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# Non-surgical peri-implantitis treatment with or without systemic antibiotics: a randomized controlled clinical trial

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## Abstract

**Objectives:** To assess the adjunctive effect of systemic amoxicillin (AMX) and metronidazole (MTZ) in patients receiving non-surgical treatment (NST) for peri-implantitis (PI).

**Materials and methods:** Thirty-seven patients were randomized into an experimental group treated with NST plus AMX + MTZ (N = 18) and a control group treated with NST alone (N = 19). Clinical parameters were evaluated at 12 weeks post-treatment. The primary outcome was the change in peri-implant pocket depth (PIPD) from baseline to 12 weeks, while secondary outcomes included bleeding on probing (BoP), suppuration on probing (SoP), and plaque. Data analysis was performed at patient level (one target site per patient).

**Results:** All 37 patients completed the study. Both groups showed a significant PIPD reduction after NST. The antibiotics group showed a higher mean reduction in PIPD at 12 weeks, compared with the control group (2.28 ± 1.49 mm vs. 1.47 ± 1.95 mm), however, this difference did not reach statistical significance. There was no significant effect of various potential confounders on PIPD reduction. Neither treatment resulted in significant improvements in BoP at follow-up; 30 of 37 (81%) target sites still had BoP after treatment. Only two implants, one in each group, exhibited a successful outcome defined as PIPD < 5 mm, and absence of BoP and SoP.

**Conclusions:** Non-surgical treatment was able to reduce PIPD at implants with PI. The adjunctive use of systemic AMX and MTZ did not show statistically significant better results compared to NST alone. NST with or without antibiotics was ineffective to completely resolve inflammation around dental implants.

**KEYWORDS**
bacteria, debridement, non-surgical treatment, peri-implantitis, systemic antibiotics

## 1 | INTRODUCTION

The importance of biofilms in the etiology of peri-implantitis (PI), as an initial trigger for inflammatory reactions, has been well established (Lindhe et al., 1992). Dysbiotic biofilms may cause tissue inflammation, which alters the ecology and favors further growth of dysbiotic microbial communities, leading to a vicious cycle, similar to periodontitis (Hajishengallis et al., 2020; Loos & Van Dyke, 2020).

Although the microbial composition associated with PI is similar to periodontitis, the peri-implant microbiome is more complex

including non-cultivable gram-negative species (Lafaurie et al., 2017). Well-recognized periodontal pathogens such as *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Treponema denticola* are present in higher proportions in deep peri-implant pockets (Polymeri et al., 2021). Consequently, the current protocols for the treatment of PI are based on the evidence available from periodontal treatment and focus on resolution of inflammation and elimination of biofilm from the implant surfaces (Renvert & Polyzois, 2018). Although most periodontitis cases respond favorably to treatment and maintain long-term periodontal stability (Lindhe & Nyman, 1984), this does not hold true for PI; most probably due to structural differences in supporting tissues between implants and teeth, differences in the histopathologic features of the two lesions, and the surface characteristics of implants (de Avila et al., 2020; Berglundh et al., 2011). Therefore, existing therapeutic strategies are unpredictable in arresting peri-implant tissue inflammation and current evidence does not support a gold standard treatment protocol (Garaicoa-Pazmino et al., 2019).

As that may be, the non-surgical treatment (NST) is the first step in PI treatment and may lead to some reduction in the extent of inflammation and in some cases to peri-implant pocket depth (PIPD) reduction of up to 1 mm (Renvert et al., 2019). The adjunctive use of antibiotics, especially metronidazole (MTZ) or the combination of amoxicillin (AMX) and MTZ, in the non-surgical treatment of periodontitis has been widely investigated and has shown to improve the clinical and microbiological parameters (Berglundh et al., 1998; Teughels & Feres, 2020). Antimicrobials have also been proposed for PI treatment and are widely used empirically by clinicians from all over the globe, although the scientific evidence of their benefits is still limited (Heitz-Mayfield & Lang, 2004; Polymeri et al., 2021). Several studies have demonstrated that the adjunctive administration of systemic antibiotics has led to favorable results in terms of PIPD, tissue inflammation, and even radiographic defect reduction (Blanco et al., 2022; Liñares et al., 2019; Mombelli & Lang, 1992; Nart et al., 2020; Stein et al., 2018). On the other hand, two RCTs have shown no additional benefit to NST when systemic antibiotics were used adjunctively (De Waal et al., 2021; Shibli & Ferrari, 2019). Hence, the scientific evidence for the use of systemic antibiotics in combination with NST for PI is still inconclusive.

Some of the aforementioned studies used a single antimicrobial of the nitroimidazole group, most frequently metronidazole (Blanco et al., 2022; Liñares et al., 2019; Nart et al., 2020) and ornidazole (Mombelli & Lang, 1992). On the other hand, other studies preferred the combination of amoxicillin and metronidazole (De Waal et al., 2021; Shibli & Ferrari, 2019; Stein et al., 2018). An in vitro study showed that the combination of metronidazole and amoxicillin was effective in lower concentration than mono-therapy, suggesting a synergistic mode of action for these agents (Walter et al., 2011). Therefore, we chose to use the combination of amoxicillin and metronidazole at low concentrations.

The purpose of the present randomized controlled clinical trial of PI treatment was to evaluate the clinical results of the combined use of systemic AMX and MTZ in conjunction with NST, in comparison to NST alone. The null hypothesis was that there are no differences between the two treatment strategies.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and ethical approval

The study was carried out as a randomized, controlled, single-blinded, clinical trial. The study protocol was approved by the ethical committee of the VU Medical Centre, Amsterdam (NL 39371.018.12), and was registered at the ISRCTN (https://www.isrctn.com/ISRCTN10896644). The study was conducted in accordance with the principles outlined in the revision of the Declaration of Helsinki (2008).

### 2.2 | Study population

The present study is in compliance with the CONSORT guidelines. The study participants were referred to the Department of Oral Implantology and Prosthetic Dentistry or the Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), for treatment of PI.

Systemically healthy, adult patients (≥18 years old) with at least one dental implant were included, if the implant had been in function for more than 1 year, presented with PIPD ≥5 mm, bleeding and/or suppuration on probing (BoP and/or SoP), as well as marginal bone loss ≥3 mm detected radiographically. Exclusion criteria included the use of systemic antibiotics within the past 3 months, any chronic medical disease or condition, known allergy to penicillin or metronidazole, use of anti-inflammatory prescription medications within the past 4 weeks, pregnancy or lactation, and presence of implant mobility. Each participant was informed about the aims, the potential risks and benefits of the study, and provided written informed consent. The long-cone parallel technique was performed for the digital radiographic evaluation. The implant with the deepest PIPD was selected for the study (target implant). For each target implant, the PIPD was evaluated at six sites and the deepest of them was defined as "target site" and was selected for analysis.

The study was conducted between 2012 and 2018. The limited availability of referral cases which fulfilled the inclusion criteria, and the fact that the individuals who were responsible for recruiting the patients, making clinical evaluations, and providing the treatment (D.A.M. and J.V.D.H.) were working at ACTA part-time, delayed the completion of the study. Using a block randomization design, patients who met the inclusion criteria were assigned into one of the following treatment protocols: non-surgical treatment (NST) with systemic antibiotics (AMX and MTZ) and chlorhexidine rinses (experimental group) or NST with chlorhexidine rinses (control group) (Figure 1).

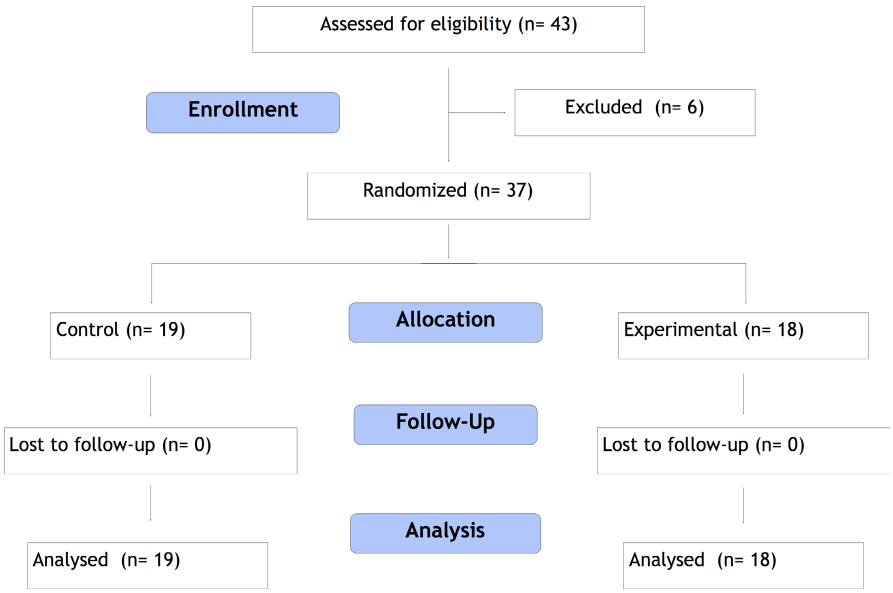


**FIGURE 1** Consort diagram of patient distribution

## 2.3 | Non-surgical treatment and follow-up

After anamneses, clinical and radiographic assessments, and prophylaxis/oral hygiene instruction, the participants received one session of mechanical debridement. After local anesthesia (Ultracain-DS forte®, Sanofi, Frankfurt, Germany), the implant surfaces were treated with 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). The implant supported restorations were not removed during treatment. The treatment was performed by one experienced clinician (J.V.D.H.). On the day of treatment, patients started with systemic AMX 375 mg and MTZ 250 mg, 1 tablet each, every 8 h for 7 days. All patients were instructed to start rinsing with chlorhexidine 0.12%, two times a day for 4 weeks. In those patients presented with periodontitis, this was treated first and more sessions were planned if necessary to complete the treatment of the whole dentition. At 4 weeks, an oral hygiene check was performed which included supragingival debridement, polishing with a rubber cup and a low-abrasive paste, and oral hygiene instructions as needed.

Twelve weeks after treatment, a clinical examination was performed in order to evaluate the outcome of treatment. A successful outcome was defined based on the following clinical criteria: implant survival with absence of PIPD ≥5 mm, and absence of BoP and/or SoP, modified from Heitz-Mayfield et al. (2018). The modification is based on the exclusion of the radiographic evaluation at 12 weeks, as it has been established that the radiographic evaluation does not permit accurate detection of minor resorptive changes in the crestal bone (Ramadan & Mitchell, 1962). Treatment success was assessed at target site level and at patient level. In case of an unsuccessful outcome, the patient was advised to seek further surgical treatment either at ACTA or at the referring dentist or referring oral surgeon, but this was outside the scope of the current study. In case of treatment success, the patient entered into a 3-month recall program, consisting of soft tissue examination, oral hygiene reinforcement as needed, supragingival instrumentation, and annual clinical evaluation.

## 2.4 | Demographic data

At the beginning of the study, the following demographic data were recorded: age, sex, body mass index (BMI; expressed as kg/m$^2$), smoking status (smoker, non-smoker), history of periodontitis (yes/no), periodontal stability (yes/no), full mouth plaque score (presence/absence, %), implant position (maxilla/mandible and anterior/posterior), type of prosthesis connection (screw vs. cement retained), dental status (partially edentulous/fully edentulous), number of dental implants (≥4 vs. <4), and implant brand.

A periodontitis case was determined on the basis of clinical attachment loss (CAL). When interdental CAL was detected at ≥2 non-adjacent teeth or buccal or oral CAL ≥3 mm with probing depths >3 mm detectable in ≥2 teeth, and the observed CAL could not be associated with non-periodontitis related causes, the patient was considered a periodontitis case (Papapanou et al., 2018). In cases of fully edentulous patients, where previous periodontal charts or radiographs were not available, history of periodontitis was self-reported by the patient. Periodontal stability was defined as <10% bleeding sites with probing depths ≤3 mm (Chapple et al., 2018).

## 2.5 | Clinical examination

Baseline clinical measurements of the target implant included: (1) PIPD measured to the closest mm from the mucosal margin to the base of the pocket, (2) BoP (presence or absence), (3) SoP (presence

or absence), and (4) plaque (presence or absence). All clinical measurements were performed at six sites. The above clinical measurements were repeated at 12 weeks. All clinical measurements were performed using a periodontal probe (PCP-UNC 15; Hu-Friedy, Chicago, IL, USA) by one calibrated examiner (D.A.M.) who was blinded to the study group allocation.

### 2.6 | Statistical analysis

At the time of the study design, no data from RCTs were available for the non-surgical treatment of PI with the use of systemic antibiotics, therefore the power calculation to determine the sample size was based on a previous study of periodontal patients receiving non-surgical treatment alone or combined with AMX and MTZ (Silva et al., 2011). The sample size was calculated at https://clincalc.com/stats/samplesize.aspx considering a mean difference in PIPD after treatment of 1 mm between the experimental and control group with standard deviation of 1 mm (Silva et al., 2011). Based on these calculations, it was determined that 16 subjects per group would be sufficient to provide a power of 80% with an $\alpha$ of 0.05. A dropout rate of 10% was considered acceptable, therefore we aimed to recruit at least 35 patients. The Cohen's d was also calculated post hoc for the between-group change in PIPD after treatment to evaluate the effect size. A commonly used interpretation suggested by Cohen is to categorize the effect sizes as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) (Lakens, 2013).

The primary outcome parameter was the change in PIPD from baseline to 12 weeks, while secondary outcomes included BoP, SoP, and PI. Analysis was performed at one target site per patient. Descriptive statistics included mean ± SD and percentages (%) for numerical and categorical variables, respectively, and were reported at patient level. The Shapiro–Wilk test was used to assess the normality of data distribution. Independent samples *t*-test and paired *t*-test were used to analyze inter-group and intra-group differences, respectively, for continuous data. The Chi-squared test or Fisher's exact test was used for inter-group differences in categorical variables. Intra-group comparisons of categorical variables were performed using the McNemar's Chi-squared test. The SPSS version 19.00 software (SPSS Inc., Chicago, IL, USA) was used for all analyses. The level of significance was set at $p < 0.05$.

In order to explore whether the prescribed antimicrobials have an effect on PIPD reduction after controlling for potential confounding factors, we applied a linear mixed model (LMM) with random intercept and random slope including baseline PIPD and antibiotics usage (yes/no) as fixed factors (Model 0) (R 4.0.4, www.r-project.org). Age, sex (m/f), body mass index (BMI), smoking (yes/no), history of periodontitis (yes/no), presence of natural teeth (yes/no), number of implants, type of prosthesis (screw retained/cement retained), number of sites with SoP at baseline, full mouth plaque score at baseline, and implant brand (Straumann, Nobel, BioMet 3i or other) were evaluated as potential confounders. Each of the aforementioned factors was first individually screened in Model 0. Any factor that showed a *p*-value of <.1 in these screening models was to be included in the final LMM model as confounder.

## 3 | RESULTS

### 3.1 | Patient characteristics

Of the 43 patients screened, 37 were found eligible and were randomized to the experimental ($n = 18$) or to the control group ($n = 19$) (Figure 1). All randomized patients completed the study and were included in the analysis. The characteristics of the participants are presented in Table 1. The majority of patients (65%) were female. Age ranged from 25 to 84 years, mean 59.6 ± 11.2 years. Regarding smoking habits, 11 patients (30%) were smokers, and 26 patients (70%) were non-smokers at the time of the study. The majority of the participants had no history of periodontitis ($n = 21$, 57%), however, the majority of dentate patients included in the study ($n = 24$, 83%) appeared periodontally non stable. Most implants were placed in the mandible (60%) and in the posterior region (54%). The baseline characteristics of the included implants are presented in Table 2. The two groups were comparable in terms of baseline demographic and implant characteristics.

### 3.2 | Clinical outcomes

None of the patients reported side effects associated with the use of antibiotics or the clinical procedures performed in the study. The clinical parameters at baseline and at 12 weeks are presented in Figures 2 and 3 and in Table S1. At baseline, all clinical parameters were comparable in both groups. At 12 weeks, both treatment modalities resulted in improvements in clinical parameters. After NST alone, the mean PIPD of the target sites changed from 8.00 ± 1.41 mm at baseline to 6.53 ± 2.59 mm at 12 weeks ($p = .004$). After NST with the addition of antibiotics, the mean PIPD of the target sites changed from 7.44 ± 1.38 mm at baseline to 5.17 ± 1.92 mm at 12 weeks ($p < .001$). Regarding the secondary outcomes, intra-group analysis showed that none of the two groups achieved statistically significant reduction in BoP of target sites. Nevertheless, for both groups, the target sites showed a statistically significant reduction in SoP at 12 weeks ($p < .01$). Although plaque was reduced at follow-up for both groups, only in the control group a statistically significant reduction in target sites with plaque was observed ($p < .05$). At 12 weeks, none of the clinical parameters were significantly different between the two groups.

When the change (Δ) in PIPD from baseline to 12 weeks was evaluated, the experimental group showed a larger mean PIPD reduction of 2.28 ± 1.49 mm, as compared to 1.47 ± 1.95 mm in the control group. Nevertheless, the difference in mean PIPD reduction between the two groups did not reach statistical significance ($p = .170$). The Cohen's d effect size for the between-group change in PIPD was found to be 0.466, suggesting a medium-effect size.

Clinical outcomes according to baseline PIPD of all six peri-implant sites are displayed in Table 3. At baseline, approximately half (54%) of the participants presented with PIPD ≥8 mm, 41% presented with PIPD ≥9 mm, and 8% presented with PIPD ≥10 mm. NST with antibiotics resulted in a statistically significant reduction in

**TABLE 1** Study population characteristics at baseline

| Variable | NST ($n = 19$) | NST with AMX + MTZ ($n = 18$) | Test statistic, $p$-value |
|---|---|---|---|
| Age, mean ± SD (range), years | 60.8 ± 14.8 (25–84) | 58.3 ± 13.9 (27–79) | T = 0.532, $p = 0.598$† |
| Sex, *n* (%) | | | $X^2 = 0.217$, $p = 0.737$‡ |
| Male | 6 (32%) | 7 (39%) | |
| Female | 13 (68%) | 11 (61%) | |
| Smoking status, *n* (%) | | | $X^2 = 3.633$, $p = 0.056$‡ |
| Smoker | 3 (16%) | 8 (44%) | |
| Non-smoker | 16 (84%) | 10 (56%) | |
| BMI, mean ± SD (range), kg/m$^2$ | 25.3 ± 4.0 (19.6–34.1) | 23.3 ± 2.8 (18.5–28.7) | T = 1.764, $p = 0.087$† |
| Dental status, *n* (%) | | | Fisher's exact test, $p = 1.000$ |
| Fully edentulous | 4 (21%) | 4 (22%) | |
| Partially edentulous | 15 (79%) | 14 (78%) | |
| Number of natural teeth in dentate patients, mean ± SD (range) | 21.3 ± 5.4 (10–28) | 21.8 ± 4.9 (10–27) | T = 0.294, $p = 0.770$† |
| History of periodontitis, *n* (%) | | | $X^2 = 0.652$, $p = 0.515$‡ |
| Yes | 7 (37%) | 9 (50%) | |
| No | 12 (63%) | 9 (50%) | |
| §Periodontal stability, *n* (%) | | | Fisher's exact test, $p = 0.893$ |
| Yes | 2 (13%) | 3 (21%) | |
| No | 13 (87%) | 11 (79%) | |
| FMPS % mean ± SD (range) | 40 ± 27.3 (0–100) | 30.3 ± 28.1 (0–100) | T = 0.189, $p = 0.851$† |
| Number of implants, *n* (%) | | | $X^2 = 0.021$, $p = 0.886$‡ |
| ≥4 implants | 8 (42%) | 8 (44%) | |
| <4 implants | 11 (58%) | 10 (56%) | |

Abbreviations: AMX, Amoxicillin; BMI, Body mass index; FMPS, Full mouth plaque score; MTZ, Metronidazole; NST, Non-surgical treatment; SD, Standard deviation.

†Independent sample t-test.

‡Chi-square test.

§Periodontal stability was evaluated in dentate patients.

the frequency of patients with baseline PIPDs ≥6 mm and ≥7 mm at 12 weeks, as compared to baseline. At 12 weeks, 16 patients (84%) of the control group and 14 patients (78%) of the experimental group had residual PIPDs ≥5 mm. Nevertheless, there were no statistically significant differences in the distribution of sites with different PIPDs between control and experimental group neither at baseline nor at the re-evaluation.

Regarding treatment success at the 12-week follow-up, only three target sites in the control group and two target sites in the experimental group were treated successfully ($p = 1.000$), with complete absence of BoP and SoP. Considering all six sites around the target implant, two implants (e.g., two patients), one in each group, exhibited a successful outcome.

Of all the factors examined as potential confounders (including age, sex, BMI, smoking, history of periodontitis, presence of natural teeth, number of implants, type of prosthesis, number of sites with SoP, full mouth plaque score, and implant brand), none was identified as significant confounder with $p$-value < .1 in the initial LMM. Therefore, the final model remained Model 0 including baseline PIPD and antibiotics usage as fixed factors, without any confounders (Table S2). From this model, the adjusted PIPD reduction in the experimental group is 0.80 mm larger than that in the control group, however, without reaching statistical significance (*adjusted* $p$-value = .169).

## 4 | DISCUSSION

In the present study, the change in PIPD was the primary outcome. It has been demonstrated that PIPD determines the microbial ecology of the peri-implant site, with deep pockets favoring the outgrowth of Gram-negative anaerobic species, which are compatible with peri-implant disease (Mombelli & Decaillet, 2011). This is based on the knowledge about the microbial communities in deep periodontitis

**TABLE 2** Implant characteristics at baseline

| Variable | NST ($n = 19$) | NST with AMX + MTZ ($n = 18$) | Test statistic, $p$-value |
|---|---|---|---|
| Implant location, *n* (%) | | | $X^2 = 0.040$, $p = 1.000^{‡}$ |
| Maxilla | 8 (42%) | 7 (39%) | |
| Mandible | 11 (58%) | 11 (61%) | |
| Implant position, *n* (%) | | | $X^2 = 3.246$, $p = 0.103^{‡}$ |
| Anterior | 6 (32%) | 11 (61%) | |
| Posterior | 13 (68%) | 7 (39%) | |
| Type of connection, *n* (%) | | | $X^2 = 0.232$, $p = 0.630^{‡}$ |
| Screw retained | 8 (42%) | 9 (50%) | |
| Cement retained | 11 (58%) | 9 (50%) | |
| Implant brand, *n* (%) | | | $X^2 = 3.896$, $p = 0.272^{‡}$ |
| Nobel | 5 (26%) | 9 (50%) | |
| Straumann | 5 (26%) | 4 (22%) | |
| Biomet 3i | 5 (26%) | 1 (6%) | |
| Other | 4 (21%) | 4 (22%) | |

Abbreviations: AMX, Amoxicillin; MTZ, Metronidazole; NST, Non-surgical treatment.

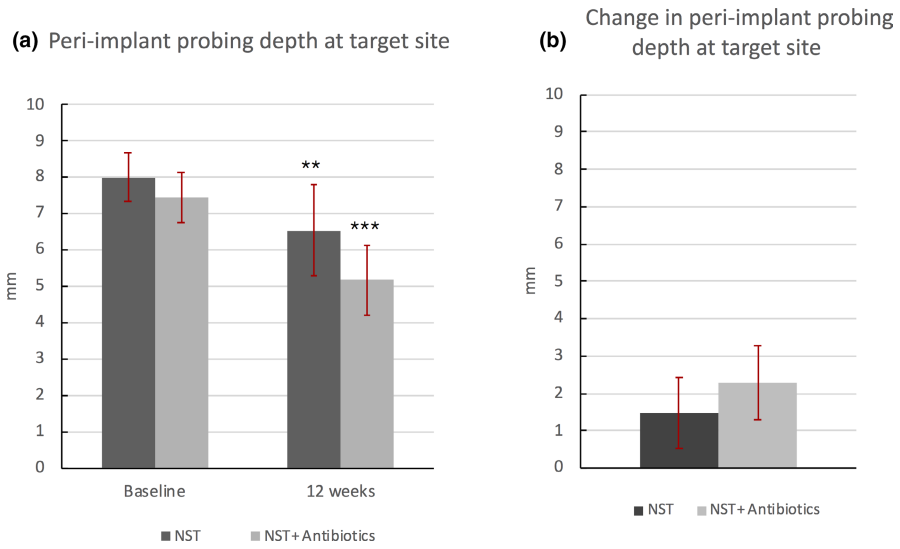


**FIGURE 2** The histograms illustrate the peri-implant probing depth (PIPD) at target site. (a) Mean PIPD at baseline and at 12 weeks, (b) mean change in PIPD between baseline and 12 weeks for the control and experimental group. There were no inter-group differences. The asterisks (**$p < .01$ and ***; $p < .001$) represent statistically significant intra-group differences from baseline to 12 weeks. Error bars: 95% confidence interval

lesions (Hajishengallis & Lamont, 2021). According to the results of the present study, a reduction in mean PIPD following NST plus administration of AMX and MTZ was observed after 12 weeks (mean 2.28 mm) which was greater than NST alone (mean 1.47 mm), although not reaching statistical significance. The current results are in accordance with three recent studies, one cohort and two RCTs, which evaluated the use of systemic AMX and MTZ as an adjunct in the NST of PI (De Waal et al., 2021; Shibli & Ferrari, 2019; Stein et al., 2018). These studies reported that both NST alone and NST with antibiotics led to PIPD reduction ranging from 0.40 to 1.67 mm at 3 months (De Waal et al., 2021) and 12 months (Shibli & Ferrari, 2019; Stein et al., 2018). Taken together, from the current study and three previous studies, it seems not justified to prescribe systemic AMX and MTZ in the NST of PI. On the other hand, an RCT where systemic MTZ was prescribed for 7 days reported a mean reduction in PIPD of 2.53 mm in the experimental group versus 1.02 mm in the placebo group ($p < .05$) after 12 months (Blanco et al., 2022). That reduction in PIPD was also accompanied by a mean reduction of 2.33 mm in the intra-bony component of the peri-implant defect in the experimental group, as compared with 1.13 mm in the placebo group ($p < .05$). The latter study, however, included re-contouring of the prostheses where needed in order to facilitate oral hygiene. Furthermore, the implant-supported restorations were removed if possible during NST (Blanco et al., 2022).

In the present study, the success rate was very low; only three target sites in the control group and two target sites in the experimental group (or one patient in each group) showed complete resolution of the disease (PIPD <5 mm, no BoP and/or SoP). This could be attributed to the fact that 81% of the target sites still had BoP after treatment. Similar results in BoP reduction at 12 weeks after treatment were reported by Shibli et al., even though BoP further decreased at the 1 year follow-up (mean BoP 40.3% and 35.6%

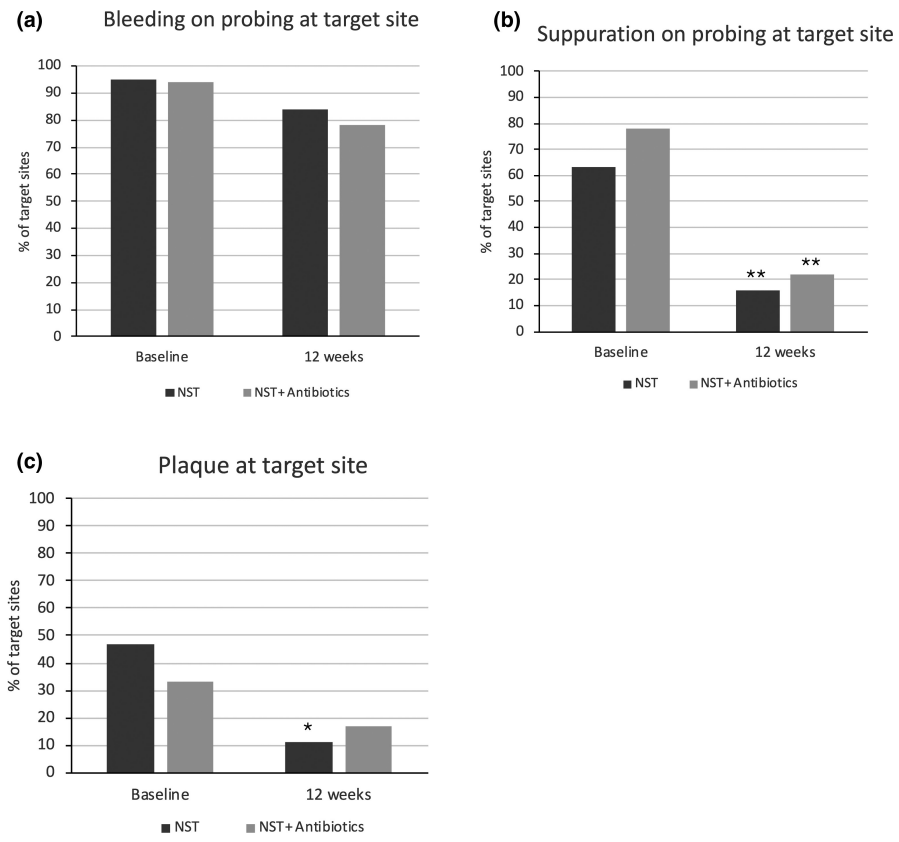


**FIGURE 3** The bar graphs illustrate the frequencies of the secondary outcome parameters (a) bleeding on probing (BoP), (b) suppuration on probing (SoP), and (c) plaque at target site level for the control and the experimental group at baseline and at 12 weeks. The data are expressed as percentage (%) of target sites which present BoP, SoP and plaque respectively. The asterisks (*; $p < .05$ and **; $p < .001$) represent statistically significant intra-group differences from baseline to 12 weeks

**TABLE 3** Clinical outcomes according to baseline PIPD of all six peri-implant sites

| | NST ($n = 19$) | NST with AMX + MTZ ($n = 18$) | Between-group test statistic, $p$ value |
|---|---|---|---|
| PIPD ≥5 mm | | | |
| Baseline | 19 (100%) | 18 (100%) | N/A |
| Week 12 | 16 (84%) | 14 (78%) | Fisher's exact test, $p = 0.693$ |
| PIPD ≥6 mm | | | |
| Baseline | 19 (100%) | 16 (89%) | Fisher's exact test, $p = 0.230$ |
| Week 12 | 14 (74%) | 8 (44%)* | $X^2 = 3.278$, $p = 0.070$ |
| PIPD ≥7 mm | | | |
| Baseline | 15 (79%) | 12 (67%) | Fisher's exact test, 0.476 |
| Week 12 | 10 (53%) | 4 (22%)* | $X^2 = 3.278$, $p = 0.057$ |
| PIPD ≥8 mm | | | |
| Baseline | 11 (58%) | 9 (50%) | $X^2 = 0.232$, $p = 0.630$ |
| Week 12 | 8 (42%) | 4 (22%) | $X^2 = 1.668$, $p = 0.197$ |
| PIPD ≥9 mm | | | |
| Baseline | 9 (47%) | 6 (33%) | $X^2 = 0.755$, $p = 0.385$ |
| Week 12 | 7 (37%) | 3 (17%) | Fisher's exact test, $p = 0.269$ |
| PIPD ≥10 mm | | | |
| Baseline | 2 (11%) | 1 (6%) | Fisher's exact test, $p = 1.000$ |
| Week 12 | 2 (11%) | 1 (6%) | Fisher's exact test, $p = 1.000$ |

*Note:* The values represent frequency of patients ($n$, %) having PIPD ≥5, ≥6, ≥7, ≥8, ≥9, and ≥10 mm at baseline and at 12 weeks, for the experimental group and for the control group.

Abbreviations: AMX, Amoxicillin; MTZ, Metronidazole; NST, Non-surgical treatment; PIPD, Peri-implant pocket depth.

*Significant difference between baseline and 12 weeks ($p < .01$). McNemar's Chi-square test.

at control and experimental group, respectively) (Shibli & Ferrari, 2019). In any case, all previous studies and the current study agree that NST (with or without antimicrobials) is ineffective to completely resolve BoP around dental implants (De Waal et al., 2021; Nart et al., 2020; Stein et al., 2018). Factors that might account for the low success rates of NST for PI could be related to the inherent difficulties in removing the biofilm from the implant surfaces, to the type of instruments used to perform the debridement (ultrasonic and hand instruments vs. air-abrasive devices), and to the fact that no removal and cleaning or modification of the suprastructure was performed in conjunction with NST (de Avila et al., 2020; Ronay et al., 2017). Perhaps a more strict monitoring of the patients during the study period (e.g., a biweekly hygiene check) could have resulted in more favorable outcomes in terms of inflammatory parameters (Machtei et al., 2021), but practically it is not easily applicable to a regular dental office.

This study had several limitations; first, the presence of potential local etiological factors including implant positioning, excess cement, presence of keratinized attached gingiva (Monje et al., 2019), to name a few, was not evaluated. Second, 54% of the patients included in this study were presented with deep PIPD ≥8 mm. The low success rate observed in this study supports previous literature reports that in severe PI cases non-surgical treatment alone is insufficient to arrest the disease and eliminate bacteria from the rough surfaces of implants and from the concavities between implant threads (Faggion Jr et al., 2013; Persson et al., 2010; Renvert et al., 2019). Therefore, severe PI maybe best treated by NST first, followed by surgical therapy (Renvert et al., 2012). Third, the follow-up period was rather short, however, it was not considered appropriate to delay further treatment for the cases with residual inflamed deep PIPDs. Thus, the long-term effect of the current NST modality, on implant survival and prevention of further progression of PI, for example, could not be evaluated. Finally, although an a priori power analysis was performed based on a mean difference in PIPD after treatment of 1 mm between the experimental and control group with standard deviation of 1 mm, the actual difference in PIPD reduction between the two groups was smaller than expected (0.81 mm) and the standard deviation was 1.95 mm, almost double than the one used in the power analysis. Also, we found the effect size of change in PIPD to be moderate. This indicates that the study was underpowered and we cannot rule out that with an increased number of patients the power of the study would have increased and with that a small adjunctive, statistically significant effect of antibiotics would have been found. Nevertheless, whether such statistically significant effect would be clinically relevant needs to be seen.

The existing data regarding the benefits of use of systemic antibiotics on the microbiological parameters of the patients are contradictory. Two recent RCTs, which evaluated the submucosal peri-implant biofilm profiles using targeted techniques after NST with or without the combination of systemically administered AMX and MTZ, did not find any beneficial microbiological effects with the use of antibiotics (De Waal et al., 2021; Shibli & Ferrari, 2019). Both studies reported that at follow-up (1 year and 3 months, respectively), many implants had become recolonized with periodontal pathogens, and that there were no statistically significant differences between control and experimental groups (De Waal et al., 2021; Shibli & Ferrari, 2019). On the other hand, (Blanco et al., 2022) reported a significantly greater decrease in the counts of *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Campylobacter rectus* at 12 months in patients receiving systemic MTZ compared with the control group (Blanco et al., 2022). That being said, when prescribing systemic antibiotics for the treatment of PI, we should take into consideration the potential side-effects (Heta & Robo, 2018), the risk of superinfection with opportunistic bacteria, yeast, and viruses, which may be difficult to eradicate (Verdugo, 2018), the development of bacterial resistance (Rams et al., 2014), and the frequent need for surgery anyway to further treat residual PIPD (Faggion Jr et al., 2013; Renvert et al., 2019). Therefore, the decision to administer adjunctive systemic antibiotics should be made with caution, and the practitioner should consider the medical history of the patient, concomitant medications, and the ultimate goal of the treatment (i.e., shallow residual pockets around the implant where PI was present).

In conclusion, the present study showed no clinical benefit from the adjunctive use of systemic AMX and MTZ in the NST of PI. We suggest that the routine use of systemic antibiotics in NST of PI is not recommended. Furthermore, neither of the tested treatment modalities achieved complete resolution of the disease. Although NST should always be the first step in PI treatment, which provides some improvement in clinical parameters and allows for oral hygiene improvement and better patient compliance, sufficient PIPD reduction in severe PI cases can only be accomplished after a surgical treatment phase.

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## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this study.

## AUTHOR CONTRIBUTION

**Angeliki Polymeri:** Formal analysis (lead); Investigation (supporting); Validation (equal); Visualization (lead); Writing – original draft (lead); Writing – review & editing (equal). **Joyce van der Horst:** Investigation (lead); Methodology (equal); Writing – review & editing (equal). **David Anssari-Moin:** Data curation (supporting); Investigation (lead); Methodology (equal); Writing – review & editing (equal). **Daniel Wismeijer:** Conceptualization (equal); Methodology (equal); Resources (equal); Validation (equal); Writing – review & editing (equal). **Bruno G. Loos:** Conceptualization (equal); Formal analysis (supporting); Funding acquisition (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (supporting); Writing – review & editing (equal). **Marja L. Laine:** Conceptualization (equal); Data curation (lead); Formal analysis

(supporting); Funding acquisition (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (supporting); Writing – review & editing (equal).

## DATA AVAILABILITY STATEMENT

The data that support the results of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

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