J Periodontal Implant Sci. 2022 Oct;52(5):352-369
https://doi.org/10.5051/jpis.2200340017
pISSN 2093-2278·eISSN 2093-2286

JPIS
Journal of Periodontal & Implant Science

Review
Periodontal Science

Check for updates

Azithromycin as an adjunct to subgingival professional mechanical plaque removal in the treatment of grade C periodontitis: a systematic review and meta-analysis

Oliver P Jones *, **Philippa J Hoyle**

Charles Clifford Dental Hospital, Sheffield, United Kingdom

OPEN ACCESS

Received: Dec 21, 2021
Accepted: Mar 22, 2022
Published online: Apr 15, 2022

***Correspondence:**
Oliver P Jones
Charles Clifford Dental Hospital, Wellesley Road, Sheffield, S10 2SZ, United Kingdom.
Email: oliver.jones15@nhs.net
Tel: +44-7907623443

ORCID iDs
Oliver P Jones
https://orcid.org/0000-0003-0136-014X
Philippa J Hoyle
https://orcid.org/0000-0001-9565-0185

Trial Registration
International Prospective Register of Systematic Reviews Identifier: CRD42020168195

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Oliver P Jones, Philippa J Hoyle; Formal analysis: Oliver P Jones; Investigation: Oliver P Jones, Philippa J Hoyle; Methodology: Oliver P Jones, Philippa J Hoyle;

ABSTRACT

The aim of this systematic review was to evaluate clinical and microbiological outcomes with the use of azithromycin as an adjunct to non-surgical subgingival professional mechanical plaque removal (PMPR) in the treatment of grade C periodontitis. Online database searches using high-level MeSH terms in a PICO structure were conducted along with hand-searching of relevant periodontal journals. Titles and abstracts of identified studies were independently reviewed by both authors and the full texts of studies meeting the inclusion criteria were independently reviewed. In total, 122 studies were identified through searches, of which 6 were included in the qualitative analysis and 4 in the meta-analysis. Three studies included in the meta-analysis were deemed at low risk of bias and 1 at serious risk. There were conflicting results on whether azithromycin reduced the number of subgingival pathogens or detectable subgingival *Aggregatibacter actinomycetemcomitans* between the included studies. The meta-analysis revealed a statistically significant probing depth reduction difference in favour of azithromycin compared to the control at 3 months (weighted mean difference [WMD]=−0.39 mm; 95% confidence interval [CI], −0.66 to −0.13 mm; I^2=0%) and 12 months (WMD=−1.32 mm; 95% CI, −1.71 to −0.93 mm; I^2=0%). The clinical attachment level change was also statistically significant in favour of azithromycin compared to the control at 3 months (WMD=−0.61 mm; 95% CI, −1.13 to −0.10 mm; I^2=71%) and 12 months (WMD=−0.88 mm; 95% CI, −1.32 to −0.44 mm; I^2=0%). Based upon these results, azithromycin offers additional improvements in some clinical parameters when used in conjunction with subgingival PMPR in patients with aggressive periodontitis over control groups. These improvements appear to be maintained for up to 12 months after treatment completion. However, due to a lack of well-designed studies, the conclusions that can be drawn from the available evidence are limited.

Trial Registration: International Prospective Register of Systematic Reviews Identifier: CRD42020168195

Keywords: Aggressive periodontitis; Anti-bacterial agents; Dental scaling; Periodontitis; Systematic review

JPIS Journal of Periodontal & Implant Science

Project administration: Oliver P Jones, Philippa J Hoyle; Supervision: Oliver P Jones, Philippa J Hoyle; Validation: Oliver P Jones, Philippa J Hoyle; Visualization: Oliver P Jones, Philippa J Hoyle; Writing - original draft: Oliver P Jones, Philippa J Hoyle; Writing - review & editing: Oliver P Jones, Philippa J Hoyle.

INTRODUCTION

The terminology describing periodontal diseases that are faster in progression and affect a younger cohort of patients has changed frequently. The 1989 World Workshop in Clinical Periodontics classification used the terms "juvenile periodontitis," "rapidly progressive periodontitis," and "pre-pubertal periodontitis" under the broader category of "early-onset periodontitis" [1].

This terminology was removed altogether at the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions [2] and replaced with "aggressive periodontitis," subcategorised into localised and generalised.

The primary diagnostic features included [3]:

- Systemically healthy patients
- Rapid attachment loss and bone destruction
- Familial aggregation

The secondary diagnostic characteristics not always present included [3]:

- Biofilm inconsistent with destruction levels
- Elevated Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans
- Phagocyte abnormalities
- Hyperresponsive macrophages

The features of localised aggressive periodontitis (LAP) included pubertal onset and localised attachment loss to the first molar and incisor (not affecting >2 other teeth). For generalised aggressive periodontitis (GAP), defining features included presentation below age 30, generalised interproximal attachment loss affecting ≥3 permanent teeth other than the first molars and incisors, and episodic destruction [4].

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [5] removed the term "aggressive periodontitis" as it was not believed there was sufficient evidence that chronic periodontitis and aggressive periodontitis had different aetiologies and pathophysiologies [6]. It is still recognised that certain forms of periodontitis affect a younger cohort, progress at a faster rate, and can present in a molar-incisor pattern [6,7]. Within this paper, grade C periodontitis is the terminology used, unless another term is stated within a referenced article.

The prevalence of grade C periodontitis varies according to geographical location and ethnicity [8]. In African populations, its prevalence is 1%–5%, while it is 0.1%–0.5% in Caucasian Europeans. Among Caucasians in North America, its prevalence is 0.1%–0.2%, but it is found in up to 2.6% of the Black population [8]. Although grade C periodontitis is less prevalent than other plaque-induced periodontal disease (reported to affect 46% of the adult population in the United States [9]), it can have profound implications, leading to early tooth loss, prosthetic and surgical implications, and increased restorative burdens.

Alongside effective patient-performed plaque control, non-surgical professional mechanical plaque removal therapy (PMPR) is used as a first-line treatment for biofilm-induced periodontal diseases to reduce the probing pocket depth and inflammation [10]. Systemic antimicrobials were first used as an adjunct to non-surgical treatment in grade C

https://doi.org/10.5051/jpis.2200340017

periodontitis when it was discovered that a principal microbe, *A. actinomycetemcomitans,* could penetrate the pocket epithelium rendering it beyond the effects of mechanical debridement [11]. In the treatment of grade C periodontitis, the use of adjunctive systemic antimicrobials alongside sub-gingival PMPR has been shown to improve the probing pocket depth and clinical attachment level when compared to PMPR alone [12-15].

The choice of adjunctive systemic antimicrobials has changed over time. Initially, tetracyclines were the antimicrobials of choice, as they offered improvements in both clinical and microbiological parameters [16], but concerns were raised about antimicrobial resistance. Metronidazole, which has proven efficacy against anaerobic microbes, was then shown to improve efficacy in the suppression of *A. actinomycetemcomitans* in patients with LAP, which correlated with improved clinical results [17]. Further to this, Guerrero et al. [18] assessed the effect of a 7-day adjunctive course of 500 mg of amoxicillin and 500 mg of metronidazole (TDS) in the treatment of GAP. The group receiving adjunctive antimicrobials demonstrated statistically significant improvements in the full-mouth probing pocket depth at moderate (4–6 mm) (0.4 mm; 95% confidence interval [CI], 0.1–0.7 mm) and deep (≥7 mm) (1.4 mm; 95% CI, 0.8–2 mm) sites at 6 months in comparison to placebo.

In the UK, the standard of treatment for grade C periodontitis is sub-gingival PMPR in combination with adjunctive antimicrobials where indicated [19,20]. The antimicrobial of choice is 500 mg of amoxicillin administered 3 times/day for 7 days along with 200 mg of metronidazole 3 times/day for 7 days, as this combination has been most frequently documented to be the most effective adjunct [14]. For patients with penicillin allergies, 100 mg of doxycycline once daily for 21 days with a 200-mg loading dose is recommended [19].

Although amoxicillin and metronidazole offer wide antimicrobial activity, they are not without issues. Over half of the patients in the test group in the study of Guerrero et al. [18] reported an adverse event. Additionally, this combination requires the patient to take a total of 42 capsules. Guerrero et al. [21] later demonstrated that incomplete adherence to this antibiotic regimen resulted in poorer clinical outcomes than observed in those who fully complied.

It is for these reasons that azithromycin has been suggested. The accepted regimen is 500 mg once daily for 3 days [20], therefore only requiring the patient to take 3 tablets, theoretically increasing compliance. A retrospective cohort study reviewing >16,000 case notes found that penicillins accounted for 42.11% of recorded antibiotic sensitivity reactions, whereas macrolides only accounted for 3.5% [22]. Azithromycin is a macrolide providing a broad spectrum of activity against Gram-positive and Gram-negative organisms (commonly associated with periodontal disease) [23]. As well as its antimicrobial properties, azithromycin has been shown to demonstrate anti-inflammatory activity [24]. It reaches high tissue concentrations quickly and remains at this level for longer due to its extended half-life [25]. Azithromycin is able to penetrate inflamed periodontal tissues [26,27], which is beneficial when used in the treatment of grade C periodontitis due to the ability of *A. actinomycetemcomitans* to penetrate periodontal tissues [11].

With the term “aggressive periodontitis” removed from the most recent classification system [5], clinicians may be unsure in which circumstances systemic antimicrobials offer additional benefit in conjunction with PMPR. Although the new classification [5] does not use the term “aggressive periodontitis,” diagnostic criteria are still embedded within the staging and grading-based diagnosis.

https://doi.org/10.5051/jpis.2200340017

Staging classifies disease extent and severity at the time of a patient's presentation based upon measurable destroyed tissue attributable to periodontal disease. Grading gives an indication of a patient's susceptibility to periodontal disease, accounting for cumulative risk factors throughout life. The primary criteria for grade C disease are a percentage bone-loss/age ratio >1, destruction exceeding what would be expected based on biofilm presence, and specific clinical patterns, such as a molar-incisor pattern. Therefore, grade C disease may correspond closely to what was previously termed "aggressive periodontitis." The EFP S3 guideline for the treatment of stage I–III periodontitis only recommends the adjunctive use of specific systemic antimicrobials in specific patient groups (generalised periodontitis of grade C in younger adults) [10].

Recent UK guidance [20] also recognises this and states that "Systemic antimicrobials are only recommended as an adjunct to effective mechanical debridement, oral hygiene instruction and management of modifiable risk factors in patients aged <40–45 years with rapidly progressing periodontal disease." First-line antibiotics include amoxicillin (500 mg, 3 times/day) and metronidazole (400 mg, 3 times/day) for up to 5 days, with azithromycin (500 mg, 1 time/day) for 3 days as a second line.

Whilst recommendations have been made regarding the use of azithromycin in recent guidelines [20], there have been no systematic reviews and meta-analyses focusing specifically on treatment outcomes in grade C periodontitis. The aim of this systematic review was to investigate whether the adjunctive use of systemic azithromycin improves surrogate outcome measures and microbiological outcomes in the non-surgical treatment of grade C periodontitis in comparison to a control.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [28]. The methodology was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID:CRD42020168195).

Eligibility criteria

Participants

Studies were included where participants had a diagnosis of grade C periodontitis. Alternative terms included aggressive, rapidly progressing, early-onset, and juvenile periodontitis. No restrictions were placed on the number, sex, or age of participants or the pattern of disease. Studies were excluded where participants had any other diagnosis of periodontal disease or peri-implantitis.

Interventions

Studies were eligible for inclusion if participants' treatment included non-surgical PMPR in combination with systemic azithromycin. Studies were excluded if surgical periodontal therapy was undertaken, supragingival scaling was performed, other antimicrobials were given as the intervention, or azithromycin was delivered locally.

https://doi.org/10.5051/jpis.2200340017

Comparators

Studies were included if the aforementioned interventions were compared to non-surgical periodontal therapy in conjunction with a placebo, alternative antimicrobial, or no adjunct. Exclusions were placed on surgical periodontal therapy and local delivery of the comparator.

Outcomes

The primary outcome measures were mean changes from baseline in the probing pocket depth, clinical attachment level, bleeding on probing, microbiological outcomes, and adverse events. The secondary outcomes were patient-reported outcomes if included. A minimum of a 3-month follow-up was required. Studies were excluded if pre-operative and post-operative measurements were not available.

Study design

All study designs written in English and undertaken on human subjects were considered.

Search strategy

Electronic database searches were completed for the Cochrane Library, Web of Science, Scopus, MEDLINE (Medical Literature Analysis and Retrieval System Online, via Ovid) and CINAHL (Cumulative Index to Nursing and Allied Health Literature). The grey literature database opengrey.eu was searched, as well as clinicaltrials.gov to look for ongoing trials. MeSH terms were created using the Population, Intervention, Comparison, Outcomes and Study design (PICO) framework and adapted for each database. An example search strategy for Scopus is summarised in **Table 1**. The searches were completed from the inception of the database through to May 2020.

Hand searching was completed for the following journals: *Periodontology 2000*, *Journal of Clinical Periodontology*, and *Journal of Periodontology*. The reference lists of included studies were screened for further eligible studies.

Study selection

The titles and abstracts of all identified studies were screened independently by each author (OJ, PH). For studies appearing to meet the inclusion criteria, or for studies where there was a lack of information to make a decision, the full texts were obtained and reviewed. Full texts were reviewed independently by each author (OJ, PH) to determine whether the inclusion criteria were met. Disagreements were resolved through discussion and re-evaluation, and inter-reviewer agreement was assessed using the Cohen kappa coefficient.

Data collection

Data collection for included texts was independently conducted within a computer-based data capture form by each reviewer (OJ, PH) and compared. The form was piloted prior to use to ensure all relevant information was captured. The following data were collected where available:

- Authors, year of publication, and country/setting
- Study design

Table 1. Search strategy using MeSH terms for the Scopus database

Example search terms (Scopus)	(TITLE-ABS-KEY (aggressive AND periodontitis) OR TITLE-ABS-KEY (aggressive AND periodontal AND disease) OR TITLE-ABS-KEY (juvenile AND periodontitis) OR TITLE-ABS-KEY (juvenile AND periodontal AND disease) OR TITLE-ABS-KEY (rapidly AND progressing AND periodontitis) OR TITLE-ABS-KEY (rapidly AND progressing AND periodontal AND disease) OR TITLE-ABS-KEY (early AND onset AND periodontitis) OR TITLE-ABS-KEY early AND onset AND periodontal AND disease) OR TITLE-ABS-KEY (grade AND c AND periodontitis) OR TITLE-ABS-KEY (grade AND c AND periodontal AND disease) AND TITLE-ABS-KEY (azithromycin))

https://doi.org/10.5051/jpis.2200340017

- Demographics of participants including average age, female:male (F:M) ratio, and co-morbidities
- Diagnosis given
- Interventions: details of treatment, azithromycin regimen
- Comparators: details of treatment, regimen of comparator
- Outcome measures: pocket probing depth (mm), clinical attachment level (mm), bleeding on probing (%), microbiological outcomes, adverse events, patient-reported outcomes
- Patients lost to follow-up

Risk of bias assessment

The Risk of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool [29] and the Revised Cochrane Risk of Bias tool for randomised controlled studies (RoB2) [30] were used to assess the risk of bias for individual studies. Each tool looked at specific domains from which bias could arise, culminating in an overall risk of bias for that study. If sufficient studies were eligible (at least 10), publication bias was assessed through the use of a funnel plot [31].

Quality assessment

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Pro Guideline Development Tool [32].

Statistical analysis

The included studies were all subject to a qualitative review. Where appropriate, studies with sufficient methodological homogeneity were included in a quantitative review through a meta-analysis with the use of Review Manager [33] version 5.3.

RESULTS

Literature search

The study selection process is outlined in **Figure 1**. A total of 122 records were identified through online and hand searching after duplicates were removed. Eighty-six articles were excluded after screening as they did not meet the inclusion criteria, leaving 36 articles for full-text review. The full-text review identified 6 articles [34-39] eligible for inclusion in the qualitative review and 4 articles suitable for the quantitative meta-analysis based on an evaluation of clinical and methodological homogeneity [34,35,37,39]. The authors decided to include the study of Martande et al. [39], although it did not meet the eligibility criteria for the population investigated. This study investigated patients with "*A. actinomycetemcomitans*-associated periodontitis (AAAP)." It was stated that AAAP is rapidly progressive and has certain microbiological and immunological characteristics influencing the course and progression of destruction. The authors concluded that this classification was sufficiently similar to previous classifications of grade C periodontitis that it should be included.

The inter-reviewer agreement for the inclusion of articles for full-text review calculated using the Cohen kappa coefficient was 0.86, and the corresponding coefficient for inter-assessor agreement at the final stage for articles to be included was 0.81. This indicated a good degree of inter-assessor agreement at both stages.

https://doi.org/10.5051/jpis.2200340017

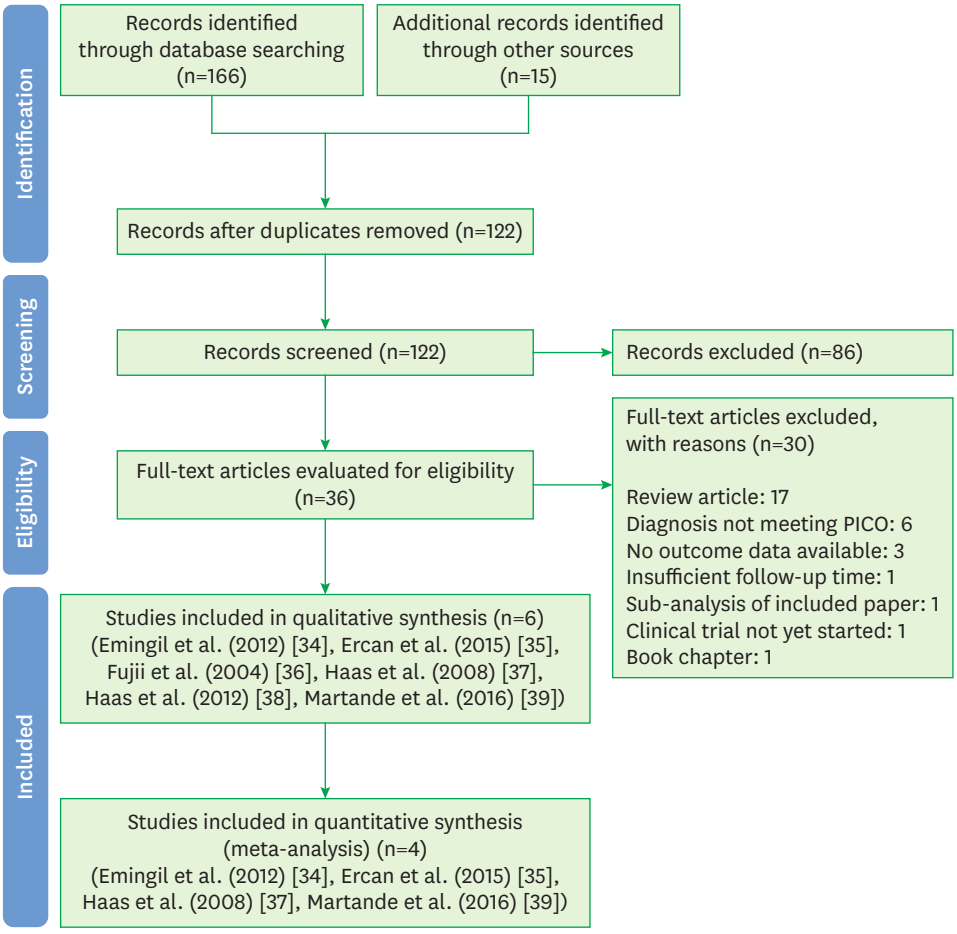

Figure 1. PRISMA study selection flow diagram.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis, PICO: Population, Intervention, Comparison, Outcomes and Study design.

Description of the studies

Table 2 outlines the data captured from each article included in the review. Four randomised controlled trials [34,37-39], 1 non-randomised controlled trial [36], and 1 retrospective analysis [35] were included in the qualitative analysis. The study of Haas et al. [38] was included as a narrative review of microbiological outcomes.

Risk of bias assessment

Table 3 outlines the risk of bias outcomes for each of the 6 included studies. The 4 included randomised controlled trials [34,37-39] were all deemed to have a low risk of bias due to their robust methodology. The retrospective analysis [35] had a serious risk of bias due to a lack of information surrounding confounding baseline factors, and the non-randomised controlled trial [36] had a critical risk of bias due to incomplete reporting of outcomes.

Statistical analysis

The available outcome data from each study were divided into comparative time points (3, 6, and 12 months). Time point means were used to calculate mean changes in periodontal parameters from baseline, which were used as the summary measures for meta-analysis. Standard deviations were calculated for any studies where they were not provided.

https://doi.org/10.5051/jpis.2200340017

Table 2. Overview of study characteristics

Study	Objectives	Methods	Participants	Summary findings
Emingil et al. (2012) [34]	To investigate the efficacy of AZT on clinical, microbiological and biochemical parameters beyond that obtained by NSPT alone in patients with GAP	Design: randomized, double blind, placebo controlled, parallel arm trial. Participant diagnosis: GAP. Intervention: NSPT + 500 mg AZT once daily for 3 d, given at last visit of treatment. Comparison: NSPT + placebo capsules once daily, 3 d given at last visit of treatment. Outcomes: PPD, CAL, BOP%, PI%, adverse events, GCF, microbiological. Operators: one calibrated for pre & post-operative measurements. One calibrated for treatment and OH. Follow-up: 1, 3 and 6 mo.	Number: 36 recruited (18 test and 18 control). Dropouts: 4 (2 test and 2 control); 32 analysed after dropouts (16 test and 16 control). Mean age: test 28.75 yr, control 29.56 yr. F:M: 15:17; 7:9 test and 8:8 control. Smokers: excluded if >10 cigarettes per day. Included if <10 cigarettes per day. 7/16 smokers in test group. 6/16 smokers in control group. Comorbidities: excluded diabetes, severe systemic illness, immunological condition.	All clinical and microbiological parameters improved over the 6-mo study period with similar improvements noted in both test and control groups. Adjunctive AZT provided no additional benefit over non-surgical periodontal therapy on clinical or microbiological parameters in patients with GAP.
Ercan et al. (2015) [35]	To determine the clinical short-term effects of AZT and a combination of MTZ and AMX in combination with SRP in patients with GAP.	Design: retrospective cohort study. Participant diagnosis: GAP. Intervention: Intervention 1: SRP + AZT 500 mg, once daily for 3 d. Intervention 2: SRP + MTZ & AMX 500 mg TDS, number of days not stated. Comparison: SRP alone. Outcomes: PPD, CAL, GI, BOP%, PI%. Operators: not recorded. Follow-up: 3 mo.	Number: 45 (15 AZT group, 15 MTZ + AMX group and 15 control group). Dropouts: N/A. Mean age: AZT 29.27 yr, MTZ + AMX 29.80 yr, control 31.86 yr. F:M: 32:13; AZT 12:3, MTZ + AMX 9:6, control 11:4. Smokers: excluded. Comorbidities: excluded.	Clinical periodontal parameters improved in all 3 groups 3 months after treatment. Clinical parameters were decreased more in the AZT and MTZ + AMX groups than the control, but this difference did not reach significance.
Fujii et al. (2004) [36]	Investigate the effectiveness of AZT in the non-surgical treatment of early onset aggressive periodontitis.	Design: non-randomised control trial. Participant diagnosis: early onset aggressive periodontitis. Intervention: NSPT + AZT 500 mg once daily for 3 d. Not stated if before or after treatment. Comparison: NSPT alone. Outcomes: PPD, BOP%, treatment time. Operators: not recorded. Follow-up: not specified.	Number: 11 (5 test and 6 control). Dropouts: 0. Mean age: not recorded. F:M: 8:3. Smokers: not recorded. Comorbidities: not recorded.	The use of AZT improved clinical parameters and shortened the time span of the initial treatment phase.
Haas et al. (2008) [37]	Compare the long-term clinical effect of the adjunctive use of AZT or placebo with NSPT in the treatment of aggressive periodontitis.	Design: randomized, double blind, placebo controlled, parallel design trial. Participant diagnosis: presence of PPD & clinical attachment loss of >4 mm, with bleeding on probing in at least one incisor & one first molar. Intervention: NSPT + AZT 500 mg, once daily for 3 d at the start of treatment. Comparison: NSPT + placebo capsules once daily for 3 d. Outcomes: PPD, CAL, BOP%. Operators: one for treatment, one for examination. Follow-up: 12 mo.	Number: 25 recruited (12 test and 13 control). Dropouts: 1; 24 analysed after dropouts (12 test and 12 control). Mean age: test 22.5 yr, control 20.1 yr. F:M: 11:13; test 7:5 and control 4:8. Smokers: included as stratified variable, 5/24. Comorbidities: not recorded.	Periodontal probing depth and clinical attachment level improved significantly from baseline to 12 months in both groups, with the test group showing significantly more reduction in mean probing depths compared with controls.
Haas et al. (2012) [38]	Compare the microbiological outcomes of the use of AZT or placebo as adjuncts to NSPT in the treatment of young subjects with aggressive periodontitis.	Design: randomized, double blind, placebo controlled, parallel design trial. Participant diagnosis: presence of PPD & clinical attachment loss of >4 mm, with bleeding on probing in at least one incisor & one first molar. Intervention: NSPT + AZT 500 mg, once daily for 3 d at the start of treatment. Comparison: NSPT + placebo capsules once daily for 3 d. Outcomes: microbiological. Operators: one for treatment, one for examination. Follow-up: 12 mo.	Number: 25 recruited (12 test and 13 control). Dropouts: 1; 24 analysed after dropouts (12 test and 12 control). Mean age: test 22.5 yr, control 20.1 yr. F:M: 11:13 (test 7:5 and control 4:8). Smokers: included as stratified variable, 5/24. Comorbidities: not recorded.	AZT was ineffective in lowering the subgingival levels of important putative periodontal pathogens in young aggressive periodontitis subjects compared to placebo.
Martande et al. (2014) [39]	Evaluate and compare the clinical and microbiological effects of NSPT alone or in combination with systemic AZT in the treatment of AAAP.	Design: randomized, double blind, placebo controlled, parallel design trial. Participant diagnosis: AAAP. Intervention: NSPT + AZT 500 mg, once daily for 3 d at the end of treatment. Comparison: NSPT + placebo once daily for 3 d starting after completion of treatment. Outcomes: CAL, PPD, BOP%, adverse events, microbiological. Operators: one for treatment, one for examination. Follow-up: 3, 6 and 12 mo.	Number: 70 (35 test and 35 control). Dropouts: 0. Mean age: test 32.6 yr, control 33.3 yr. F:M: 30:40; test 16:19 and control 14:21. Smokers: excluded. Comorbidities: systemic diseases such as diabetes mellitus excluded.	The AZT group showed statistically significant reduction in mean probing depths compared to placebo, while clinical attachment level gain was significant in the AZT group compared to the placebo group. There was a statistically significant reduction in the number of subjects positive for *A. actinomycetemcomitans* in the AZT group.

AZT: azithromycin, GAP: generalised aggressive periodontitis, NSPT: non-surgical periodontal therapy, PPD: probing pocket depth, CAL: clinical attachment level, BOP: bleeding on probing, PI: plaque index, GCF: gingival crevicular fluid, MTZ: metronidazole, AMX: amoxicillin, SRP: scaling and root planing, TDS: three times a day, GI: gingival index, N/A: not applicable, AAAP: *Aggregatibacter actinomycetemcomitans*-associated periodontitis.

https://doi.org/10.5051/jpis.2200340017

Table 3. Risk of bias assessment for all included studies

Paper	Method	Overall risk of bias	Domain
Emingil et al. (2012) [34]	Cochrane RoB V2, (Sterne et al., 2019 [30])	Low	Risk of bias arising from the randomization process: Low Risk of bias due to deviations from the intended interventions: Low Missing outcome data: Low Risk of bias in measurement of the outcome: Low Risk of bias in selection of the reported result: Low
Haas et al. (2008) [37]	Cochrane RoB V2, (Sterne et al., 2019 [30])	Low	Risk of bias arising from the randomization process: Low Risk of bias due to deviations from the intended interventions: Low Missing outcome data: Low Risk of bias in measurement of the outcome: Low Risk of bias in selection of the reported result: Low
Haas et al. (2012) [38]	Cochrane RoB V2, (Sterne et al., 2019 [30])	Low	Risk of bias arising from the randomization process: Low Risk of bias due to deviations from the intended interventions: Low Missing outcome data: Low Risk of bias in measurement of the outcome: Low Risk of bias in selection of the reported result: Low
Martande et al. (2014) [39]	Cochrane RoB V2, (Sterne et al., 2019 [30])	Low	Risk of bias arising from the randomization process: Low Risk of bias due to deviations from the intended interventions: Low Missing outcome data: Low Risk of bias in measurement of the outcome: Low Risk of bias in selection of the reported result: Low
Fujii et al. (2004) [36]	Robins-I (Sterne et al., 2016 [29])	Critical	Bias due to confounding: Critical Bias in selection of participants into the study: Low Bias in classification of interventions: Low Bias due to deviations from intended interventions: Moderate Bias due to missing data: Critical Bias in measurement of outcomes: Moderate Bias in selection of the reported result: Moderate
Ercan et al. (2015) [35]	Robins-I (Sterne et al., 2016 [29])	Serious	Bias due to confounding: Serious Bias in selection of participants into the study: Serious Bias in classification of interventions: Low Bias due to deviations from intended interventions: Low Bias due to missing data: Low Bias in measurement of outcomes: Moderate Bias in selection of the reported result: Low

Methodological and clinical heterogeneity were assessed descriptively for the included studies by comparing PICO study characteristics (**Table 2**). Four studies [34,35,37,39] were deemed to have sufficient methodological homogeneity, particularly at the comparative time points, for a meta-analysis to be undertaken using Review Manager [33] version 5.3.

Clinical outcomes

Of the 6 studies included in the qualitative review, 4 studies were included in the quantitative analysis after assessment of heterogeneity [34,35,37,39] and 2 were not [36,38]. Statistical heterogeneity was assessed using χ^2 and I^2 in the Review Manager [33] version 5.3, which found significant heterogeneity for the clinical attachment level (χ^2=6.92, P=0.03, I^2=71%) at the 3-month time point and PPD (χ^2=18.45, P<0.001, I^2=95%) and the clinical attachment level (χ^2=4.19, P=0.04, I^2=77%) at the 6-month time point. These heterogeneity results should be interpreted with caution due to the limited number of studies; therefore, a random-effects model was used for statistical analyses.

Qualitative summary of the individual included studies

All participants complied with the recommended intervention/control regimens in all studies except for 1 patient in the study of Haas et al. [37]. After unblinding, this patient was in the placebo group and they were excluded from final analysis as they were lost to

https://doi.org/10.5051/jpis.2200340017

follow-up. Three out of the 6 studies [34,37,38] conducted stratified analyses according to smoking status, 2 studies [35,39] excluded smokers, and 1 study did not discuss this potential confounder [36]. Three of the studies also excluded patients with comorbidities [34,35,39], while 3 studies did not consider this confounder [36-38]. All of the included randomised controlled trials [34,37-39] were powered to 80% with an alpha of 0.05 and were deemed to have a low risk of bias (**Table 3**).

Emingil et al. [34] reported statistically significant improvements in periodontal parameters (probing depth, clinical attachment loss, and bleeding on probing) for both the azithromycin and placebo group (P<0.05), which were similar at all time points (P>0.05).

Ercan et al. [35] reported significant reductions in the probing depth (azithromycin: P<0.01, metronidazole and amoxicillin: P<0.001, and control: P<0.001), clinical attachment level (azithromycin: P<0.01, metronidazole and amoxicillin: P<0.001, and control: P<0.01) and bleeding on probing (azithromycin: P<0.001, metronidazole and amoxicillin: P<0.001, and control: P<0.001) from baseline to 3 months. The differences between the groups were not found to be statistically significant, concluding that all treatments improved clinical parameters.

Fujii et al. [36] presented only a narrative discussion, and the results should be interpreted with caution due to a critical risk of bias. Within the azithromycin group, significant reductions were noted in the probing depth (P<0.01), change in the percentage of pockets ≥4 mm (P<0.01), and bleeding on probing (P<0.05). However, the authors did not record the time points at which these measurements were made, and there were no comparative outcome data for the control group.

Haas et al. [37] reported statistically significant reductions in probing pocket depths at 12 months from baseline between the azithromycin (2.88±0.23 mm) and placebo (1.85±0.36 mm) group (P=0.025). A statistically significant difference in the gain in the clinical attachment level was also found between the azithromycin (1.68±0.20 mm) and placebo (0.97±0.29 mm) groups (P=0.05). The difference in bleeding on probing was not found to be statistically significant (P=0.91).

Haas et al. [38] only analysed the microbiological outcomes of the patients first reported in an earlier study [37]. These findings are described in section 3.6.

Martande et al. [39] reported statistically significant differences in the mean reduction of probing depth, favouring the azithromycin group at all time points from baseline (1 month: P=0.022; 3 months: P=0.002; 6 months: P<0.001; and 12 months: P<0.001). This was also seen for clinical attachment level gain at 3, 6, and 12 months, favouring the azithromycin group (3 months: P<0.001; 6 months: P<0.001; and 12 months: P<0.001). A significant between-group difference in bleeding on probing percent was only noted at the 6-month time point (P=0.027).

Quantitative review and meta-analysis

At 3 months, based upon 3 studies [34,35,39] with 132 participants (test F:M ratio: 35:31, mean age 30.2 years and control F:M ratio: 33:33, mean age 31.5 years) a statistically significant difference in favour of azithromycin was found for probing pocket depth reduction (**Figure 2**) (weighted mean difference [WMD]=-0.39 mm; 95% CI, −0.66 to −0.13 mm; I^2=0%) and clinical attachment level (**Figure 3**) (WMD=−0.61 mm; 95% CI, −1.13 to −0.10 mm; I^2=71%)

https://doi.org/10.5051/jpis.2200340017

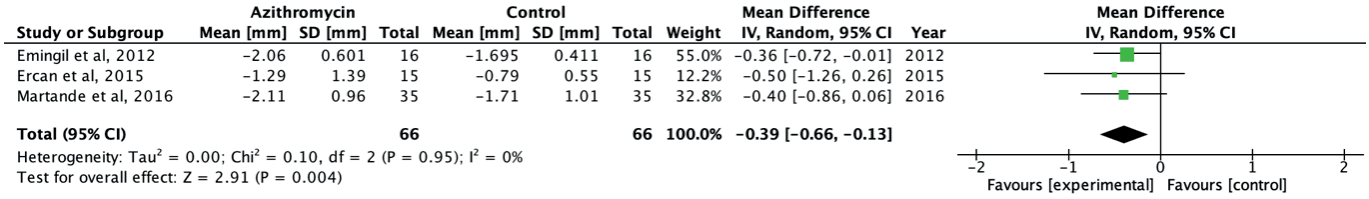

Figure 2. Probing pocket depth (mm) changes at 3 months from baseline.
SD: standard deviation, CI: confidence interval.

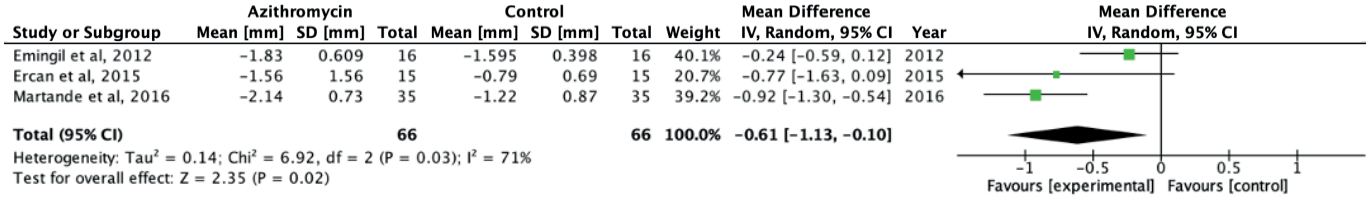

Figure 3. Clinical attachment level (mm) changes at 3 months from baseline.
SD: standard deviation, CI: confidence interval.

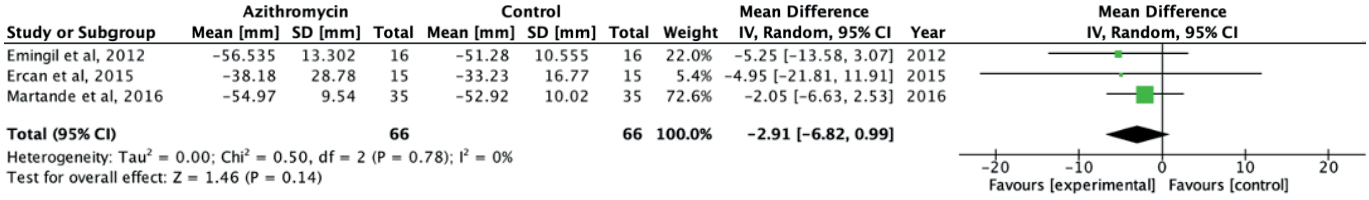

Figure 4. Bleeding on probing (%) changes at 3 months from baseline.
SD: standard deviation, CI: confidence interval.

but not for bleeding on probing (**Figure 4**) (WMD=−2.91%; 95% CI. −6.82% to 0.99%; I^2=0%) when compared to a placebo or no adjuncts alongside PMPR. For the 3-month outcomes, the certainty of the evidence was deemed to be low as assessed by using the GRADE Pro Guideline Development Tool [32] due to the risk of bias and imprecision of results (**Supplementary Figure 1**).

At 6 months, based upon 2 studies [34,39] with 102 participants (test F:M ratio: 23:28, mean age 30.7 years and control F:M ratio: 22:29, mean age 31.4 years), there was no difference noted for probing pocket depth reduction (**Figure 5**) (WMD=−0.88 mm; 95% CI, −2.10 to 0.34 mm; I^2=95%) or clinical attachment level (**Figure 6**) (WMD=−0.58 mm; 95% CI, −1.26 to 0.10 mm; I^2=76%) between the azithromycin and the placebo groups. Bleeding on probing was lower in the azithromycin group than in the placebo group (**Figure 7**) (WMD=−4.89%; 95% CI, −8.85% to −0.93%; I^2=0%). The certainty of the evidence was deemed to be moderate for the probing pocket depth and clinical attachment level outcomes due to the imprecision of the results, and high for bleeding on probing (**Supplementary Figure 1**).

At 12 months, based upon 2 studies [37,39] with 94 participants (test F:M ratio: 23:24, mean age 27.6 years and control F:M ratio: 18:29, mean age 26.7 years), a statistically significant difference was detected in favour of azithromycin for probing pocket depth reduction (**Figure 8**) (WMD=−1.32 mm; 95% CI, −1.71 to −0.93 mm; I^2=0%) and clinical attachment level (**Figure 9**) (WMD=−0.88 mm; 95% CI, −1.32 to −0.44 mm; I^2=0%) in comparison to placebo groups when

https://doi.org/10.5051/jpis.2200340017

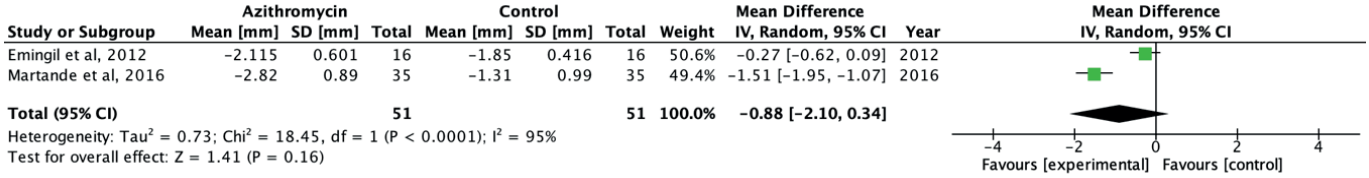

Figure 5. Probing pocket depth (mm) changes at 6 months from baseline.
SD: standard deviation, CI: confidence interval.

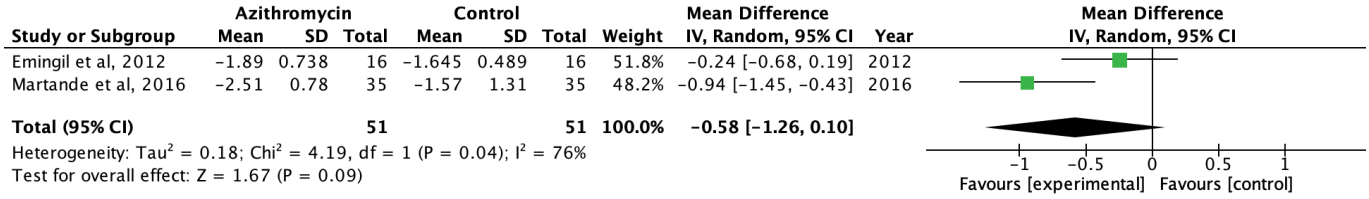

Figure 6. Clinical attachment level (mm) changes at 6 months from baseline.\xe2\x80\xa8SD: standard deviation, CI: confidence interval.

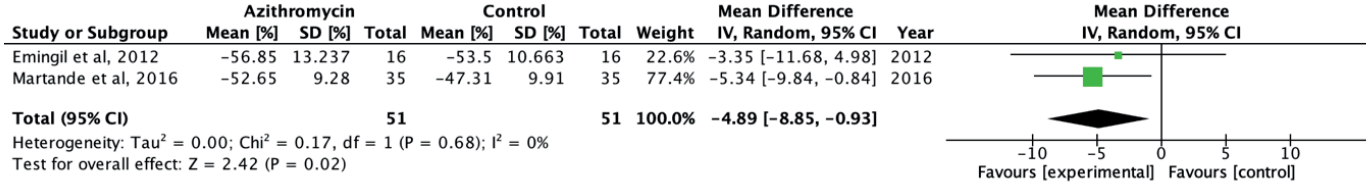

Figure 7. Bleeding on probing (%) changes at 6 months from baseline.
SD: standard deviation, CI: confidence interval.

used in conjunction with PMPR. No statistically significant difference was detected for bleeding on probing (**Figure 10**) (WMD=−3.36%; 95% CI, −7.47% to 0.76%; I^2=0%). The certainty of the evidence was deemed to be high for the probing pocket depth and clinical attachment level and moderate for bleeding on probing, rated down for imprecision (**Supplementary Figure 1**).

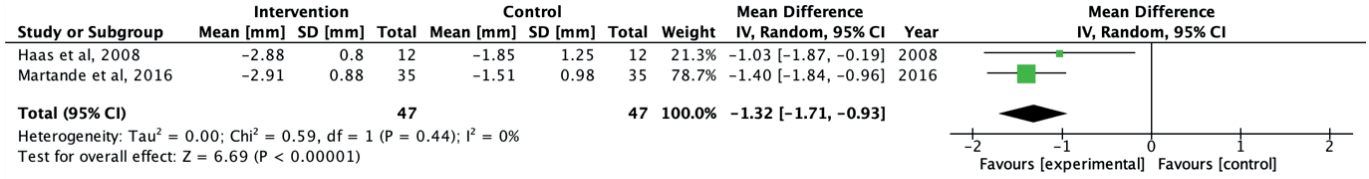

Figure 8. Probing pocket depth (mm) changes at 12 months from baseline.
SD: standard deviation, CI: confidence interval.

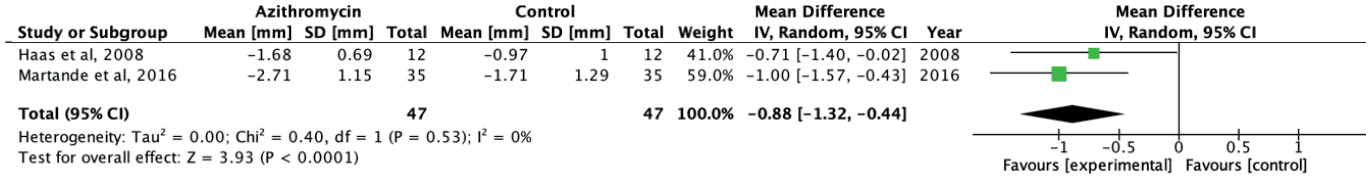

Figure 9. Clinical attachment level (mm) changes at 12 months from baseline.
SD: standard deviation, CI: confidence interval.

https://doi.org/10.5051/jpis.2200340017

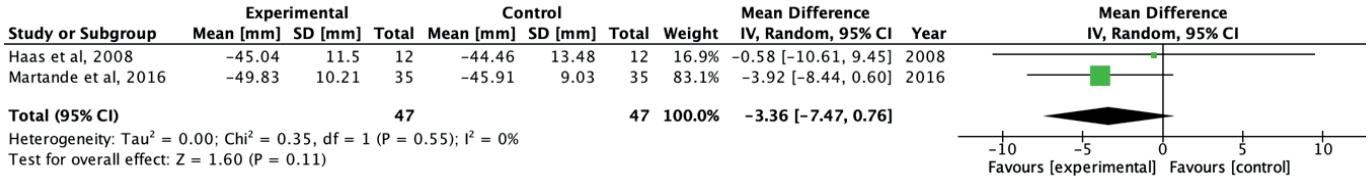

Figure 10. Bleeding on probing (%) changes at 12 months from baseline.
SD: standard deviation, CI: confidence interval.

Microbiological outcomes

Three studies reported microbiological outcomes [34,38,39]. These were not included in the meta-analysis due to clinical heterogeneity and differences in sampling and analysis methods.

Haas et al. [38], took microbiological samples at baseline, 15 days after supragingival plaque control, and then 3, 6, and 12 months post-treatment. Three subgingival plaque pools were collected for each patient using a sterile paper point: healthy site, a diseased site of the maxilla, and a diseased site of the mandible. Similar results were found in the intervention and control groups for the change between baseline and 15 days in the reduction of bacterial species. When all subjects were combined, diseased sites showed a significant reduction in *Actinomyces gerencseriae* (*P*=0.028), *Capnocytophaga ochracea* (*P*=0.035), and *Treponema denticola* (*P*=0.04), whereas healthy sites did not show a significant reduction in bacterial levels. Between baseline and 12 months post-treatment, the majority of bacterial species decreased in both groups, but without a significant difference. The authors concluded that although azithromycin demonstrated beneficial clinical results when compared to a placebo and non-surgical periodontal treatment, it did not show significant effects on the subgingival microflora.

Emingil et al. [34] performed subgingival plaque sampling at baseline, immediately post-treatment, and 2 weeks, 1 month, and 6 months post-treatment for microbiological analysis. Samples were obtained using sterile paper points placed into ≥6 mm pockets at the mesio-buccal site of 2 pre-selected teeth. *A. actinomycetemcomitans* was detected in 2 of 16 participants in the azithromycin group and 5 of 16 participants in the placebo group at baseline; these proportions decreased to 1/16 and 1/16, respectively, at 6 months. Overall, both groups demonstrated similar levels of bacterial reduction between baseline and 6 months, but over half of the sites sampled still remained positive for the species after treatment.

Martande et al. [39] took subgingival plaque samples from the deepest site in each quadrant at baseline and 3, 6, and 12 months to analyse levels of *A. actinomycetemcomitans*. At each time-point, the number of individuals with detectable subgingival *A. actinomycetemcomitans* was significantly lower (*P*<0.001) in the test group than in the control group. At 3 months, 2 of 35 participants (5.71%) in the test group and 25 of 35 (65.71%) in the control group demonstrated detectable *A. actinomycetemcomitans.* At 6 months, these proportions were 3/35 (8.57%) and 27/35 (77.14%), respectively, and at 12 months, they were 5/35 (14.28%) and 28/35 (80%), respectively.

The reduction in the overall number of periodontal pathogens was similar between the azithromycin and control groups in both the Haas et al. [38] and Emingil et al. [34] studies. Conflicting results were found for the specific reduction of subgingival *A. actinomycetemcomitans*. Martande et al. [39] demonstrated a significant reduction in the test group, whereas Emingil et al. [34] demonstrated similar reductions between groups.

https://doi.org/10.5051/jpis.2200340017

Adverse events

Adverse events were reported in 3 of the studies [34,37,39]. No patients in the azithromycin groups experienced side effects. One patient in the study of Haas et al. [37] reported a headache after administration of the medicine; however, after unblinding it was confirmed that this patient was in the placebo group.

Patient-reported outcomes

No study included in the analysis presented patient-reported outcomes.

DISCUSSION

This systematic review identified 4 studies with a follow-up of at least 3 months that analyzed the effect of adjunctive systemic azithromycin in comparison to a control (either a placebo or no adjunct) for the non-surgical treatment of grade C periodontitis; these 4 studies were included in the meta-analysis.

Overall, the meta-analysis demonstrated a statistically significant difference in favour of azithromycin in combination with non-surgical PMPR over the control for probing pocket depth reduction at 3 (P=0.004) and 12 months (P<0.001), clinical attachment level at 3 (P=0.03) and 12 (P<0.001) months, and bleeding on probing reduction at 6 months (P=0.02). No statistically significant differences were noted for bleeding on probing at 3 months (P=0.14) and 12 months (P=0.11), probing pocket depth at 6 months (P=0.16), or clinical attachment level at 6 months (P=0.09) between the intervention and control groups.

The certainty of the evidence for the 3-month outcomes was lower than that for the 6- and 12-month outcomes. This was because a retrospective cohort study that provided data for the 3-month outcomes [35] was at serious risk of bias. The remaining papers that were included in the meta-analysis were all randomised control trials deemed to be at low risk of bias after assessment using the RoB2 tool [30] and were adequately powered to 80%. Steps were taken within the studies to control confounding factors such as smoking status and comorbidities by either stratifying them as a variable in the randomisation process or excluding them from the trial. The GRADE summary of findings table (**Supplementary Figure 1**) highlights those specific outcomes, which were rated down for imprecision where there was a wide spread of data between the studies, resulting in the certainty of evidence for probing depth reduction and clinical attachment level at 6 months, and bleeding on probing at 12 months being deemed moderate.

There was significant methodological heterogeneity between studies, which precluded a meta-analysis of the microbiological outcomes between the test and control groups. Narratively, there were conflicting results on whether azithromycin reduced the number of subgingival pathogens or detectable subgingival *A. actinomycetemcomitans.*

The 3 randomised controlled trials were all superiority trials rather than noninferiority trials and compared azithromycin against a placebo rather than the more commonly accepted regimen of amoxicillin and metronidazole. It is therefore difficult to compare clinical outcomes between the 2 adjunctive antimicrobial regimens. Ercan et al. [35] did collect data for a regimen of amoxicillin (500 mg) and metronidazole (500 mg), both 3 times a day, but did not state the number of days of the regimen. This paper concluded that all regimens

https://doi.org/10.5051/jpis.2200340017

(azithromycin, amoxicillin and metronidazole, and periodontal treatment only) resulted in statistically significant reductions in outcome measures from baseline, but no statistically significant difference was found between the regimens.

When comparing the results from this systematic review to systematic reviews analysing the use of amoxicillin and metronidazole in the treatment of grade C periodontitis, the changes in PPD (mm) for the adjunctive use of azithromycin are comparable.

Keestra et al. [14] reported that at 3 months, a combination of metronidazole and amoxicillin resulted in a statistically significant mean pocket probing depth reduction difference of 0.39±0.16 mm (8 studies, 248 patients) in comparison to the control. In this current review, a comparable statistically significant probing depth reduction difference in favour of azithromycin to the control at 3 months was also noted (WMD=−0.39 mm; 95% CI, −0.66 to −0.13, I^2=0%).

At 6 months, Teughels et al. [15] reported a statistically significant difference in PPD (mm) for the use of amoxicillin and metronidazole in the treatment of aggressive periodontitis in comparison to a control (PMPR and placebo only) (WMD=0.505 mm; 95% CI, 0.356 to 0.654 mm). Keestra et al. [14] reported that metronidazole and amoxicillin resulted in a statistically significant mean pocket probing depth reduction difference of 0.51±0.09 mm (7 studies, 214 patients) when compared to the control. In this present review, there was no significant difference noted for probing pocket depth reduction (WMD=−0.88 mm; 95% CI, −2.10 to 0.34 mm; I^2=95%) between the azithromycin and control groups at 6 months.

At 12 months, Teughels et al. [15] also reported a statistically significant difference in PPD (mm) for the use of amoxicillin and metronidazole in the treatment of aggressive periodontitis in comparison to a control (WMD=0.519 mm; 95% CI, 0.230 to 0.807 mm). Keestra et al. [14] reported a statistically significant mean pocket probing depth reduction difference of 0.51±0.38 mm (2 studies, 65 patients) in favour of amoxicillin and metronidazole over controls. In this present review, a larger statistically significant difference was detected in favour of azithromycin for probing pocket depth reduction over placebo-controlled groups (WMD=−1.32mm; 95% CI, −1.71 to −0.93 mm; I^2=0%), although this result is only based upon 2 studies (94 participants).

The main limitation of this systematic review is the small number of studies that were eligible for meta-analysis. Although 4 studies were included in the meta-analysis, only 3 were available to assess 3-month time points and 2 studies for each of the 6- and 12-month time points. These results should therefore be interpreted with caution due to the limited number of comparable clinical outcomes for the adjunctive use of azithromycin with subgingival PMPR in patients with grade C periodontitis.

Although the results from this systematic review and meta-analysis show additional benefits of adjunctive azithromycin in the non-surgical periodontal treatment of patients with grade C periodontitis for certain clinical outcomes at certain time points, the prescription of antimicrobials must be undertaken with care. One of the many roles of dental practitioners is to act as antimicrobial stewards, ensuring that antimicrobials are always prescribed in a judicious way to preserve their future effectiveness [40]. In the UK, the National Institute for Health and Care Excellent (NICE) released antimicrobial stewardship guidelines [40] to prevent over-prescribing in order to slow the emergence of antimicrobial resistance and ensure that they remain an effective treatment for infection. Dentists should, therefore, always follow

https://doi.org/10.5051/jpis.2200340017

evidence-based prescribing and ensure that antimicrobials are only used where there are proven benefits to patients. Within the UK, the treatment of patients with grade C or stage IV periodontitis, which are described as warranting adjunctive antimicrobials [20], is defined as level 3 complexity treatment [41]. In practicality, this means that patients with this staging and grading can be referred to registered periodontal specialists or consultants within the National Health Service (NHS) system and may not be treated in the setting of general dental care.

In conclusion, this review has found evidence that azithromycin as an adjunct to subgingival PMPR improves clinical outcomes (PPD and the clinical attachment level at 3 months, BoP at 6 months, and PPD and the clinical attachment level at 12 months) in comparison to a placebo or no alternative, when treating patients for grade C periodontitis, which appears to be maintained for up to 12 months. It should be noted that these conclusions are based on a small number of studies. Further, well-designed studies with longer follow-up times are required to investigate whether the adjunctive use of azithromycin with subgingival PMPR offers clinical improvements over non-surgical treatment alone or alternative antimicrobial regimens in cases of grade C periodontitis. There is also an opportunity to further investigate patient-reported outcomes of the treatment of grade C periodontitis with azithromycin in comparison to certain control groups.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) summary of findings table for azithromycin compared to placebo/alternative adjunct in combination with non-surgical professional mechanical plaque removal in the treatment of grade C periodontitis.

Click here to view

REFERENCES

1. American Academy of Periodontology. Proceedings of the world workshop in clinical periodontics. Chicago (IL): American Academy of Periodontology; 1989.
2. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.
PUBMED | CROSSREF
3. Lang N, Bartold PM, Cullinan M, Jeffcoat M, Mombelli A, Murakami S, et al. Consensus report: aggressive periodontitis. Ann Periodontol 1999;4:53.
CROSSREF
4. Albandar JM. Aggressive periodontitis: case definition and diagnostic criteria. Periodontol 2000 2014;65:13-26.
PUBMED | CROSSREF
5. Caton JG, Armitage G, Berglundh T, Chapple IL, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol 2018;89 Suppl 1:S1-8.
PUBMED | CROSSREF
6. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol 2018;89 Suppl 1:S173-82.
PUBMED | CROSSREF

7. Fine DH, Patil AG, Loos BG. Classification and diagnosis of aggressive periodontitis. J Clin Periodontol 2018;45 Suppl 20:S95-111.
PUBMED | CROSSREF
8. Susin C, Haas AN, Albandar JM. Epidemiology and demographics of aggressive periodontitis. Periodontol 2000 2014;65:27-45.
PUBMED | CROSSREF
9. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol 2015;86:611-22.
PUBMED | CROSSREF
10. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Beglundh T, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. J Clin Periodontol 2020;47 Suppl 22:4-60.
PUBMED | CROSSREF
11. Deas DE, Mealey BL. Response of chronic and aggressive periodontitis to treatment. Periodontol 2000 2010;53:154-66.
PUBMED | CROSSREF
12. Herrera D, Sanz M, Jepsen S, Needleman I, Roldán S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. J Clin Periodontol 2002;29 Suppl 3:136-59.
PUBMED | CROSSREF
13. Rabelo CC, Feres M, Gonçalves C, Figueiredo LC, Faveri M, Tu YK, et al. Systemic antibiotics in the treatment of aggressive periodontitis. A systematic review and a Bayesian Network meta-analysis. J Clin Periodontol 2015;42:647-57.
PUBMED | CROSSREF
14. Keestra JA, Grosjean I, Coucke W, Quirynen M, Teughels W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. J Periodontal Res 2015;50:294-314.
PUBMED | CROSSREF
15. Teughels W, Feres M, Oud V, Martín C, Matesanz P, Herrera D. Adjunctive effect of systemic antimicrobials in periodontitis therapy: a systematic review and meta-analysis. J Clin Periodontol 2020;47 Suppl 22:257-81.
PUBMED | CROSSREF
16. Slots J, Rosling BG. Suppression of the periodontopathic microflora in localized juvenile periodontitis by systemic tetracycline. J Clin Periodontol 1983;10:465-86.
PUBMED | CROSSREF
17. Saxén L, Asikainen S. Metronidazole in the treatment of localized juvenile periodontitis. J Clin Periodontol 1993;20:166-71.
PUBMED | CROSSREF
18. Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, et al. Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized placebo-controlled clinical trial. J Clin Periodontol 2005;32:1096-107.
PUBMED | CROSSREF
19. British Society of Periodontology. The good practitioner's guide to periodontology [Internet]. Liverpool: British Society of Periodontology; 2016 [cited 2021 Sep 7]. Available from: https://www.bsperio.org.uk/assets/downloads/good_practitioners_guide_2016.pdf.
20. Palmer N. Antimicrobial prescribing in dentistry: good practice guidelines [Internet]. London: Faculty of General Dental Practice (UK); Faculty of Dental Surgery (UK); 2020 [cited 2021 Sep 11]. Available from: https://www.rcseng.ac.uk/-/media/files/rcs/fds/publications/fds-amp-2020.pdf.
21. Guerrero A, Echeverría JJ, Tonetti MS. Incomplete adherence to an adjunctive systemic antibiotic regimen decreases clinical outcomes in generalized aggressive periodontitis patients: a pilot retrospective study. J Clin Periodontol 2007;34:897-902.
PUBMED | CROSSREF
22. Jourdan A, Sangha B, Kim E, Nawaz S, Malik V, Vij R, et al. Antibiotic hypersensitivity and adverse reactions: management and implications in clinical practice. Allergy Asthma Clin Immunol 2020;16:6.
PUBMED | CROSSREF
23. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990;25 Suppl A:73-82.
PUBMED | CROSSREF
24. Ianaro A, Ialenti A, Maffia P, Sautebin L, Rombolà L, Carnuccio R, et al. Anti-inflammatory activity of macrolide antibiotics. J Pharmacol Exp Ther 2000;292:156-63.
PUBMED

25. Foulds G, Johnson RB. Selection of dose regimens of azithromycin. J Antimicrob Chemother 1993;31 Suppl E:39-50.
PUBMED | CROSSREF

26. Blandizzi C, Malizia T, Lupetti A, Pesce D, Gabriele M, Giuca MR, et al. Periodontal tissue disposition of azithromycin in patients affected by chronic inflammatory periodontal diseases. J Periodontol 1999;70:960-6.
PUBMED | CROSSREF

27. Gomi K, Yashima A, Iino F, Kanazashi M, Nagano T, Shibukawa N, et al. Drug concentration in inflamed periodontal tissues after systemically administered azithromycin. J Periodontol 2007;78:918-23.
PUBMED | CROSSREF

28. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
PUBMED | CROSSREF

29. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
PUBMED | CROSSREF

30. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
PUBMED | CROSSREF

31. Page MJ, Higgins JP, Sterne JA. Assessing risk of bias due to missing results in a synthesis. Cochrane handbook for systematic reviews of interventions [Internet]. London: Cochrane; 2019 [cited 2021 Aug 21]. Available from: https://training.cochrane.org/handbook.

32. GRADEpro (GDT). GRADEpro guideline development tool (software) [Internet]. Hamilton: McMaster University; 2020 [cited 2021 Jul 29]. Available from: https://www.gradepro.org/.

33. Nordic Cochrane Centre; Cochrane Collaboration. Review Manager, version 5.3. London: Cochrane; 2014.

34. Emingil G, Han B, Özdemir G, Tervahartiala T, Vural C, Atilla G, et al. Effect of azithromycin, as an adjunct to nonsurgical periodontal treatment, on microbiological parameters and gingival crevicular fluid biomarkers in generalized aggressive periodontitis. J Periodontal Res 2012;47:729-39.
PUBMED | CROSSREF

35. Ercan E, Uzun BC, Ustaoglu G. Effects of azithromycin versus metronidazole-amoxicillin combination as an adjunct to nonsurgical periodontal therapy of generalized aggressive periodontitis. Niger J Clin Pract 2015;18:506-10.
PUBMED | CROSSREF

36. Fujii T, Wang PL, Hosokawa Y, Shirai S, Tamura A, Hikita K, et al. Effect of systemically administered azithromycin in early onset aggressive periodontitis. Periodontal Pract Today 2004;1:321-5.

37. Haas AN, de Castro GD, Moreno T, Susin C, Albandar JM, Oppermann RV, et al. Azithromycin as an adjunctive treatment of aggressive periodontitis: 12-months randomized clinical trial. J Clin Periodontol 2008;35:696-704.
PUBMED | CROSSREF

38. Haas AN, Silva-Boghossian CM, Colombo AP, Susin C, Albandar JM, Oppermann RV, et al. Adjunctive azithromycin in the treatment of aggressive periodontitis: microbiological findings of a 12-month randomized clinical trial. J Dent 2012;40:556-63.
PUBMED | CROSSREF

39. Martande SS, Pradeep AR, Singh SP, Kumari M, Naik SB, Suke DK, et al. Clinical and microbiological effects of systemic azithromycin in adjunct to nonsurgical periodontal therapy in treatment of *Aggregatibacter actinomycetemcomitans* associated periodontitis: a randomized placebo-controlled clinical trial. J Investig Clin Dent 2016;7:72-80.
PUBMED | CROSSREF

40. National Institute for Health and Care Excellence (UK). Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use [Internet]. London: National Institute for Health and Care Excellence; 2015 [cited 2021 Aug 13]. Available from: https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469.

41. NHS England and NHS Improvement. Commissioning standard for restorative dentistry [Internet]. Leeds: NHS England and NHS Improvement; 2019 [cited 2021 Jul 1]. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/07/commissioning-standard-for-restorative-dentistry-v1.pdf.