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Do systemic amoxicillin and metronidazole during the non-surgical peri-implantitis treatment phase prevent the need for future surgical treatment? A retrospective long-term cohort study

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# Do systemic amoxicillin and metronidazole during the non-surgical peri-implantitis treatment phase prevent the need for future surgical treatment? A retrospective long-term cohort study

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## Abstract

**Aim:** The aim of this retrospective long-term follow-up of a 3-month RCT was to assess whether non-surgical peri-implantitis treatment with adjunctive systemic antibiotics influenced the need for additional surgical treatment.

**Materials and Methods:** Patients enrolled in an aftercare programme following non-surgical peri-implantitis treatment, with or without systemic amoxicillin and metronidazole, were analysed. Data had previously been collected pre-treatment ( $T_0$ ) and 3 months after treatment ( $T_1$ ) and were additionally collected during subsequent aftercare visits, until the final assessment ( $T_2$ ). Primary outcome was the need for additional surgical peri-implantitis therapy during the aftercare programme, analysed via Kaplan–Meier analysis and Cox regression. Secondary outcomes involved clinical parameters, assessed using parametric and non-parametric tests.

**Results:** Forty-five patients (22 AB– group, 23 AB+ group) were included. The mean follow-up time between  $T_1$  and  $T_2$  was 35.9 months (SD = 21.0). 73.9% of the AB+ group and 50.0% of the AB– group did not receive additional surgical therapy (log-rank test,  $p = .110$ ). The adjusted Cox regression model did not provide a significant result for antibiotics ( $\beta = .441$ , 95% CI = 0.159–1.220,  $p = .115$ ). Univariable regression analysis highlighted the influence of baseline peri-implant pocket depth on the need for surgical treatment ( $\beta = 1.446$ , 95% CI = 1.035–2.020,  $p = .031$ ).

**Conclusions:** Systemic amoxicillin and metronidazole administered during non-surgical peri-implantitis treatment do not seem to prevent the need for additional surgical therapy in the long term, during a structured aftercare programme.

## KEYWORDS

dental implants, periodontal diseases

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### Clinical Relevance

*Scientific rationale for study:* There is limited scientific evidence to evaluate the long-term effects of non-surgical peri-implantitis treatment supplemented with systemic antibiotics.

*Principal findings:* Administration of systemic amoxicillin and metronidazole during non-surgical peri-implantitis treatment did not significantly lower the number of patients requiring additional surgical peri-implantitis treatment during the long-term follow-up period.

*Practical implications:* In the long term, systemic antibiotics do not seem to prevent the need for an additional surgical intervention after non-surgical peri-implantitis treatment. However, individually selected cases may benefit from additional systemic antibiotics as part of the non-surgical treatment phase.

## 1 | INTRODUCTION

Peri-implantitis is a multifactorial pathological condition occurring in the tissues that surround dental implants, characterized by mucosal inflammation and subsequent progressive peri-implant bone loss (Berglundh et al., 2018). Non-surgical and surgical treatment interventions aim at reducing this inflammatory process, decreasing the probing pocket depth (PD) and halting peri-implant bone reduction. It has been demonstrated that clinical parameters, such as bleeding scores (BS), tend to improve after non-surgical sub-marginal instrumentation (NSI), but treatment sites frequently show residual or recurrent signs of inflammation (Ramanaukaite et al., 2021). Therefore, additional therapeutic measures that aim at improving the outcome of non-surgical peri-implantitis treatment are frequently investigated. One such measure is the administration of adjunctive systemic antimicrobials.

The available literature is inconsistent with regard to the benefits of adjunctive antibiotics during the non-surgical treatment phase. Short-term studies (with a 3-month follow-up) suggest that the clinical benefits of adjunctive antibiotics are limited. Systemically administered amoxicillin and metronidazole tend to improve BS and peri-implant PD, but not significantly more than NSI alone (De Waal et al., 2021; Polymeri et al., 2022). In the systematic review by Liñares et al. (2023), it was concluded that NSI with adjunctive systemic antibiotics might enhance PD reduction, especially in deeper pockets. This conclusion is based on three RCTs with a 12-month follow-up. However, the results between these three studies were not consistent. Shibli et al. (2019) observed an improvement in peri-implant PD in patients who received NSI with adjunctive systemically administered amoxicillin and metronidazole. However, no significant differences in PD, clinical attachment levels (CAL) and proportions of *red complex* pathogens could be detected after 1 year when this result was compared with the control group (NSI with a placebo). Similar results were reported by Almohareb et al. (2020) who observed an equal reduction in severe peri-implant symptoms after NSI was supplemented with either photodynamic therapy or systemic amoxicillin and metronidazole, after 6 months. On the other hand, Blanco et al. (2022) did report significant additional improvements in clinical, radiographic and microbiologic parameters, 12 months after NSI was supplemented with systemic metronidazole. It should be noted that, in this study, NSI was followed by granulation tissue removal and soft

tissue curettage. Whether this therapy is a form of non-surgical treatment can be debated. In short, these findings seem to confirm the notion that there are insufficient data present to support a specific antibiotic protocol to treat peri-implantitis using non-surgical therapy (Feres et al., 2023).

When NSI has not succeeded in reinstating peri-implant health (residual probing depths  $\leq 5$  mm, no bleeding on probing  $\geq 1$  probing site and no suppuration on probing), a surgical treatment approach is indicated. While the routine prescription of antimicrobials is not recommended, specific cases exhibiting severe peri-implantitis (e.g., initially deep pockets  $\geq 7$  mm, extensive suppuration) might benefit from systemic antibiotics during non-surgical peri-implantitis therapy (Herrera et al., 2023). This could potentially reduce the need for additional peri-implantitis surgery. It is desirable to prevent the burden of peri-implantitis surgery and/or the possible necessity for implant removal if this is clinically feasible. The desired beneficial effects of a systemic antibiotic therapy should however be weighed against the potential side effects of the drugs (Herrera et al., 2023).

The purpose of this study was to evaluate the long-term effects of systemically administered amoxicillin and metronidazole, administered in addition to non-surgical sub-marginal instrumentation and focus on the need for additional surgical therapy during the aftercare programme. It is hypothesized that there is no significant difference in need for additional surgical therapy between patients who received non-surgical peri-implantitis treatment with or without adjunctive systemic amoxicillin and metronidazole (null hypothesis).

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This study is a retrospective cohort study with a mean follow-up of 36 months assessing the long-term clinical effectiveness of systemic amoxicillin and metronidazole as an adjunctive treatment to NSI. The primary aim was to evaluate whether adjunctive systemic antibiotics prevents the need for additional surgical therapy in the long term. This study presents the long-term follow-up results of a cohort of patients who previously participated in a 3-month RCT (De Waal et al., 2021).

## 2.2 | Participants

Data were retrospectively collected from patient files of the *The Hague Clinic for Periodontology*, The Netherlands. Patients who had previously received NSI for peri-implantitis (marginal bone loss  $\geq 2$  mm combined with bleeding and/or suppuration on probing and peri-implant probing depth  $\geq 5$  mm) with (AB+) or without (AB-) systemic antibiotics were included (De Waal et al., 2021). Clinical and radiographic data had previously been collected prior to NSI ( $T_0$ ) and 3 months after NSI ( $T_1$ ). After treatment evaluation, patients were invited to participate in an individually-tailored supportive peri-implant care programme, including oral hygiene coaching and professional mechanical plaque removal with an interval of 3–4 months. The need for additional surgical peri-implantitis treatment was assessed during each visit by an experienced periodontist (TV) based on the following criteria:

- peri-implantitis PD > 5 mm;
- concomitant bleeding and/or suppuration on probing.

The clinical effect of the additional treatment was monitored afterwards until the last available follow-up visit ( $T_2$ ). Approval for this study was granted by the review board of the University Medical Center Groningen (no. 20220007), and its composition adhered to the Declaration of Helsinki. The formulation of the manuscript followed the STROBE guidelines.

## 2.3 | Intervention

The non-surgical intervention is described in detail by De Waal et al. (2021). In brief, patients underwent thorough mechanical cleaning of both implants and teeth in up to five sessions administered by skilled dental hygienists. Implants were cleansed supra- and submucosally using an air polisher with a sub-gingival tip (EMS Air-flow<sup>®</sup> with erythritol-based powder containing chlorhexidine) and ultrasonic instruments (PL1 and PL2 instruments, EMS Piezon<sup>®</sup>), focusing solely on exposed screw threads. Teeth were cleansed supra- and subgingivally utilizing ultrasonic instruments (EMS Piezon<sup>®</sup>) and hand instruments (Hu-friedly). Throughout each session, patients received personalized oral hygiene instructions, including electric toothbrush usage, interdental brush application with 1% chlorhexidine gel (Corsodyl<sup>®</sup>, GlaxoSmithKline) at implants, and implant-specific flossing with either Oral-B<sup>®</sup> superfloss (Procter & Gamble Company) or Meridol<sup>®</sup> floss (Colgate-Palmolive Company). After NSI, patients were randomly allocated to receive additional systemic antibiotics (systemic amoxicillin and metronidazole) (500/500 mg, three times daily for 7 days, AB+) or not (AB-).

## 2.4 | Outcomes

The primary outcome variable was defined as 'the need for additional surgical therapy after NSI (yes/no)'. Surgical treatment was defined as either surgical peri-implantitis treatment or implant removal.

Secondary outcome variables were changes between  $T_0$ ,  $T_1$  and  $T_2$  in mean peri-implant and periodontal full-mouth probing pocket depths (PDs), BS, suppuration scores (SS) and plaque scores (PS). Furthermore, the clinical treatment success (yes/no) on  $T_2$  was evaluated on patient and implant level and was defined as a composite treatment outcome based on the end points of the non-surgical step of peri-implantitis treatment as stated by Herrera et al. (2023):

- residual probing depths  $\leq 5$  mm;
- no bleeding on probing  $\geq 1$  probing site;
- no suppuration on probing.

## 2.4.1 | Clinical parameters

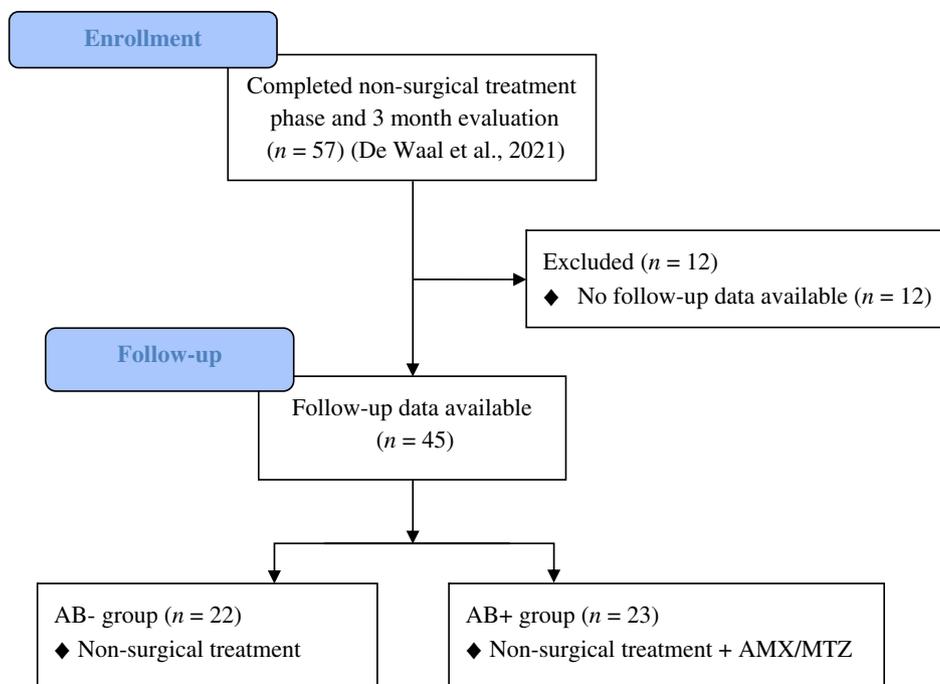
The clinical parameters were scored at six sites per tooth or implant by one experienced periodontist (TV). The presence of plaque was visually analysed using a dental probe and scored as either present or absent. The PD was assessed in mm using a Hu-Friedly<sup>®</sup> PCPUNC156 periodontal probe. Subsequent bleeding and/or suppuration was scored as either present or absent.

## 2.5 | Sample size

This study aimed at retrieving data from all 57 patients who completed the 3-month follow-up of the previous RCT (De Waal et al., 2021). No literature specifically assessing the need for surgical treatment after non-surgical peri-implantitis therapy is currently present, and thus, a convenience sample was used that could serve as a benchmark for future research.

## 2.6 | Statistical methods

The primary outcome was evaluated using a Kaplan–Meier analysis. A log-rank test was performed to evaluate when and how often the indication for peri-implantitis surgery was made between the AB+ and AB- groups and whether this was statistically different. The data were analysed by calculating the difference in months between  $T_1$  and  $T_2$ . For patients who received additional surgical treatment during this timeframe, the number of months that passed between  $T_1$  and the date of surgery was also calculated. The surgery date then replaced the  $T_2$  date, thus creating a data set where the months until surgical treatment served as a cut-off point. Cox regression was used to analyse to what extent the effect of antibiotics was influenced by other variables over time. Crude analysis was adjusted using the variables 'mean full-mouth PS at  $T_0$  (%)', 'mean peri-implant radiographic bone loss at  $T_0$  (mm)' and smoking status, based on the available literature (De Waal et al., 2016; Lee et al., 2022; Vilarrasa et al., 2023). Furthermore, to explore other variables that might potentially influence the need for surgery, separate univariable regression analyses were performed. Variables that showed a significant result were incorporated in a multiple



**FIGURE 1** Flow chart with regard to data retrieval.

regression analysis. The secondary outcomes BS, SS and PS were scored as a percentage. For the outcome variable PD, mean scores were calculated for all included implants and teeth. These parameters were collected on  $T_0$ ,  $T_1$  and  $T_2$ . Within-subjects analyses for the normally distributed data were analysed using a repeated measures ANOVA. Data that were not normally distributed were analysed using the Friedman test. Post hoc analyses were performed using the Bonferroni correction (normally distributed data) and Wilcoxon signed-rank tests (non-normally distributed data). To assess potential attrition bias, the data underwent analysis by comparing the baseline patient characteristics and the baseline clinical parameters of the patients who were lost to follow-up with those who participated in the follow-up programme, for which independent samples *t*-tests and Chi-square tests were used. Descriptive statistics were analysed using SPSS (IBM, Armonk, NY, USA). Kaplan–Meier figures were drafted using GraphPad Prism (Dotmatics, Boston, MA, USA).

### 3 | RESULTS

Figure 1 displays the flow chart outlining the study's follow-up. Among the initial 57 patients, 12 individuals did not partake in the aftercare programme at *The Hague Clinic for Periodontology*. Consequently, there are no available data from these patients, resulting in a final dataset of 45 patients. Patient characteristics are detailed in Table 1. The findings with regard to the attrition bias analysis are presented in Table 2. No significant differences were observed between the patients who participated in the aftercare programme and the patients who were lost to follow-up.

The average follow-up duration between  $T_1$  and  $T_2$  for the study population was 35.9 months (standard deviation [SD] = 21.0;

range = 6.0–80.0). Figure 2 depicts the Kaplan–Meier analysis, evaluating the necessity for additional peri-implantitis surgery for both the AB+ and AB− groups. Overall, 62.2% of the study participants did not receive additional surgical therapy, comprising 50.0% of AB− group patients and 73.9% of AB+ group patients. Observation of the Kaplan–Meier curves indicates a difference in the number of indicated surgeries during the initial 36 months. In the AB+ group, there is an increase in the number of surgeries happening after this timeframe, suggesting a potential period of approximately 3 years during which antibiotics, within a robust postoperative care protocol, seem to exhibit an effect in this patient cohort. However, the overall outcome did not reach statistical significance (log-rank test,  $p = .110$ ). Table 3 shows the output of the Cox regression models. The covariates did not seem to be time-dependent (proportional hazards assumption based on raw analysis of the survival curves and by introducing a dichotomous time indicator;  $p > .05$  in all models). Adjusting the crude analysis did not significantly alter the hazard ratio for future surgery with regard to adjunctive antibiotic treatment during NSI ( $\beta = .441$ , 95% CI = 0.159–1.220,  $p = .115$ ). Univariable analyses highlighted a significant result with regard to the baseline peri-implant PD. However, this did not substantially alter the result for antibiotics after incorporation into the multiple regression model ( $\beta = .464$ , 95% CI = 0.169–1.269,  $p = .135$ ).

Table 4 represents the clinical data on the periodontal and peri-implantitis parameters with the corresponding *p*-values. In both groups, there was a significant reduction in peri-implantitis PD and BS from  $T_0$  to  $T_1$ . Subsequently, there was a further decrease from  $T_1$  to  $T_2$ , reaching significance in the AB− group but not in the AB+ group ( $\Delta$  PD  $T_1 - T_2$  in AB− and AB+ equals  $-1.2$  vs.  $-0.6$  mm, respectively;  $\Delta$  BS  $T_1 - T_2$  in AB− and AB+ equals  $-28.0\%$  vs.  $-18.5\%$ , respectively). Moreover, both groups experienced a significant reduction in peri-implantitis SS and PS between  $T_0$  and  $T_1$ . Although a decrease was observed between  $T_1$  and

**TABLE 1** Patient characteristics and treatment success at different time points.

Characteristics	AB- group	AB+ group
Number of patients ( <i>n</i> = 45)	22	23
Number of implants that received NSI at T <sub>0</sub> ( <i>n</i> = 98)	48	50
Age (years; mean [SD])	54.9 (11.5)	59.4 (10.8)
Gender; F (female)/M (male)	18/4	11/12
Current smoking status		
Yes	5	4
No	17	19
Surgical follow-up treatment of dentition		
Surgical resective treatment; <i>n</i> patients	3	1
Surgical regenerative treatment; <i>n</i> patients	2	1
Dental extractions; <i>n</i> patients	7	8
Follow-up treatment of implants		
Non-surgical retreatment; <i>n</i> patients	2	0
Surgical therapy; <i>n</i> patients	11	6
Type of surgical therapy; <i>n</i> patients		
Access flap surgery	4	1
Regenerative surgery	5	2
Explantation	2	3
Total number of implants surgically treated or removed ( <i>n</i> = 32)	21	11
Treatment success		
Treatment success at T <sub>1</sub>		
Patients (%)	31.8	43.4
Implants (%)	50.0	62.0
Treatment success at T <sub>2</sub>		
Patients (%)	27.3	47.8
Implants (%)	41.7	56.0

Abbreviation: NSI, non-surgical sub-marginal instrumentation.

**TABLE 2** Attrition bias analysis.

Characteristics	Patients included ( <i>n</i> = 45)	Patients lost to follow-up ( <i>n</i> = 12)	<i>p</i> -value
Gender; F (female)/M (male)	29/16	4/8	.097 <sup>a</sup>
Age (years; mean [SD])	57.20 (11.29)	54.58 (10.55)	.880 <sup>b</sup>
PD (mean; mm [SD])	5.73 (1.38)	5.71 (1.18)	.530 <sup>b</sup>
BS (mean; % [SD])	89.28 (16.68)	94.56 (10.13)	.060 <sup>b</sup>
SS (mean; % [SD])	10.41 (13.67)	14.85 (14.58)	.904 <sup>b</sup>
PS (mean; % [SD])	44.36 (28.67)	34.22 (31.30)	.667 <sup>b</sup>

Abbreviations: BS, bleeding scores; PD, pocket depth; PS, plaque scores; SS, suppuration scores.

<sup>a</sup>Chi-square test.

<sup>b</sup>Independent samples *t*-test.

T<sub>2</sub>, only the reduction in peri-implantitis PS in the AB- group was significant. A marginal increase in peri-implantitis PS is evident in both groups at T<sub>2</sub>. The data on periodontal parameters highlight that the most substantial changes occurred between T<sub>0</sub> and T<sub>1</sub>.

## 4 | DISCUSSION

The aim of this study was to retrospectively evaluate the difference in need for additional peri-implantitis surgery after NSI with or without adjunctive amoxicillin and metronidazole. The data show that there is no significant difference in need for additional surgical peri-implantitis treatment between the AB+ and AB- group, and therefore, the null hypothesis should be accepted. It is worth noting that this finding might be influenced by the broad range in follow-up time. In this sense, despite retaining the null hypothesis, it is important to underline the trend that the systemic antimicrobial therapy with amoxicillin and metronidazole reduced the indication for peri-implantitis surgery for 36 months after NSI in this study. There is a 23.9% difference in indicated surgeries in favour of the antibiotics group throughout the entire follow-up period. Furthermore, the adjusted Cox regression model also did not provide a significant result regarding the influence of systemic amoxicillin and metronidazole to the need for additional surgical peri-implantitis during the follow-up. In addition, irrespective

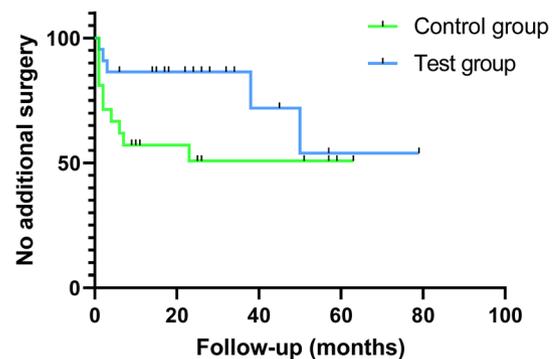
**FIGURE 2** Survival curves for the antibiotics (AB+) group and the group that did not receive antibiotics (AB-).

TABLE 3 Cox regression.

Outcome variable	Crude model			Adjusted model		
	$\beta$	95% CI	p-value	$\beta$	95% CI	p-value
Antibiotics (y/n)	.459	0.169–1.244	.126	.441	0.159–1.220	.115
	Univariable regression analysis			Multiple regression analysis		
	$\beta$	95% CI	p-value	$\beta$	95% CI	p-value
Gender (m/f)	.939	0.347–2.543	.902			
Smoking (y/n)	1.170	0.380–3.598	.784			
Antibiotics (y/n)	.459	0.169–1.244	.126	.464	0.169–1.269	.135
FMPS (%) <sup>a</sup>	.986	0.963–1.010	.246			
PIBL (mm) <sup>b</sup>	1.141	0.878–1.483	.322			
PIPD (mm) <sup>c</sup>	1.446	1.035–2.020	.031	1.422	1.027–1.969	.034
PISup (y/n) <sup>d</sup>	1.057	0.407–2.746	.909			
SuccT <sub>1</sub> (y/n) <sup>e</sup>	.470	0.152–1.452	.190			
PISC (months) <sup>f</sup>	.669	0.232–1.924	.455			

<sup>a</sup>Mean full-mouth plaque scores at T<sub>0</sub> (%).

<sup>b</sup>Mean peri-implant radiographic bone loss at T<sub>0</sub> (mm).

<sup>c</sup>Mean peri-implant pocket depth at T<sub>0</sub> (mm).

<sup>d</sup>Peri-implant suppuration at T<sub>0</sub> (y/n).

<sup>e</sup>Treatment success at T<sub>1</sub> (y/n).

<sup>f</sup>Frequency of peri-implant supportive care after T<sub>1</sub> (months).

of the systemic antibiotics, univariable regression showed that baseline peri-implant PD significantly increased the hazard of having to undergo surgery during the follow-up after NSI in this cohort ( $\beta = 1.422$ , 95% CI 1.027–1.969,  $p = .034$ ). This could be attributed to the fact that non-surgical treatment alone typically leads to a reduction in PD of approximately 0.5–1.0 mm (Renvert et al., 2019), indicating that initially deep pockets are unlikely to decrease to a level where surgical intervention is deemed to be unnecessary.

The majority of the surgeries in the AB– group were performed early during the follow-up phase compared with the AB+ group, indicating that several cases were deemed to be treated non-successfully on, or shortly after, 3 months. This is supported by Renvert et al. (2019), who concluded that conventional non-surgical mechanical debridement as a monotherapy (i.e., not supplemented with additional decontamination protocols) generally does not suffice. However, both groups in the present study showed a reduction in clinical parameters during the follow-up period and the clinical parameters seemed to reduce to a similar level for both the AB– and the AB+ group. This finding emphasizes the need to prospectively explore the extent to which a thorough post-treatment protocol can effectively manage peri-implantitis over the long term. Similar observations were made by Hentenaar et al. (2021) who analysed the non-surgical peri-implantitis treatment using either an air polishing device or piezoelectric ultrasonic scaling. Although the effects of both therapies were limited after 3 months, a gradual improvement of peri-implant parameters was observed in successfully treated patients after 12 months when supportive treatment and oral self-care reinforcement was performed after 6 and 9 months.

In the initially performed randomized controlled trial, De Waal et al. (2021) did not observe significant benefits in the group that

received systemic antibiotics with regard to the clinical and microbiological outcomes. Despite this, both groups displayed notable clinical improvements 3 months after non-surgical treatment. The observed effect seems to persist in the remaining cohort. This observation is corroborated by analogous clinical studies, which failed to demonstrate a noteworthy advantage of systemic antibiotics as an adjunct to non-surgical peri-implantitis treatment (Almohareb et al., 2020; Polymeri et al., 2022; Shibli et al., 2019). In contrast, Blanco et al. (2022) evaluated the beneficial effects of metronidazole as an adjunct to non-surgical mechanical debridement and observed significant additional improvements in radiographic, clinical and microbiological parameters after 12 months of follow-up. Still, in that study, only 56.3% of the test group met the success criteria as opposed to 25% in the control group. The justification for routinely prescribing systemic antibiotics as a complement to non-surgical peri-implantitis treatment could therefore be questioned, in light of the general principles of antibiotic stewardship and the public health goal to curtail the unnecessary utilization of antibiotics in dentistry (Herrera et al., 2023).

Aside from improvements in clinical aspects such as reduced bleeding tendency and minor PD reduction, achieving complete resolution of severe peri-implantitis cases appeared difficult in the present study. In the AB+ group, the indications for additional surgical therapy were made later on during the aftercare programme. It seems that systemic antibiotics as an adjunct to NSI provide a short-term reduction in clinical inflammatory parameters, but are unable to suppress peri-implant pathology on a longer term. Similar results were presented by Gomi et al. (2015), who supplemented full-mouth scaling and root planing in periodontitis and peri-implantitis patients with azithromycin and observed that after 6 months, periodontal pathogens increased again around implants. All patients in our study also presented with both

**TABLE 4** Parameters and corresponding *p*-values regarding the clinical peri-implantitis and periodontal data.

Parameters	AB- group (n = 22)			AB+ group (n = 23)				
	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>	T <sub>0</sub>	T <sub>1</sub>	T <sub>2</sub>		
Peri-implantitis parameters								
PD (mean; mm [SD])	5.9 (1.5)	4.5 (1.4)	3.3 (1.4)	5.6 (1.3)	3.9 (1.3)	3.3 (0.7)		
BS (mean; % [SD])	95.6 (8.3)	59.9 (29.6)	31.9 (23.4)	83.3 (20.3)	47.3 (31.8)	28.8 (28.9)		
SS (median; % [IQR])	4.2 (16.7)	0.0 (0.0)	0.0 (0.0)	6.7 (16.7)	0.0 (5.6)	0.0 (0.0)		
PS (median; % [IQR])	44.5 (58.3)	0.0 (0.0)	2.1 (22.2)	44.4 (33.3)	0.0 (16.7)	5.6 (33.3)		
Periodontal parameters								
PD (mean; mm [SD])	3.1 (0.5)	2.4 (0.4)	2.5 (0.4)	3.1 (0.6)	2.3 (0.4)	2.4 (0.3)		
BS (mean; % [SD])	47.2 (19.2)	17.8 (10.7)	16.9 (15.9)	40.2 (16.7)	14.1 (9.7)	12.1 (8.3)		
SS (median; % [IQR])	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)		
PS (median; % [IQR])	41.8 (36.3)	6.0 (64.2)	7.8 (14.9)	36.8 (28.5)	9.0 (34.0)	8.3 (28.7)		
Main test <i>p</i> -values		Post hoc analyses <i>p</i> -values						
		AB- group (n = 22)			AB+ group (n = 23)			
		T <sub>0</sub> → T <sub>1</sub>	T <sub>0</sub> → T <sub>2</sub>	T <sub>1</sub> → T <sub>2</sub>	T <sub>0</sub> → T <sub>1</sub>	T <sub>0</sub> → T <sub>2</sub>	T <sub>1</sub> → T <sub>2</sub>	
Peri-implantitis parameters								
PD <sup>a</sup>	<.001	<.001	<.001	<.001	.013	<.001	<.001	0.153
BS <sup>a</sup>	<.001	<.001	.007	<.001	<.001	<.001	<.001	.144
SS <sup>b</sup>	<.001	<.001	.005	.040	.715	.015	.003	.125
PS <sup>b</sup>	<.001	<.001	<.001	<.001	.033	<.001	<.001	.550
Periodontal parameters								
PD <sup>a</sup>	<.001	<.001	<.001	<.001	1.000	<.001	<.001	.279
BS <sup>a</sup>	<.001	<.001	<.001	<.001	1.000	<.001	<.001	.928
SS <sup>b</sup>	.068	.174	NA	NA	NA	NA	NA	NA
PS <sup>b</sup>	<.001	<.001	<.001	<.001	.715	<.001	<.001	.709

Abbreviations: BS, bleeding scores; NA, not applicable; PD, pocket depth; PS, plaque scores; SS, suppuration scores.

<sup>a</sup>Repeated measures ANOVA, post hoc Bonferroni corrections.

<sup>b</sup>Friedman test, post hoc Wilcoxon signed-rank tests.

peri-implantitis and periodontitis at baseline, which were both treated simultaneously. A wide array of studies has focused on the association between peri-implantitis and periodontitis, and it seems that both the presence and the history of periodontitis are positively associated with a susceptibility of developing peri-implantitis (Dreyer et al., 2018). Treating periodontal pathology and maintaining a healthy periodontium is therefore of vital importance to maintain healthy peri-implant tissues.

Several limitations to the study must be addressed. For one, the results should be interpreted with caution given that the data presented were retrieved retrospectively. This means that there was no uniform policy regarding the data storage in the patient files. As the aftercare programme was individually tailored, no clear duration of the follow-up was determined. This resulted in a wide range of follow-up frequencies and total span of the follow-up period. Furthermore, treatment success was based on clinical parameters alone, due to the absence of radiographic recordings. Therefore, it was not possible to monitor the extent of any peri-implant bone loss that could have occurred during the follow-up. The number of patients included in this study could be considered limited. This was

caused by the fact that several patients did not adhere to the aftercare programme and could therefore not provide reliable data, resulting in a convenience sample of 45 patients. However, when evaluating Table 2, it seems that the group that was lost to follow-up shows overall similarities with the evaluated patient cohort, indicating that the influence of attrition bias could be considered minimal.

## 5 | CONCLUSION

Within the limitations of this study, it seems that the use of amoxicillin and metronidazole as an adjunct to NSI did not prevent the need for additional surgical peri-implantitis treatment in this patient cohort on the long term, but might have a beneficial effect during the first 3 years after NSI if supportive peri-implant aftercare is also provided. Therefore, the effect of systemic antibiotics seems to be temporary in nature, delaying the moment that peri-implantitis surgery is indicated. Furthermore, deeper baseline PDs seemingly increased the need for surgery after NSI in this patient cohort.

## AUTHOR CONTRIBUTIONS

JH drafted the article, interpreted the data and initiated the project. TEV performed clinical examinations and surgical procedures, and contributed to the article revision. AJVW was involved in substantial contribution to article revision. YCMDW was involved in project initiation, data interpretation, study design and article revision.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

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

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# QUESTIONNAIRE

B4(25)

## Do systemic amoxicillin and metronidazole during the non-surgical peri-implantitis treatment phase prevent the need for future surgical treatment? A retrospective long-term cohort study

### INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

### Introduction

**Question 1:** Peri-implantitis is characterised by which of the following?

- A: Progressive peri-implant bone loss
- B: Decreased probing pocket depth
- C: Increased gingival recession
- D: Mucosal inflammation

**Question 2:** What are the goals of surgical and non-surgical peri-implantitis treatment?

- A: Reducing the inflammatory process
- B: Eliminating dental plaque
- C: Decreasing probing pocket depth
- D: Halting peri-implant bone reduction

**Question 3:** What clinical parameters are typically seen after non-surgical sub-marginal instrumentation (NSI)?

- A: Improvement in bleeding scores (BS)
- B: Treatment sites frequently show residual or recurrent inflammation
- C: Treatment sites periodically show residual inflammation

**Question 4:** What statement is **NOT TRUE** regarding short-term studies (with 3-month follow-up) on adjunctive antibiotics in non-surgical treatment?

- A: They show no significant benefits over NSI alone
- B: They show limited clinical benefits
- C: They tend to improve bleeding scores
- D: They tend to improve peri-implant probing depth
- E: They tend to improve BS and peri-implant PD significantly more than NSI alone

**Question 5:** What was the purpose of this study?

- A: To evaluate the long-term effects of systemically administered amoxicillin and metronidazole in addition to NSI
- B: To assess the need for additional surgical therapy without additional administration of antibiotics
- C: To focus on aftercare program outcomes without additional surgical therapy
- D: To focus on the need for additional surgical therapy during the aftercare program
- E: Comparing different antibiotic regimens

### Materials and methods

**Question 6:** Based on which criteria was the need for additional surgical peri-implantitis treatment assessed?

- A: Peri-implantitis PD > 5 mm
- B: Presence of concomitant bleeding on probing
- C: Presence of suppuration on probing
- D: Progressive bone loss

**Question 7:** The clinical treatment success on the last follow-up visit was defined as .....

- A: Residual probing depths of  $\geq 5$  mm, some bleeding on probing  $\geq 1$  probing site, and little suppuration on probing
- B: Residual probing depths of  $\geq 5$  mm, no bleeding on probing  $\geq 1$  probing site, and some suppuration on probing
- C: Residual probing depths of  $\leq 5$  mm, some bleeding on probing  $\geq 1$  probing site, and some suppuration on probing
- D: Residual probing depths of  $\geq 5$  mm, no bleeding on probing  $\geq 1$  probing site, and no suppuration on probing
- E: Residual probing depths of  $\leq 5$  mm, no bleeding on probing  $\geq 1$  probing site, and no suppuration on probing

**Question 8:** Which of the following are **CORRECT** about how the clinical parameters were assessed?

- A:** Parameters were scored at four sites per tooth or implant
- B:** Plaque was visually analysed using a dental probe
- C:** PD was assessed using a Hu-Friedy® PCPUNC156 periodontal probe
- D:** Bleeding was scored only as absent
- E:** Subsequent bleeding and/or suppuration were scored either as absent or present

### Discussion

**Question 9:** What were the **TWO** observed trends in this study regarding systemic antimicrobial therapy with amoxicillin and metronidazole?

- A:** It reduced the indication for peri-implantitis surgery for 36 months after NSI
- B:** It reduced the indication for peri-implantitis surgery for 24 months after NSI
- C:** It showed a 45.9% difference in indicated surgeries in favour of the antibiotics group throughout the entire follow-up period
- D:** It showed a 23.9% difference in indicated surgeries in favour of the antibiotics group throughout the entire follow-up period

**Question 10:** What was found regarding baseline peri-implant PD?

- A:** Deep initial pockets were likely to decrease without surgical intervention
- B:** Univariable regression showed that baseline peri-implant PD significantly increased the hazard of having to undergo surgery during follow-up after NSI
- C:** Non-surgical treatment alone typically led to PD reduction of 0.5-1.0 mm

**Question 11: TRUE or FALSE?**

"The majority of surgeries in both groups were performed early during the follow-up phase."

- A:** TRUE
- B:** FALSE

**Question 12:** What were the findings regarding the association between peri-implantitis and periodontitis?

- A:** Only peri-implantitis was present in all patients at baseline
- B:** Presence of periodontitis is positively associated with peri-implantitis
- C:** History of periodontitis is positively associated with peri-implantitis
- D:** Treating periodontal pathology is vital for maintaining healthy peri-implant tissues

**Question 13:** Which one of the following limitations of this study is **INCORRECT**?

- A:** A uniform policy regarding data storage in patient files
- B:** Retrospective nature of data collection
- C:** Wide range of follow-up frequencies
- D:** Absence of radiographic recordings

**Question 14:** What was **ONE** of the main conclusions regarding systemic antibiotics in non-surgical peri-implantitis treatment?

- A:** Prevented the need for additional surgical treatment long-term
- B:** Might have a beneficial effect during the first 3 years after NSI if supportive peri-implant aftercare is provided
- C:** Had no effect at any time point

**Question 15:** Is it **TRUE** that the effect of systemic antibiotics seems to be temporary in nature, delaying the moment that peri-implantitis surgery is indicated?

- A:** YES
- B:** NO

**THE END**



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**ANSWER SHEET**

**B4(25)**

Do systemic amoxicillin and metronidazole during the non-surgical peri-implantitis treatment phase prevent the need for future surgical treatment? A retrospective long-term cohort study

*Time spent on activity						hour		min				
	A	B	C	D	E		A	B	C	D	E	
1						8						
2						9						
3						10						
4						11						
5						12						
6						13						
7						14						
						15						

How relevant was the content of this activity to your scope of practice?			
Not at all	Somewhat	Mostly	Extremely

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