

# Three periodontitis phenotypes: Bone loss patterns, antibiotic—surgical treatment and the new classification

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## Abstract

**Aim:** To compare three periodontitis clusters (A, B and C) for alveolar bone loss (ABL) patterns, antibiotic prescriptions and surgeries and to relate them to the new classification of periodontitis.

**Materials and Methods:** ABL patterns, prescription of systemic antibiotics and the number of surgeries were retrieved for all patients ( $n = 353$ ) in the clusters. Comparisons and possible predictors for antibiotics were assessed, and results also evaluated in relation to the new classification.

**Results:** Cluster A is characterized by angular defects often affecting the first molars and localized stage III/IV grade C periodontitis. Cluster B contains mainly localized or generalized stage III/IV, grade C patients. Cluster C contains mainly patients with generalized stage III/IV grade C periodontitis. Patients in cluster A received significantly more antibiotics compared to B and C (78% vs. 23% and 17%); the predictors for antibiotic prescription were young age and localized ABL. No differences in numbers of periodontal surgeries were observed between clusters ( $A = 1.0 \pm 1.4$ ,  $B = 1.3 \pm 1.4$  and  $C = 1.3 \pm 1.5$ ).

**Conclusions:** Within stage III/IV grade C periodontitis, we could detect three clusters of patients. The distinct localized ABL pattern and younger age in cluster A presumably prompted clinicians to prescribe antibiotics.

## KEYWORDS

alveolar bone loss pattern, antibiotics, classification, periodontitis, phenotypes

## 1 | INTRODUCTION

Periodontitis is a multicausal chronic inflammatory disease defined by breakdown of the periodontal soft and hard tissues. Impaired balance between the subgingival microbiome and the immune system, modified by lifestyle, genetic and systemic health factors, leads to the development of the disease (Loos, Papantonopoulos, Jepsen, & Laine, 2015; Loos & Van Dyke, 2020; Lopez, Hujoel, & Belibasakis, 2015).

Periodontal therapy usually begins with non-surgical therapy which consists of mechanical debridement of the microbial biofilm and calculus, combined with oral hygiene instructions leading to significant clinical improvement in most of the patients (Drisko, 2001, 2014). In a second stage, periodontal surgeries may follow to eliminate deep residual pockets aiming to a long-term stability of the treatment outcome (Matuliene et al., 2008).

In some cases, systemic antibiotics are used as adjunctive to non-surgical periodontal therapy. Throughout the years, different

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indications and motivations on prescribing antibiotics in addition to non-surgical periodontal therapy have been presented: (a) diagnosis of aggressive periodontitis (Herrera, Sanz, Jepsen, Needleman, & Roldán, 2002; Sgolastra, Petrucci, Gatto, & Monaco, 2012), (b) presence of deep periodontal pockets and disease severity (Herrera et al., 2002; Mombelli, Cionca, & Almaghouth, 2011; Zandbergen, Slot, Niederman, & Van der Weijden, 2016), (c) bacterial invasion and activity of the disease (Van der Velden, 2017) and (d) specific microbiological profiles of the subgingival plaque (Herrera et al., 2002; van Winkelhoff et al., 1989). Due to the absence of generally accepted guidelines, the decision of prescribing antibiotics with non-surgical therapy is mainly subject to the personal experience of the clinician (Sanz & Teughels, 2008).

In 2017, we reported on the existence of three periodontitis phenotypes (cluster A, cluster B and cluster C) based on intake radiographic (mean number of teeth with different percentages of bone loss and angular defects) and microbiological information (culture, 7 bacteria) from 392 untreated patients (Delatola, Loos, Levin, & Laine, 2017). In addition, we noted that a number of periodontitis patients (10% of the cohort) did not fit in any of the three main clusters. Cluster A comprised mainly of young individuals with a more localized disease pattern and a high prevalence and high proportions of *Aggregatibacter actinomycetemcomitans* (*Aa*). The other two clusters did not differ in microbiological composition, but they presented distinct disease severity and smoking habits. Specifically, cluster C was characterized by the most severe alveolar bone loss (ABL) and the highest percentage of current smokers (Delatola et al., 2017).

In 2018, the new classification of periodontitis was proposed (Papapanou et al., 2018). It is of interest to evaluate the phenotypes as seen in the clusters (Delatola et al., 2017), which emerged by an unsupervised learning technique based on microbiological and radiographic characteristics, in relation to the new classification. Additionally, with these clusters, *unknown* at the time of diagnosis and treatment planning, it is the question whether they have undergone different therapies, especially periodontal surgeries and antibiotic prescriptions. Noteworthy, the patients were treated without knowledge on microbiological results of sampling. We hypothesize that the three clusters contain demographic and clinical characteristics, such as radiographic ABL patterns, which correlate with treatment choices.

Therefore, in the current study, we first aimed to describe ABL patterns per phenotypic cluster; secondly to compare the number of antibiotic prescriptions and the number of surgeries performed between the three periodontitis clusters previously identified and thirdly to relate the clusters with the new classification system.

## 2 | MATERIALS AND METHODS

### 2.1 | Data collection and study population

All consecutive new periodontitis patients who visited the postgraduate clinic at the Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), in the period 1998–2006 were

### Clinical Relevance

*Scientific rationale for the study:* Bone loss patterns and follow-up for three periodontitis clusters (A, B, C) regarding antibiotic prescription and periodontal surgeries, and their correlation with the new periodontitis classification.

*Principal findings:* The majority of patients were classified as stage III/IV, grade C periodontitis. Cluster A presented a distinct localized bone loss pattern and received more frequently prescription of antibiotics. The clusters did not differ for the number of surgeries performed.

*Practical implications:* Within stage III/IV, grade C periodontitis, we can detect clusters, and one of them is associated with higher antibiotic prescription due to younger age and a distinct localized disease pattern.

eligible for the current study. The procedures for the retrospective collection of the demographic, radiographic and microbial data have been described in detail previously (Delatola et al., 2017).

In short, trained and supervised postgraduate students of the Department of Periodontology, ACTA ( $n = 24$ ) performed the periodontal diagnostics and the further required periodontal treatment of the patients. The baseline diagnostic appointment included a clinical evaluation combined with full-mouth periapical radiographs and subgingival microbial sampling. Notably, the clinicians were unaware of the microbial results throughout the whole course of the periodontal therapy. Each patient was treated by the same clinician for all diagnostic and treatment procedures. In general, residual pocket depth (pocket  $\geq 6$  mm) was the criterion to proceed with a periodontal surgery (Matuliene et al., 2008). It should be noted that in the postgraduate periodontal clinic of ACTA, the periodontal surgeries were performed around the indicated teeth, not exceeding one quadrant, and in some cases limited to a sextant. Contrary to the periodontal surgeries, there were no clear guidelines for the antibiotic prescription; the latter was subject to the clinical decision of the individual postgraduate student after consultation with one of the teachers.

As previously described, anonymized baseline full-mouth radiographs of the study cohort were evaluated retrospectively by 21 dentist and periodontitis of the Department of Periodontology, ACTA, with the aid of a modified version of the Schei ruler (Delatola et al., 2017). Angular defects were assessed as described before (Rams, Listgarten, & Slots, 2018).

Patients with incomplete demographic, radiographic or microbial data were excluded from the analysis. After screening 800 newly referred periodontitis patients, the final cohort with complete radiographic and microbial information for subsequent analysis consisted of 392 individuals. The unsupervised clustering revealed three clusters: cluster A ( $n = 18$  [5%]), cluster B ( $n = 200$  [51%]) and cluster C ( $n = 135$  [34%]). (Figure S1; Delatola

et al., 2017). The patients who did not cluster ( $n = 39$ , 10%) were not included in the current study.

The demographic, radiographic, microbial and treatment (periodontal surgeries, adjunctive antibiotics) information of the patients was entered into a secured database and was fully anonymized. The study was conducted according to the principles of the Declaration of Helsinki, and the local ethics committee approved the protocol of this study. The paper adhered to the STROBE guidelines.

## 2.2 | Data analyses

The comparison of the ABL patterns between the three clusters was performed with Principal Coordinate Analysis (PCoA) with one-way PERMANOVA and Bonferroni correction. For the analysis of the ABL and angular defects around the first molars, we used a Mann-Whitney test.

The three phenotypic clusters were analysed for the antibiotic prescription (yes/no), and the periodontal surgeries performed (yes/no, mean number) with Pearson's chi-square and one-way ANOVA tests. Also, the total antibiotic and the non-antibiotic groups were compared for the mean number of periodontal surgeries with independent samples  $t$  test. The clusters were compared for the new classification with Pearson's chi-square. Within cluster B, the patients who were classified as grade B were compared to those who were assigned to grade C for the antibiotic prescription with Pearson's chi-square, and for the mean number of periodontal surgeries, we used again independent samples  $t$  test.

For the definition of the predictors of the antibiotic prescription, the demographic and radiographic information available to the clinician was entered into the Principal Component Analysis (PCA). The patients were subsequently grouped and labelled based on the use of antibiotics (yes or no) during non-surgical periodontal therapy and analysed for differences between the two groups with one-way PERMANOVA and Bonferroni correction. The most discriminative variables for the antibiotic and the non-antibiotic groups emerging from the PCA (loading  $\geq 0.3$ ) were selected for further analysis ( $t$  test analysis).

$p$ -values  $< .05$  were considered statistically significant. The PCoA and the PCA were implemented with PAST software (v.3.14, Oslo, Norway). The other statistical analyses were conducted with the SPSS statistical software package (IBM, v.21).

## 3 | RESULTS

### 3.1 | Study population

The mean follow-up time of the patients was 11,70 months ( $\pm 8,01$  months). The demographic information revealed differences between the three clusters for: age, smoking and medical history (Delatola et al., 2017). Specifically, cluster A was dominated

by the youngest and systemically healthiest patients ( $p = .013$ ). Cluster C presented the highest percentage of current smokers ( $p = .0001$ ). Furthermore, cluster A had significantly more teeth present and significantly more teeth without ABL ( $p < .0001$ ) while cluster C presented the most severe periodontal destruction ( $p < .0001$ ). Regarding the microbiological characteristics, such for *Aa* and *Porphyromonas gingivalis* (*Pg*), cluster A presented the highest prevalence and percentage of *Aa* ( $p < .0001$ ), and the lowest prevalence and percentage of *Pg* ( $p = .0018$  and  $p = .0003$ , respectively).

### 3.2 | Alveolar bone loss (ABL) patterns

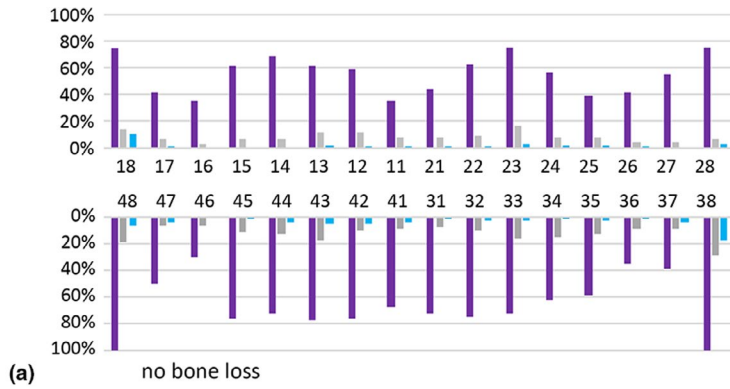
The patterns of ABL in the patients of the three clusters are presented in the Figures 1a,b and 2c,d. Figure 1a shows the percentage of teeth without ABL. The domination of the cluster A can be clearly distinguished; this group is followed by the cluster B and finally, the cluster C ( $p < .001$ ). Figure 1b illustrates the proportion of teeth with  $\leq 30\%$  ABL. Cluster B is presented with the highest percentages and a generalized pattern affecting the full dentition ( $p < .001$ ).

The distribution of the teeth with  $>50\%$  ABL is demonstrated in the Figure 2c, where cluster C presents the highest percentages ( $p < .001$ ). Interestingly, cluster A tends to approximate cluster C for the 1st molars. The Mann-Whitney analysis between the clusters A and C for the 1st molars indicated that there is not a statistically significant difference between the two groups. A similar phenomenon can be observed for the angular bony defects (Figure 2d): a statistically significant difference between the clusters exist in the dentition ( $p < .001$ ); however, for the 1st molars, the clusters A and C do not differ significantly.

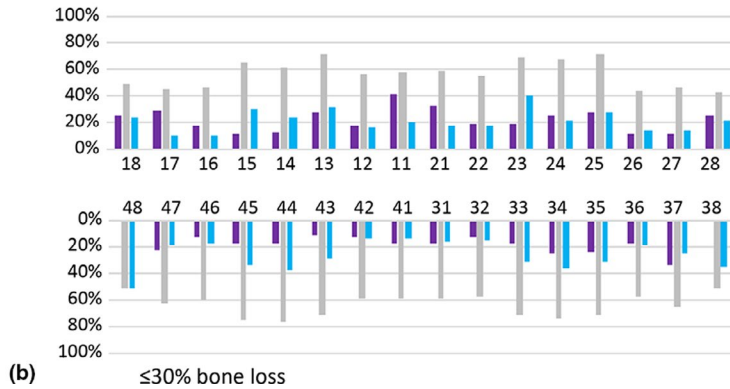
### 3.3 | Clusters in relation to the periodontitis classification system

Based on the ABL patterns, in relation to the periodontitis classification system (Papapanou et al., 2018), all patients included in this study were classified as stage III/IV. The majority of the cohort (95%) had stage III/IV grade C periodontitis: all patients in clusters A and C had grade C, while a minority of patients in cluster B had grade B ( $n = 18$ ; 9%), and the majority grade C periodontitis ( $n = 182$ ; 91%). A statistically significant difference was observed in the overall comparison between clusters for the grading ( $p = .001$ ); the pairwise comparisons revealed that the significance emerged between the clusters B and C ( $p < .001$ ). Further distinction between the clusters was on basis of the extent; cluster A being more localized ( $n = 13$ , 72%) and cluster C being more generalized ( $n = 133$ , 98%;  $p < .001$ ). Cluster A presented the tendency of molar/incisor pattern (11 out of 18 patients); however, in strict application of the current classification, 4 out of 18 patients were classified as molar/incisor stage III/IV.

Cluster A  
Cluster B  
Cluster C

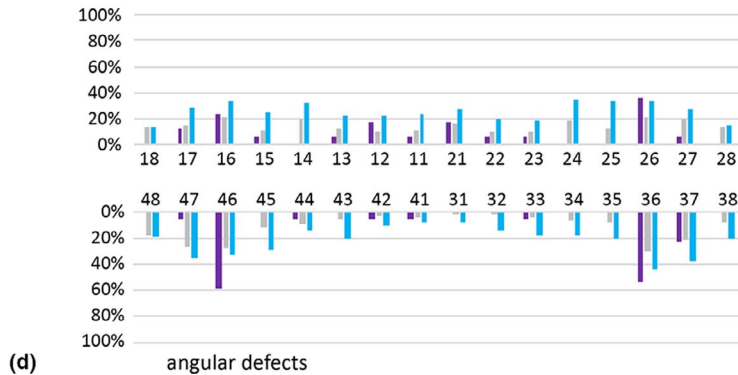
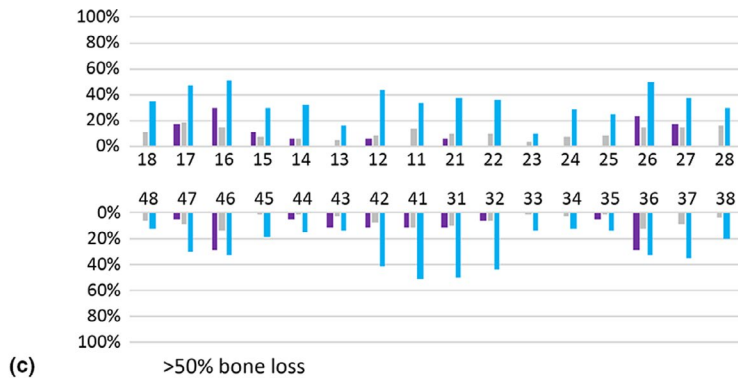


**FIGURE 1** Alveolar bone loss (ABL) patterns for the three clusters. The vertical axis represents the percentage of the teeth affected, per cluster and per tooth type. Panel a shows the percentage of teeth without ABL, panel b shows the percentage of teeth with  $\leq 30\%$  ABL



**FIGURE 2** Alveolar bone loss (ABL) patterns for the three clusters. The vertical axis represents the percentage of the teeth affected, per cluster and per tooth type. Panel c shows the percentage of teeth with  $>50\%$  ABL, panel d shows the percentage of teeth with angular defects

Cluster A  
Cluster B  
Cluster C



### 3.4 | Antibiotic prescription

In the three clusters, 83 patients (23%) received systemic antibiotics in addition to non-surgical periodontal therapy. The majority of these patients ( $n = 69, 83\%$ ) received a prescription for antibiotics

during the scaling and root planing appointments, mainly at the last appointment (74%). For a small proportion ( $n = 14, 17\%$ ), the antibiotics were prescribed at the re-evaluation appointment. For 54 patients, the combination of amoxicillin (375 mg) and metronidazole (250 mg) three times a day was prescribed for seven days; eight patients received metronidazole alone, two patients amoxicillin and

two patients the combination of cefuroxime axetil with metronidazole. For 17 patients, the information on the type of antibiotics was not present in the records. The use of a single antibiotic rather than a combination was chosen in cases of a reported allergy.

The antibiotic prescription per cluster is presented in the Table 1. A statistically significant difference was observed: 78% of the individuals in the cluster A received the prescription as opposed to 23% and 17% in the clusters B and C, respectively ( $p < .001$ ).

In total 83 (23%) patients with stage III/IV periodontitis received antibiotics, for those classified as grade C, this amounted to 25%. When we compared patients classified as localized grade C stage III/IV periodontitis to patients with generalized grade C stage III/IV periodontitis for the antibiotic prescription, no significant differences could be observed (localized stage III/IV grade C:  $n = 32$ , 29% vs. generalized stage III/IV grade C:  $n = 51$ , 23%;  $p = .230$ ). Within cluster B, we compared patients who were assigned to grade B ( $n = 18$ ) to those who were assigned to grade C category ( $n = 182$ ) for the antibiotic prescription. None of the patients in grade B category received antibiotics, contrary to 46 patients (25%) in the grade C category who received antibiotics, leading to a statistically significant difference between these groups ( $p = .015$ ).

We aimed to analyse possible predictive factors associated with the antibiotic prescription. A PCA was conducted using as grouping factor the prescription or not of antibiotics. The available information at intake was entered in the analysis, specifically demographic (age, sex and smoking status) and radiographic information (number of teeth present, number of teeth without bone loss, with mild, moderate and severe bone loss and number of teeth with angular defects). Two groups could be observed in the PCA, although some overlap was detected ( $F = 15.37$ ,  $p = .0001$ ; Figure 3). Component 1 and 2 explained 30% and 20% of the variance, respectively. The most discriminative variables for the antibiotic and the non-antibiotic groups emerging from the PCA (loading  $\geq 0.3$ ) were selected for further analysis. The antibiotic group was characterized by significantly younger individuals and a localized pattern of the disease (Table 2).

### 3.5 | Periodontal surgeries

No significant differences in the frequencies or the number of periodontal surgeries between the three clusters were detected (Table 1).

**TABLE 1** Antibiotic prescription and periodontal surgeries performed in the periodontitis clusters A, B and C ( $n = 353$ )

Treatment	Cluster A ( $n = 18$ )	Cluster B ( $n = 200$ )	Cluster C ( $n = 135$ )	<i>p</i> -value
Periodontal surgeries				
Received $\geq 1$ surgery	8 (44%)	112 (56%)	70 (52%)	.541
Mean $\pm$ SD (median)	$1.0 \pm 1.4$ (0.0)	$1.3 \pm 1.4$ (1.0)	$1.3 \pm 1.5$ (1.0)	.644
Antibiotics <sup>†</sup>	14 (78%) <sup>A†</sup>	46 (23%) <sup>a</sup>	23 (17%) <sup>a</sup>	<.0001

Note: Values represent mean numbers  $\pm$  standard deviations (medians) or numbers (%) of subjects.

<sup>†</sup>Antibiotic prescription with non-surgical periodontal therapy.

<sup>‡</sup>Capital letter as opposed to lowercase letter denotes statistically significant difference ( $p < .05$ ) between these clusters.

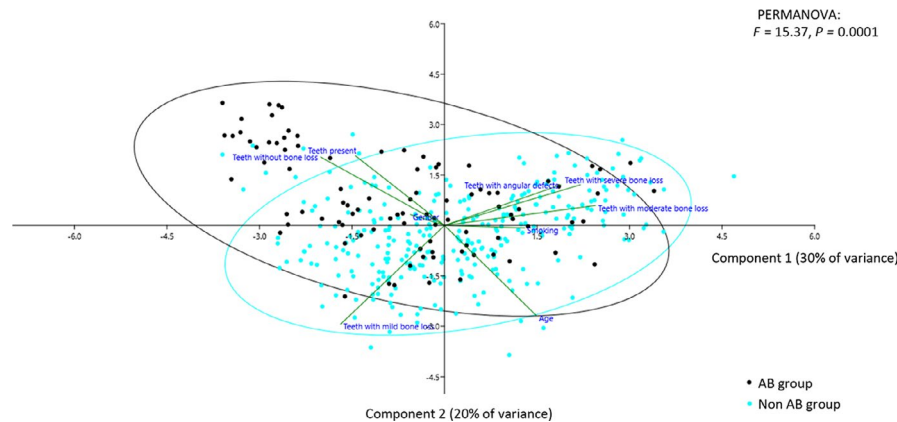
Similarly, no significant differences were observed for the mean number of periodontal surgeries performed between the different grades (grade B =  $1.78 \pm 1.51$  vs. grade C =  $1.29 \pm 1.42$ ;  $p = .170$ ) and the different extents of the classification (localized stage III/IV grade C:  $1.35 \pm 0.13$  vs. generalized stage III/IV grade C:  $1.51 \pm 0.10$ ;  $p = .662$ ).

Lastly, we evaluated the mean number of surgeries performed in relation to antibiotic prescriptions irrespective of cluster or classification assignment. No significant difference for the mean number of surgeries could be detected between the patients who received ( $n = 83$ ) or not ( $n = 270$ ) antibiotics ( $1.24 \pm 1.47$  and  $1.32 \pm 1.46$ , respectively,  $p = .673$ ).

## 4 | DISCUSSION

In the current retrospective study, we evaluated the different ABL patterns that can be encountered in periodontitis patients by analysing the three previously described periodontitis clusters A, B and C (Delatola et al., 2017); more specifically, we focused on the distribution of the ABL for the different teeth of the dentition. Cluster A was associated with localized ABL frequently affecting the first molars with  $>50\%$  bone loss and angular defects. Cluster B presented the highest percentages of teeth with  $\leq 30\%$  ABL and a disease with a generalized pattern affecting the full dentition. Cluster C presented the highest percentages of teeth with  $>50\%$  bone loss and angular defects, in a generalized pattern contrary to the cluster A. Subsequently, we followed the treatment course in respect to the periodontal surgeries performed and the antibiotic prescription in the three clusters; notably, the clinicians were unaware of the clustering and the microbiological information. The cluster A received significantly more often an antibiotic prescription; retrospectively, this group presented the highest prevalence and percentages of Aa. In our analysis, it appeared that age and ABL pattern at intake were predictors for antibiotic prescription. The localized ABL pattern and younger age in cluster A presumably prompted clinicians to prescribe antibiotics. Interestingly, the three clusters did not differ for the periodontal surgeries performed.

The vast majority of the study population was classified as stage III/IV grade C periodontitis; only 5% was classified as stage III/IV, grade B. Among all these stage III/IV patients, we were able



**FIGURE 3** Principal Component Analysis using as grouping factor the use of antibiotics; the available demographic and radiographic information was entered in the analysis. With some overlap, the antibiotic and the non-antibiotic groups could be observed ( $F = 15.37$ ,  $p = .0001$ ). Component 1 and 2 explained 30% and 20% of the variance, respectively. The most discriminative variables were age, number of teeth present, number of teeth without alveolar bone loss, number of teeth with mild/moderate/severe percentage of alveolar bone loss and number of teeth with angular defects. All these parameters contributed with a loading  $\geq 0.3$ , and this is visualized by the green lines which express the direction and the weight of the contribution of these variables in the PCA

**TABLE 2** Demographic and radiographic information of the total cohort, the antibiotic group and the non-antibiotic group

	Total ( $n = 353$ )	Antibiotic group <sup>†</sup> ( $n = 83$ )	Non-antibiotic group ( $n = 270$ )	$p$ -values antibiotic versus non-antibiotic group
Age	$42.4 \pm 11.2$ (43.0)	$33.9 \pm 12.2$ (33.0)	$45.0 \pm 9.5$ (45.0)	<b>&lt;.0001</b>
Teeth present	$27.1 \pm 3.1$ (28.0)	$28.6 \pm 3.1$ (29.0)	$26.7 \pm 2.9$ (27.0)	<b>&lt;.0001</b>
Teeth no bone loss	$2.5 \pm 4.9$ (0.0)	$4.6 \pm 7.4$ (1.0)	$1.8 \pm 3.5$ (0.0)	<b>.0012</b>
Teeth bone loss $\leq 30\%$	$11.7 \pm 6.7$ (12.0)	$11.7 \pm 6.4$ (12.0)	$11.7 \pm 6.8$ (12.0)	.451
Teeth bone loss $>30\%$ to $\leq 50\%$	$7.5 \pm 4.9$ (7.0)	$6.9 \pm 4.8$ (7.0)	$7.7 \pm 5.0$ (7.0)	.141
Teeth bone loss $>50\%$	$4.4 \pm 4.3$ (3.0)	$4.0 \pm 4.0$ (3.0)	$4.6 \pm 4.4$ (4.0)	.185
Teeth with angular defects	$4.4 \pm 2.9$ (4.0)	$4.6 \pm 2.7$ (4.0)	$4.4 \pm 3.0$ (4.0)	.632

Note: Values represent mean  $\pm$  standard deviation (median).

The most discriminative variables ( $\geq 0.3$  loading) according to the Principal Component Analysis were selected for further analysis.

<sup>†</sup>Antibiotic prescription with non-surgical periodontal therapy.

to detect the three clusters as distinct phenotypes. Cluster A was mainly characterized as localized periodontitis stage III/IV grade C, cluster C as generalized periodontitis stage III/IV grade C and cluster B as both generalized and localized periodontitis stage III/IV grade C.

Due to the need and difficulty for a collective evaluation of the criteria by an experienced clinician in order to correctly differentiate between stage III and stage IV according to the new classification (Kornman & Papapanou, 2020), we had to combine the two stages of the disease as it was also performed recently in another epidemiologic study (Bongo, Brustad, Oscarson, & Jönsson, 2020). The patients of the current study are patients referred for the initial periodontal diagnosis by general dentists. Based on the current findings, we could conclude that in a specialized periodontal practice, the majority of referred patients belong to the stage III/IV, grade C category. Interestingly, within this combined stage III/IV, we identified three phenotypes of periodontitis patients that differ in

demographic, radiographic and microbiological characteristics. One of these phenotypes (cluster A) was possibly also detected by the clinicians in this study (younger age and distinct localized ABL pattern), and they prescribed more frequently antibiotics.

Each subject may present a specific immune fitness which is influenced by (epi)genetic factors, lifestyle factors, co-morbidities, local or dental factors and the biofilm (Loos & Van Dyke, 2020). If the immune fitness is dysregulated, the resultant aberrant host response leads to a destructive periodontal inflammation that further induces a microbial dysbiosis and the latter heightens back the aberrant response in a vicious cycle (Loos & Van Dyke, 2020). The younger age and the absence of smoking in the cluster A leads to the hypothesis that the major parameter playing a role in the dysregulated immune fitness for these patients could be the presence of specific (epi)genetic factors (Shaddox et al., 2017) which provide a favourable ecosystem for certain pathobionts (such as *Aa*) into the dysbiotic biofilm (Nibali, 2015); the phenotypic result of this process is the localized

pattern of bone loss (Nibali, Tomlins, & Akcali, 2018) which presumably was identified by the clinicians in this study.

Systemic antibiotics are being used to support periodontal therapy showing additional clinical benefits in some cases (Feres, Figueiredo, Soares, & Faveri, 2015). Nevertheless, nowadays, there is increasing global attention on the antibiotic exposure of the population due to development of resistance (Quirynen, Teughels, & Steenberghe, 2003; Rams, Degener, & van Winkelhoff, 2014; Serrano et al., 2009). In the current paper, a relatively high percentage of the stage III/IV periodontitis patients received antibiotics (23% of all patients), and this was especially associated with a younger group of patients with localized ABL pattern (cluster A, 78%). However, the use of antibiotics was not associated with a reduced number of periodontal surgeries. It should be recognized that this is a retrospective study and that this study was by no means a designed randomized trial. Especially, more studies with full-mouth clinical data and long-term follow-up should be performed in the future in order to evaluate the ultimate clinical significance of the antibiotic prescription in the treatment of young patients with localized periodontitis, often presenting with a molar/incisor pattern of bone loss.

The strength of the current study originates from the relatively large sample size. Importantly, the available microbial and clustering information has been concealed from the clinicians throughout the whole course of the treatment; this allowed the retrospective evaluation of the independent clinical decisions in relation to the available information. Lastly, although several recommendations have been presented in the literature for the use of antibiotics, to our knowledge, this is the first study in a broad cohort of patients in an academic clinical setting that analysed retrospectively potential predictors affecting the clinical decision on antibiotic prescription.

The present study is not devoid of limitations. Firstly, full-mouth clinical data were not available. Thus, this information could not be evaluated in respect to the decision of the clinicians to prescribe antibiotics. Additionally, the clusters could not be compared on clinical periodontal parameters before and after treatment; however, they were compared for the number of periodontal surgeries performed. The latter represents a clinically important endpoint since it affects patient comfort and the perception of the non-surgical periodontal therapy efficacy. Furthermore, a drawback would be that different clinicians were responsible for the decision and the execution of the periodontal surgeries; however, in general, a periodontal surgery was indicated on basis of the residual pocket depth (pocket  $\geq 6$  mm) after non-surgical therapy (Matuliene et al., 2008). Another issue for cautious interpretation of the results might be the radiographic bone scoring, and this was performed by several dentists and periodontists of the Department of Periodontology, ACTA without inter-individual calibration. However, examiners used a modified version of the Schei ruler for bone scoring and received detailed oral and written instructions (Delatola et al., 2017). Lastly, there are 3 issues on the external validity of the results; (a) results may not easily apply to other countries or clinics, since the study includes patients from the greater Amsterdam area, referred

to a university periodontal clinic exclusively for periodontal diagnosis and treatment; (b) 10% ( $n = 39$ ) of the study population could not be clustered and was left out of the current analyses and (c) the antibiotic prescription was subject to the clinical decision of the individual postgraduate student after consultation with one of the teachers and this prescription behaviour may differ in various clinics and places globally. Therefore, the current findings should be validated in other cohorts.

In conclusion, the majority of the patients in a specialized periodontal clinic were classified as stage III/IV grade C periodontitis, and within this group, we could detect different clusters: the three periodontitis phenotypes by Delatola et al. (2017). One of the groups (cluster A) presented a distinct localized ABL pattern, which in combination with the younger age of these individuals was associated with more frequent antibiotic prescription.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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