1016/j.adaj.2016.02.013

Unedited

Shibli JA, Ferrari DS, Siroma RS, et al., 2019. Microbiological and clinical effects of adjunctive systemic metronidazole and amoxicillin in the non-surgical treatment of peri-implantitis: 1 year follow-up. Braz Oral Res. 33(suppl 1):e080. https://doi.org/10.1590/1807-3107bor-2019.vol33.0080

Singh Rochika, Sripada L, Singh Rajesh. 2014. Side effects of antibiotics during bacterial infection: mitochondria, the main target in host cell. Mitochondrion. 16:50–54. https://doi.org/10.1016/j.mito.2013.10.005

Smeets R, Henningsen A, Jung O, et al., 2014. Definition, etiology, prevention and treatment of peri-implantitis--a review. Head Face Med. 10:34. https://doi.org/10.1186/1746-160X-10-34

Teughels W, Seyssens L, Christiaens V, et al., 2023. Adjunctive locally and systemically delivered antimicrobials during surgical treatment of peri-implantitis: A systematic review. J Clin Periodontol. 50 Suppl 26:359–372. https://doi.org/10.1111/jcpe.13773

Verdugo F, Laksmana T, Uribarri A. 2016. Systemic antibiotics and the risk of superinfection in peri-implantitis. Arch Oral Biol. 64:39–50. https://doi.org/10.1016/j.archoralbio.2015.12.007

Vilarrasa J, Soldini MC, Pons R, et al., 2023. Outcome indicators of non-surgical therapy of peri-implantitis: a prospective case series analysis. Clin Oral Investig. 27(6):3125–3138. https://doi.org/10.1007/s00784-023-04918-2

Wang Y, Chen CY, Stathopoulou PG, et al., 2022. Efficacy of Antibiotics Used as an Adjunct in the Treatment of Peri-implant Mucositis and Peri-implantitis: A Systematic Review and Meta-analysis. *Int J Oral Maxillofac Implants*. 37(2):235-249. https://doi.org/10.11607/jomi.9220

Yong J, Gröger S, VON Bremen J, et al. 2023. Photobiomodulation therapy assisted orthodontic tooth movement: potential implications, challenges, and new perspectives. J Zhejiang Univ Sci B. 24(11):957-973. https://doi.org/10.1631/jzus.B2200706

Zhang H, Li W, Zhang L, Yan X, et al., 2018. A nomogram prediction of peri-implantitis in treated severe periodontitis patients: A 1-5-year prospective cohort study. Clin Implant Dent Relat Res. 20(6):962–968. https://doi.org/10.1111/cid.12686

Zhao X, Lin H, Ding T, et al.2023. Overview of the main biological mechanisms linked to changes in periodontal ligament stem cells and the inflammatory microenvironment. J Zhejiang Univ Sci B. 24(5):373-386. https://doi.org/10.1631/jzus.B2200576

Zhao Y, Pu R, Qian Y, et al., 2021. Antimicrobial photodynamic therapy versus antibiotics as an adjunct in the treatment of periodontitis and peri-implantitis: A systematic review and meta-analysis. Photodiagnosis Photodyn Ther. 34:102231. https://doi.org/10.1016/j.pdpdt.2021.102231

Zitzmann NU, Berglundh T, Marinello CP, et al., 2001. Experimental peri-implant mucositis in man. J Clin Periodontol. 28(6):517–523. https://doi.org/10.1034/j.1600-051x.2001.028006517.x

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Supplementary information

Tables S1-S3

Table S1 Basic information of the included studies

Reference	Study design	Smoker	Diagnostic criteria	Group evaluated	Intervention	Intervention frequency	Number of patients/implants	Follow up periods	Outcomes	Success criteria
Nonsurgical + Systemic antibiotics										
Blanco C et al. 2022	RCT	smokers and non-smokers	PPD ≥6 mm, BOP/SOP + and MBL ≥3 mm	test group	NST + 250 mg MTZ	2 capsules TID, last for 7 days	16 patients/28 implants	3, 6, 12M	Significant decrease in PPD, CAL, MBL were found in two groups as compared to baseline. Antibiotics significantly reduced PPD, CAL, MBL, Pg, Tf and Cr for intergroup comparison.	PPD was reduced to 5 mm with no BOP or to <5 mm irrespective of BOP, and no further bone loss was detected between baseline and 1 year
				control group	NST + placebo	2 capsules TID, last for 7 days	16 patients/34 implants			
Polymeri A et al. 2022	RCT	smokers and non-smokers	PPD ≥5 mm, BOP/SOP + and MBL ≥3 mm	test group	NST + 375 mg AMX and 250 mg MTZ	1 tablet TID, last for 7 days	18 patients/18 implants	3M	Significant decrease in PPD were found in two groups as compared to baseline.	PPD < 5 mm, and no BOP/SOP
				control group	NST	/	19 patients/19 implants			

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				test group	NST + 400 mg MTZ and 500 mg AMX	TID, last for 14 days	20 patients/20 implants			Between- group comparisons were non-significant. Show improvement in PPD, BOP, CAL and MBL, but no significant differences were found in two groups as compared to baseline. Between- group comparisons were non-significant.	
Shibli JA et al. 2019	RCT	Nonsmokers	PPD > 5 mm, BOP/SOP + and MBL > 4 mm	control group	NST + placebo	NST + placebo	20 patients/20 implants	3, 6, 12M			PPD <5 mm, no BOP, and no bone loss
Nonsurgical + Local antibiotics											
Park SH et al. 2021	RCT	smoke<10 cigarette a day	PPD ≥5 mm, BOP/SOP +, and the presence of peri-implant bone loss in a peri-apical radiograph	test group	NST + 201 mg MTZ and 10 mg MH ointment	administered at 1, 2, 3W	38 patients/39 implants	3M		Show improvement in PPD and BOP, but no significant differences were found in four groups as compared to baseline. Antibiotics significantly reduced	The absence of BOP, SOP, and sites showing deep PPD (PPD ≥5 mm)
				control group	NST	one application	37 patients/39 implants				

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									mean PPD, BOP and red complex counts for intergroup comparison, but not between MM and MC groups. MM contributes to a significantly greater reduction in the PPD compared to MC in deep pockets.	
Surgical + Systemic antibiotics										
Carcuac O et al. 2016	RCT	smokers and non-smokers	PPD ≥6 mm in at least 1 aspect of the implant, BOP/SOP + and MBL >3 mm	test group	ST + 750 mg AMX	BID, commenced at 3 days before surgery and last for 10 days	25 patients/46 implants	6, 12M	Show improvement in PPD and MBL, but no significant differences were found in four groups as compared to baseline. Antibiotics contributed to extra bone gain and significantly reduced PPD	PPD ≤5 mm, no BOP/SOP, and bone loss ≤0.5 mm
				control group	ST	NR	24patients/49 implants (1 lost to FU)			

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										for intergroup comparison.	
Surgical + Local antibiotics											
Cha JK et al. 2019	RCT	nonsmokers	PPD >5 mm, BOP + and MBL >2 mm	test group	ST + 1 mg MH ointment	administered at 1 and 3 M	24 patients /24 implants (1 lost to FU)	3, 6M	Show improvement in PPD, BOP and MBL, but no significant differences were found in two groups as compared to baseline. Antibiotics significantly reduced PPD and MBL for intergroup comparison.	PPD <5 mm, no BOP/SOP, and no further bone loss	
				control group	ST + placebo	administered at 1, 3 M	22 patients /22 implants (3 lost to FU)				
Emanuel N et al. 2020	RCT	nonsmokers	PPD 6 to 10 mm, BOP/SOP +, and radiographic evidence for bone loss > 2 mm.	test group	ST + D-PLEX500(0.65% docycycline hyclate)	one application	14 patients/18 implants	6, 12M	Significant decrease in MBL were found only in test group compared to baseline. Antibiotics significantly reduced PPD, CAL and MBL at 12M for intergroup	NR	
				control group	ST	NR	13 patients/ 14 implants				

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comparison.

RCT, randomized clinical trial; PPD, pocket probing depth; BOP, bleeding on probing; SOP, suppuration on probing; MBL, marginal bone loss; CAL, clinical attachment level; NST, nonsurgical treatment; ST, surgical treatment; SRP, scaling and root planning; MTZ, metronidazole; AMX, amoxicillin; MH, minocycline; BID, twice a day; TID, three times a day; W, week; M, month; NR, Not reported.

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Table 2 Statistical data of the included studies

Reference	Group evaluated	Outcomes													
		Δ PPD (mm)			Δ CAL (mm)			Δ BOP (%)			Δ BL (mm)			Success rate%	Microbiology results
		3M	6M	12M	3M	6M	12M	3M	6M	12M	3M	6M	12M		
Nonsurgical + Systemic antibiotics															
Blanco C et al. 2022	Antibiotics	2.13‡	2.24‡	2.42‡	1.69‡	1.76‡	1.73‡	44.30b/21.10‡ PD 5-6mm/>6mm	35.30/24.2‡ PD 5-6mm/>6mm	52.90b/39.1‡ PD 5-6mm/>6mm	0.40	1.32	2.15‡	57.1 (16/28)	Quantitative reduction: Porphyromonas gingivalis (antibiotics group，6m) Porphyromonas gingivalis and Tannerella Forsythia (antibiotics
	Control	0.59	0.76‡	0.89‡	0.11‡	0.40‡	0.50‡	25.10b/14.5‡ PD	31.40/10.9‡ PD	37.20b/20.5‡ PD	0.24	0.81	0.95‡	23.5 (8/34)	

								5-6mm/>6mm	5-6mm/>6mm	5-6mm/>6mm					group , 12m)
Polymeri A et al. 2022	Antibiotics	2.28†	NR	NR	NR	NR	NR	16	NR	NR	MR	NR	NR	5 (1/18)	NR
	Control	1.47†	NR	NR	NR	NR	NR	11	NR	NR	NR	NR	NR	5 (1/19)	
Shibli JA et al. 2019	Antibiotics	NR	NR	3.1	NR	NR	2.6	NR	NR	51.0	NR	NR	0.41	65 (13/50)	Quantitative reduction: red complex species (both groups, 14d and 3m)
	Control	NR	NR	1.8	NR	NR	1.4	NR	NR	44.7	NR	NR	0.47	55 (11/50)	Quantitative regrowth: red complex pathogens (both groups, 3m to 1y)
Nonsurgical + Local antibiotics															
Park SH et al. 2021	Antibiotics	1.95‡	NR	NR	NR	NR	NR	-51‡	NR	NR	NR	NR	NR	31.6 (12/39)	Quantitative reduction: P. gingivalis, T. forsythia, T. denticola, P.intermedia, C. rectus, and F.nucleatum (antibiotics group, 12w)
	Control	1.28‡	NR	NR	NR	NR	NR	-33‡	NR	NR	NR	NR	NR	20.5 (8/39)	
Surgical + Systemic antibiotics															

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Carcuac O et al. 2016	Antibiotics	NR	3.49‡	3.44‡	NR	NR	NR	NR	52.2	34.8	NR	NR	0.51‡	65.2 (30/46)	Quantitative reduction: Total DNA probe counts (both groups, 12m) Quantitative regrowth: Fusobacterium nucleatum and Prevotella intermedia/Prevotella nigrescens (both groups, 12m)
	Control	NR	2.18‡	2.16‡	NR	NR	NR	NR	56.5	44.4	NR	NR	-0.69‡	37.5 (18/48)	
Surgical + Local antibiotics															
Cha JK et al. 2019	Antibiotics	NR	2.68‡	NR	NR	NR	NR	NR	49	NR	NR	0.72‡	NR	66.7 (16/24)	Quantitative reduction: Red complex bacteria (both groups, 6m)
	Control	NR	1.55‡	NR	NR	NR	NR	NR	31	NR	NR	0.31‡	NR	35.3 (8/22)	
Emanuel N et al. 2020	Antibiotics	NR	1.59	2.40	NR	1.59	2.21‡	NR	19.6	36.3‡	NR	1.08‡	0.88	NR	NR
	Control	NR	1.33	0.96	NR	0.89	0.42‡	NR	13.0	15.2	NR	-0.24‡	-0.33	NR	

PPD, pocket probing depth; BOP, bleeding on probing; SOP, suppuration on probing; MBL, marginal bone loss; CAL, clinical attachment level; NST, nonsurgical treatment; ST, surgical treatment; SRP, scaling and root planning; MTZ, metronidazole; AMX, amoxicillin; MH, minocycline; BID, twice a day; TID, three times a day; W, week; M, month; NR: not reported.

Δ: Mean change from baseline to last follow-up.

†: Statistically significant compared with baseline.

‡: Statistically significant between groups (on superior group).

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Table 3 Detailed information about treatment of the included studies

rence	Group evaluated	Before treatment	Surgical / nonsurgical treatment	Instrument	Implant supported restorations	After treatment	Follow up periods	Analyzed time point
gical + Systemic antibiotics								
C et al.	Antibiotics	rinsed with 0.12%CHX digluconate	supra-and submucosal mechanical debridement+remove granulation tissue and minor mucosal curettage+irrigated with 0.12%CHX digluconate	ultrasonic stainless steel scaling inserts (EMS®, Electro Medical Systems), stainless steel Columbia 4R/4L curette (LM Instruments Oy)	removed if possible	MTZ 250mg (2 tablets TID,7D)	3, 6, 12m	6m
	Control					placebo pills (2 tablets TID,7D)		
i A et al.	Antibiotics	NR	nonsurgical debridement	ultrasonic devices (EMS, Electro Medical Systems, Nyon, Switzerland) with the Polyether Ether Ketone (PEEK) fiber tip (PI instrument®, EMS, Nyon, Switzerland), and carbon fiber reinforced plastic hand instruments (Universal Implant Deplaquer®; Kerr Dental, Bioggio, Switzerland)	not removed	AMX 375 mg、MTZ 250 mg (1 tablet TID , 7D) +0.12%CHX (BID,4W)	3m	3m
	Control					0.12%CHX (BID,4W)		
A et al.	Antibiotics	NR	nonsurgical debridement	Teflon curettes	NR	MTZ400 mg 、AMX500 mg	3, 6, 12m	12m

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						(TID,14D)		
	Control					placebo pills (TID,14D)		
gical + Local antibiotics								
et al.	Antibiotics	oral hygiene	nonsurgical debridement	ultrasonic scaler (EMS, Nyon, Switzerland)	NR	MTZ 201mg + MH 10 mg ointment	1, 2, 3m	3m
	Control					NR		
+ Systemic antibiotics								
O et al.	Antibiotics	oral hygiene+ 750mg AMX BID 3d	pocket elimination+implant decontamination with saline	titanium-coated curettes (Hu-Friedy)	removed	AMX750mg (BID,7D)+CHX0.2% (BID,14D)	6, 12m	6m,12m
	Control	oral hygiene	pocket elimination+implant decontamination with 0.2%CHX			CHX0.2% (BID,14D)		
+ Local antibiotics								
t al.	Antibiotics	NR	pocket elimination+implant surface clean	titanium-coated curettes (Gracey; Hu-Friedy), a metallic copper-alloy ultrasonic scaler tip (B&L Biotech), a titanium brush (Dentium), an air-powder abrasive device (Air-Flow Master; Electronic Medical Systems)	NR	MH 10mg ointment+ AMX 500mg、ibuprofen (TID,3D)	1, 3, 6m	6m
	Control					placebo ointment+ AMX500mg、ibuprofen (TID, 3D)		
N et al.	Antibiotics	NR	pocket elimination	NR	NR	D-PLEX500（0.65% docycycline	6, 12m	6m

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