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Is progression of periodontitis relevantly influenced by systemic antibiotics? A clinical randomized trial

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Abstract

Aim: We investigated the long-term impact of adjunctive systemic antibiotics on periodontal disease progression. Periodontal therapy is frequently supplemented by systemic antibiotics, although its impact on the course of disease is still unclear.

Material & Methods: This prospective, randomized, double-blind, placebo-controlled multi-centre trial comprising patients suffering from moderate to severe periodontitis evaluated the impact of rational adjunctive use of systemic amoxicillin 500 mg plus metronidazole 400 mg (3x/day, 7 days) on attachment loss. The primary outcome was the percentage of sites showing further attachment loss (PSAL) ≥1.3 mm after the 27.5 months observation period. Standardized therapy comprised mechanical debridement in conjunction with antibiotics or placebo administration, and maintenance therapy at 3 months intervals.

Results: From 506 participating patients, 406 were included in the intention to treat analysis. Median PSAL observed in placebo group was 7.8% compared to 5.3% in antibiotics group (Q25 4.7%/Q75 14.1%; Q25 3.1%/Q75 9.9%; $p < 0.001$ respectively).

Conclusions: Both treatments were effective in preventing disease progression. Compared to placebo, the prescription of empiric adjunctive systemic antibiotics showed a small absolute, although statistically significant, additional reduction in further attachment loss. Therapists should consider the patient's overall risk for periodontal disease when deciding for or against adjunctive antibiotics prescription.

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Key words: amoxicillin/metronidazole; attachment loss; clinical relevance; debridement; outcome parameter; periodontitis; randomised controlled trial; systemic antibiotics

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Periodontitis is an inflammatory disease caused by a microbial biofilm (Socransky et al. 1998, Paster et al. 2001, Darveau 2010), characterized by periodontal pocket formation, attachment loss and loss of supporting alveolar bone. Periodontally compromised teeth lose function and may have to be extracted, which often requires costly

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prosthetic rehabilitations. In industrialized countries, approximately 50% of the adult population suffers from moderate or severe periodontits (Holtfreter et al. 2010, Eke et al. 2012). Basic periodontal therapy usually comprises mechanical debridement of the teeth, that is the disruption of biofilm, followed by lifelong maintenance therapy (AAP 2000).

Mechanical debridement in patients with moderate to severe periodontitis can be supplemented with systemic antibiotics, such as amoxicillin and metronidazole. The rationale for the adjunctive use of antibiotics is to exert an antimicrobial effect at sites inaccessible to mechanical therapy, and possibly to suppress periodontal pathogens (Pavicić et al. 1994, Flemmig et al. 1998). However, the uncritical use of antibiotics could increase bacterial resistances (Spellberg et al. 2008). Therefore, a critical appraisal of routine prescription and its clinical relevance is mandatory (Man-Son-Hing et al. 2002). Systematic reviews state that prescription of adjunctive systemic antibiotics improved clinical conditions, but due to data inhomogeneity, final recommendations for its routine use are difficult. Methodological weaknesses and the heterogeneous design of existing studies such as small sample size, patients with severe disease only and weak endpoints for determination of disease progression were criticized (Herrera et al. 2002, Haffajee et al. 2003). Most trials substantiated the relevance of the superior outcomes of adjunctive antibiotic therapy in periodontal treatment on the basis of statistical significance, nevertheless it remains questionable if these differences are clinically relevant. Therefore, there is a need for trials on larger patient samples with sufficient observation periods and clinically relevant endpoints.

This large multi-centre trial aimed at determining the efficacy of systemic antibiotics on periodontal disease progression. Our hypothesis was that empiric systemic adjunctive antibiotics reduce the proportion of sites exhibiting further disease progression.

Patients and Methods

Study design

The study was a prospective, randomized, stratified, double-blind, multicentre (eight university hospital centres) trial with parallel-group design (Harks et al. 2014). Patients with untreated moderate to severe chronic and aggressive periodontitis were included (for inclusion/exclusion criteria see Table 1). The institutional review boards of the participating centres approved the protocol and all patients provided written informed consent. An independent data and safety monitoring board reviewed the safety data throughout the trial. The trial was registered (Current Controlled Trials: ISRCTN64254080; Clinical Trials.gov Identifier NCT00707369).

Per patient, 12 visits over 27.5 months were scheduled (Fig. 1a). The sponsor's safety desk was responsible for serious adverse events (SAE) management and fulfilled safety reporting obligations. Participants were divided into four strata according to the extent of periodontal disease [localized: <38%; generalized: ≥38% of teeth with pocket probing depths (PPD) ≥6 mm] and smoking habit [non-/light smoker: <7 ppm CO in exhaled air; moderate to heavy smoker: ≥7 ppm (Bedfont-Smokerlyzer®, Bedfont, UK)]. The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Randomization

Quad-block randomization lists were computer generated for each stratum per centre by a statistician otherwise not being involved in trial affairs. Randomization lists for participating centres were stored exclusively at the study centre. To allocate a patient into a treatment group, the central study nurse was informed about the

Table 1. Inclusion, exclusion and withdrawal criteria

Inclusion criteria	Exclusion criteria	Withdrawal criteria
• CPITN of IV in at least one sextant • Age range from 18 to 75 years • Clinical and radiographic signs of moderate (clinical attachment loss of 3–4 mm) to severe (clinical attachment loss 5 mm or more) chronic or aggressive periodontitis • At least 10 natural teeth in situ • Pocket probing depths (PPDs) of ≥6 mm at a minimum of four teeth • Willingness to participate and to be available at any time as required for participation • Willingness to abstain from using antimicrobial mouth-rinse during the study except for those explicitly prescribed • Informed consent signed by the patient • Sufficient knowledge of the German language	• Confirmed or assumed allergies or hypersensitive skin reactions to amoxicillin and/or metronidazole • show confirmed lactose intolerance (parents or siblings) • Down Syndrome • Suffer from AIDS/HIV • Take systematic medication affecting the periodontal conditions, e.g. phenytoine, nifedipine, and/or steroid drugs • Professional periodontal therapy during the past 6 months prior to baseline • Require an antibiotic coverage for dental treatments • Undergoing or require an extensive dental or orthodontic treatment • Pregnant or breastfeeding • Rampant caries • Oral or extra oral piercing in or around the oral cavity with ornaments or accessory jewellery • Dental students or dental professionals • Participated in a clinical dental trial during the 6 months preceding the study • Cognitive deficits	• Admitted offending against or are no longer willing to follow the protocol • Do not keep the appointments • Have serious adverse reactions related to the medications prescribed in the trial (i.e. allergic reactions to the prescribed antibiotics)

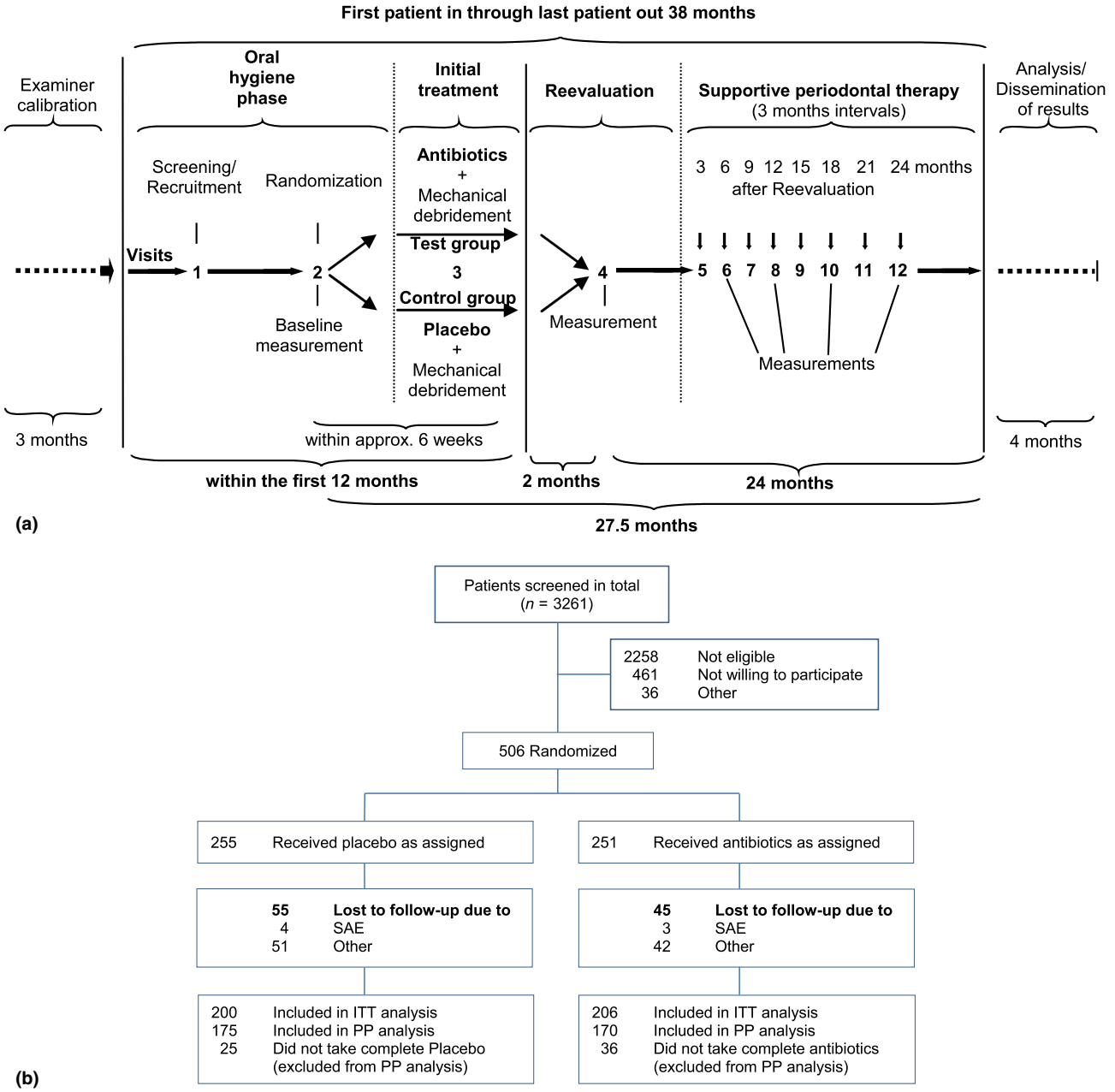

Fig. 1. Study design and flow. (a) The timeline for the trial is illustrated. After screening (visit1), baseline measurements and subsequent randomization was performed (visit 2). After dental biofilms were disrupted during initial treatment (mechanical debridement), blinded amoxicillin/metronidazole or placebo was dispensed (visit 3). Re-evaluation (visit 4) was performed 3.5 months after visit 2. Maintenance therapy (mechanical debridement) was carried out at 3 months intervals (visits 5 through 12). Measurements were also conducted 9.5, 15.5, 21.5 and 27.5 months after visit 2 (visits 6, 8, 10 and 12). (b) Sequence of screening, randomization, drop outs, serious adverse events and follow-up of participants are illustrated. From 506 randomized patients, 93 dropped out over the 27.5 months study period. Overall, 406 patients were included in the intention to treat analyses, but, due to incomplete medication intake, only 345 patients were included into the per-protocol analysis.

patients' disease extent and CO level in exhaled air by a phone call. Due to this information, patients were assigned to one of the four strata and thereafter allocated into one treatment group according to the stratum's randomized list. Every position on the randomization list corresponded to a medication package number corresponding to a prepacked medication box. The central study nurse informed the respective centre about the corresponding medication box. Labelled trial medication was stored at the participating centres.

Periodontal therapy and intervention

Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days (visit 3, Fig. 1a). All mechanical therapy was performed

with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the antibiotics group patients received two empiric antibiotics [amoxicillin $3H_2O$ 574 mg (Amoxicillin-ratiopharm 500 mg®, Ratiopharm, Germany); metronidazole 400 mg (Flagyl® 400, Sanofi-Aventis, Germany)] and placebo group patients two placebo drugs, each to be taken three times a day for 7 days. Medication was repacked in neutral capsules with identical appearance by the university pharmacy in Dresden, Germany. Each patient received two medication packages with consecutive numbers according to the randomization list. The patients kept a medication diary to document drug adherence. Patients were informed about the medications' side effects according to the package inserts of amoxicillin and metronidazole.

Re-evaluation (visit 4) was performed 3.5 months after baseline. Thereafter, all patients received maintenance therapy, including full-mouth supra- and subgingival debridement and oral hygiene instruction at 3 months intervals (visits 5 through 12, Fig. 1a). Sites with PPD ≥4 mm also received subgingival re-debridement. All treatments were performed by blinded qualified dentists or dental hygienists.

Examinations and endpoints

Full-mouth periodontal measurements were carried out at six sites of each tooth by blinded examiners not involved in periodontal therapy. Examiners were calibrated for relative attachments level (RAL) measurements 3 months before examining participants and annually thereafter (Harks et al. 2014). RAL measurements, corresponding to the distance from occlusal surface to the bottom of the periodontal pocket, were performed in duplicate with an electronic pressure-sensitive probe (Florida Disk probe, Gainesville, FL, USA) in increments of 0.2 mm. The difference between baseline and follow-up RAL readings described the changes of the clinical attachment level (gain or loss of tooth supporting tissue).

The primary outcome was the proportion of sites per patient with new clinical attachment loss (PSAL) ≥1.3 mm between baseline and the 27.5 months visit. The ≥1.3 mm threshold was considered clinically relevant, because conversely, 1.3 mm gain in clinical attachment after periodontal therapy is considered a relevant outcome, too (Cobb 1996). Attachment loss was used as outcome variable instead of attachment gain, because it is associated with tooth loss, which constitutes a true endpoint (Hujoel et al. 1999). Therefore, the presence of attachment loss is tantamount to disease progression. The following secondary endpoints were assessed exploratorily (Florida standard probe, Gainesville, FL, USA): PPD, clinical attachment, gingival bleeding on probing (Lang et al. 1990) and supragingival plaque (O'Leary et al. 1972). All measurements were performed at "baseline" (visit 2), after 3.5 months (re-evaluation, visit 4), and at 9.5, 15.5, 21.5 and 27.5 months "follow-ups" (visits 6, 8, 10 and 12; Fig. 1a).

The medical history and the body mass index were assessed at visit 1, and non-fasting blood samples were drawn to determine the HbA1c levels (visits 1, 8 and 12). As an indicator of subjective oral health perception, the German version of the Oral Health Impact Profile (OHIP-G 49) was recorded at visits 1, 8 and 12 (John et al. 2002).

Statistics

Former study results were used for sample size estimation and we expected the percentage of sites per patient showing new attachment loss during the trial period of at least 15% in the placebo and 7% in the antibiotics group (Berglundh et al. 1998, Tinoco et al. 1998, Ehmke et al. 2005, Guerrero et al. 2005). The confirmatory objective was to detect a clinically relevant difference of 15% (placebo group) and 7% (antibiotics group) in PSAL with standard deviation (SD) = 25%, type-I error rate $\alpha = 0.05$ and power $1-\beta = 0.8$. In total, 175 evaluable patients per group were required. The hypothesis was that oral administration of systemic adjunctive antibiotics will reduce the proportion of sites exhibiting PSAL ≥1.3 mm from 15% to 7%.

Due to the assumption of a non-normally distributed primary endpoint (PSAL), the two-sided stratified Wilcoxon test (van Elteren test) was applied and a p-value ≤0.05 was regarded as statistically significant (van Elteren 1960). Secondary endpoints were analysed at each visit using van Elteren tests, that is the percentage of sites showing PPD ≥5 mm or attachment gain, mean PPD, mean attachment level, bleeding on probing and supragingival plaque index. The resulting p-values were intended to be exploratory instead of confirmatory, and represent a metric of evidence against the respective null hypothesis of no effect. No adjustment for multiple testing was performed and p-values ≤0.05 were considered as statistically noticeable.

Standard descriptive analyses were performed. Variables regarded as normally distributed were presented as mean ± SD; non-normally distributed variables were described by median (25% quantile Q25/75% quantile Q75). Categorical variables were reported as absolute and relative frequencies compared with Fisher's exact tests. Mean periodontal measures were computed as percentages of sites per person and then averaged across all participants within each treatment group.

In addition, PPD values on site level were analysed according to their baseline probing depth category (≤3.4 mm, 3.5–6.4 mm, ≥6.5 mm) and the proportion of patients showing PPD ≥5 mm at ≤4 sites was calculated. Cohen's D was calculated to assess the effect size in mean differences between the treatment groups for changes in the OHIP scores.

All efficacy analyses were based on the intention to treat principle, comparing groups according to the randomly assigned treatment and strata. Primary and secondary endpoints were evaluated in the per-protocol collective at each visit. A sensitivity analysis was performed with PSAL ≥2 mm.

Statistical analyses were performed using Version 9.3 of the SAS System for Windows software (SAS Institute Inc., 100 SAS Campus DriveCary, NC, USA).

Results

Patient enrolment

Patient recruitment started in July 2008 and finished in October 2009. Overall 3261 patients were screened,

1003 met the inclusion criteria, 461 declined to participate, 36 dropped out before randomization and 506 were randomized (Fig. 1b). All follow-up examinations were finished by December 2011. The study database was closed in March 2012.

Of 506 randomized patients, 406 (intention to treat collective, ITT; placebo: $n = 200$, antibiotics $n = 206$) finished the therapy regime by visit 12 (drop out $n = 100$; 19.8%). All patients who followed the study timeline according to the protocol and took all tablets within 6 through 8 days according to their medication diaries were included in the per-protocol collective (PP, 345 patients, placebo: $n = 175$, antibiotics: $n = 170$). For baseline demographic and clinical characteristics see Tables 2 and 3, respectively. Due to the clinical and demographic characteristics, the patients were rather a sample of chronic periodontitis.

Primary outcome

In the ITT-collective, the median PSAL ≥1.3 mm over the 27.5 months period was 7.8% (Q25 4.7%/Q75 14.1%) in the placebo *versus* 5.3% (Q25 3.1%/Q75 9.9%) in the antibiotics group. The difference between the patient groups was significant ($p < 0.001$, Fig. 2a, Table 4). For results of the PP-collective see Table 4.

Secondary outcomes

The median PSAL ≥1.3 mm over the 27.5 months trial period according to the baseline probing depth categories (≤3.4 mm, 3.5–6.4 mm, ≥6.5 mm) are shown in Table 4. For results of the PP-collective see also Table 4. Results of PSAL after applying a threshold of ≥2 mm are shown in Table 5.

At baseline (ITT-collective), the median proportion of sites displaying PPD of ≥5 mm (Fig. 2b) was 15.7% (Q25 10.4%/Q75 27.8%) for the placebo and 17.5% (Q25 10.3%/Q75 27.8%) for the antibiotics group ($p = 0.66$). At 27.5 month, % PPD of ≥5 mm had decreased to 5.5% (Q25 1.7%/Q75 12.6%) in the placebo and to 2.1% (Q25 0.6%/Q75 5.8%) in the antibiotics group ($p < 0.001$).

The median proportion (ITT-collective) of sites with attachment gain ≥1.3 mm over the 27.5 months period was 12.2% (Q25 7.1%/Q75 23.0%) for the placebo and 19.4% (Q25 10.4%/Q75 32.7%) for the antibiotics group ($p < 0.001$). Clinical attachment level overall improved over the study period: mean attachment gain was 0.4 ± 0.7 mm for the placebo and 0.6 ± 0.7 mm for the antibiotics group ($p < 0.001$). In both groups, this gain was considerably more pronounced at sites with initially advanced probing depths of ≥6.5 mm (placebo 2.1 ± 1.7 mm *versus* antibiotics 2.8 ± 1.5 mm; $p < 0.001$).

In summary, other secondary parameters, for example proportions of PPD and absolute PPD and bleeding on probing improved over the 27.5 months observation period, whereas the plaque index scores improved initially, but returned to baseline levels later (Table 3).

The proportion of patients showing PPD ≥5 mm at ≤4 sites are shown in Table 6 and the corresponding PSAL values are presented in Table 7.

Serious adverse events (ITT-collective)

Overall, 90 SAE, 39 in the placebo and 43 in the antibiotic group were reported over the course of the study. Eight SAE occurred prior to medication intake. Seven patients dropped out due to un-blinding following an SAE occurrence (Fig. 1b). One case of anaphylactic reaction related to the study medication (antibiotics group) was reported. Other SAE and Medical Dictionary for Regulatory Activities codes were equally distributed between placebo and antibiotics group and not related to the study medication.

Subjective perception of treatment (ITT-collective)

At baseline, the mean OHIP scores were 39.2 ± 27.2 for the placebo and 46.0 ± 33.8 for the antibiotics group. These scores decreased in the course of the study to 32.2 ± 29.4 and 32.9 ± 29.4 for placebo and antibiotics patients with mean changes of −5.5 ± 21.3 and −11.0 ± 26.1 respectively. The effect size (Cohen's *d*) of the score changes from baseline to 27.5 months between the two groups was $d = 0.23$ (95% CI 0.03; 0.44).

Table 2. Patient demography at baseline (visit 2) by treatment groups and collectives[†]

	Intention to treat collective		Per-protocol collective	
	Placebo group	Antibiotics group	Placebo group	Antibiotics group
n	200	206	175	170
Age – yr	50.5 ± 10.5	52.6 ± 10.4	52.3 ± 10.8	53.5 ± 10.1
Female sex – no. (%)	101 (50.4)	102 (49.6)	87 (49.7)	85 (50.0)
Active smokers – no. (%)	53 (26.5)	61 (29.6)	44 (25.1)	49 (28.8)
Former smokers – no. (%)	76 (44.7)	75 (44.4)	63 (36)	64 (37.6)
CO non-smoker – ppm	0.7 ± 1.1	0.7 ± 1.2	0.7 ± 1.1	0.7 ± 1.1
CO smoker– ppm	16.4 ± 10.3	13.5 ± 10.4	13.7 ± 8.7	13.5 ± 10.5
Medication intake[‡]				
Median	21	21	21	21
Range Min./Max.	3/24	0/24	18/23	18/23
HbA1c >6.5% (Diabetes) – no.	11	14	10	7
HbA1c – %	5.4 ± 0.9	5.5 ± 0.8	5.3 ± 0.7	5.5 ± 0.8
Body mass index – kg/m^2	25.9 ± 4.7	25.7 ± 4.5	25.9 ± 4.7	25.5 ± 4.5

[†]Continuous variables are shown as mean ± SD, categorical variables are shown as absolute and relative frequencies. No statistically noticeable differences were noted between the groups at baseline either in the intention to treat collective or in the per-protocol collective.
[‡]Total number of time points with medication intake; every patient was advised to take two tablets (amoxicillin plus metronidazole or two placebo tablets) 21 times.

Discussion

In the presented patient sample, from a clinical point of view, both therapeutic approaches were very effective and the absolute clinical differences between placebo and antibiotics groups were small. The median proportion of sites with disease progression of about 7.6% in the placebo and 5.2% in the antibiotics group was low, as was the median

Table 3. Patient periodontal characteristics at baseline (visit 2) and 27.5 months follow-up (visit 12)[†]

	Placebo group		Antibiotics group	
	Baseline	27.5 months	Baseline	27.5 months
Intention to Treat Collective				
Total no. of teeth	24.8 ± 4.3	24.0 ± 4.8	24.4 ± 4.2	23.8 ± 4.4
Mean probing depth – mm	3.5 ± 0.8	2.7 ± 0.7	3.6 ± 0.7	2.4 ± 0.5[‡]
Proportion of probing depths				
% ≤3.4 – mm	59.2 ± 18.1	79.1 ± 15.9	58.3 ± 16.6	85.8 ± 12.6[‡]
% 3.5–6.4 – mm	32.9 ± 12.6	18.1 ± 12.9	34.0 ± 12.1	13.2 ± 11.6[‡]
% ≥6.5 – mm	7.9 ± 8.9	2.8 ± 4.5	7.6 ± 8.7	0.9 ± 1.8[‡]
Mean attachment Level – mm	4.1 ± 1.0	3.7 ± 1.0	4.1 ± 0.9	3.4 ± 0.9[‡]
Sites with gingival bleeding –%	34.2 ± 18.1	19.6 ± 14.9	36.3 ± 19.2	13.1 ± 12.6[‡]
Sites with detectable plaque–%	36.5 ± 24.3	37.3 ± 23.4	38.7 ± 24.2	39.3 ± 24.6
Per-Protocol Collective				
Total no. of teeth	25.0 ± 4.3	24.1 ± 4.6	24.5 ± 4.0	23.8 ± 4.2
Mean probing depth – mm	3.5 ± 0.7	2.6 ± 0.7	3.5 ± 0.7	2.3 ± 0.5[‡]
Proportion of probing depths				
% ≤3.4 – mm	59.9 ± 17.6	79.9 ± 14.8	59.6 ± 16.0	85.9 ± 12.6[‡]
% 3.5–6.4 – mm	32.2 ± 12.5	17.4 ± 12.1	33.0 ± 11.4	13.2 ± 11.7[‡]
% ≥6.5 – mm	7.9 ± 8.2	2.7 ± 4.2	7.4 ± 8.4	0.9 ± 1.6[‡]
Mean attachment Level – mm	4.1 ± 0.9	3.6 ± 1.0	4.0 ± 0.9	3.0 ± 0.9[‡]
Sites with gingival bleeding – %	34.3 ± 16.8	18.9 ± 14.2	36.4 ± 19.6	12.8 ± 12.0[‡]
Sites with detectable plaque – %	35.8 ± 23.8	36.7 ± 23.3	38.2 ± 24.2	38.9 ± 24.7

[†]Continuous variables are shown as mean ± SD. No statistically noticeable differences were noted between the groups at baseline either in the intention to treat collective or in the per-protocol collective.
[‡]Statistically noticeable differences between placebo and antibiotic groups after 27.5 months, $p < 0.001$; van Elteren Test.

proportion of residual deep periodontal pockets (e.g. % PPD ≥5 mm; 5.5% *versus* 2.1% respectively). On the other hand it is noteworthy that the administration of the empiric antibiotic therapy as an adjunctive to mechanical debridement resulted in statistically noticeable better outcomes compared to placebo. The small absolute differences between the groups and the explicit statistical significance raise the question about the definition of treatment success and the appraisal of clinical relevance.

Retrospective cohort studies detected a higher risk of tooth loss with increasing proportions of persistent probing depths ≥5 mm or ≥6 mm (McGuire & Nunn 1996, Matuliene et al. 2008), therefore, those parameters are frequently used as surrogates for tooth loss. In most of the antibiotic studies surrogates such as changes of probing pocket depths or proportion of remaining deep pockets were used to determine treatment success (Loesche et al. 1991, Winkel et al. 2001, Feres et al. 2012, Mombelli et al. 2013). The majority of these studies attested positive effects for different adjunctive systemic antibiotic regimes on pocket reduction and therefore finally justified the prescription of antibiotics (Herrera et al. 2002). However, our observation was that proper mechanical debridement alone prevents new attachment loss much more predictable than it reduces the proportion of patients displaying deep pockets below arbitrary levels. As an example, while the incidence of new attachment loss in the placebo and antibiotics groups were, irrespective of statistical differences, in a similar low range (Fig. 2 a), the large differences in outcome of both therapies concerning the proportion of patients showing PPD ≥5 mm at ≤4 sites would be doubtlessly interpreted as clinically meaningful (Table 6). It would fit a pathophysiological logic that in patients with PPD ≥5 mm at only ≤4 sites, the proportions of sites with further attachment loss should decrease, too. But as shown in Table 7, the strong changes in the number of deep sites must not inevitably result in also strong lowered disease progression rates and furthermore depends on the chosen baseline point (visit 2 *versus* visit 4), too. This means that the estimation of clinical success and efficacy of a procedure strongly depends on the criteria used to define it (Lundgren et al. 2001).

If periodontal therapy aims at maintaining teeth in function for a lifetime, a parameter should be selected which represents or is tantamount to disease progression. Ideally, true parameters should be used to evaluate success of a therapeutic approach. The true success parameter and clinical endpoint for periodontal therapy is possibly tooth loss, but beside others, the reasonable duration of prospective studies is too short to use tooth loss as an endpoint (Eickholz et al. 2008). Due to that problem, ongoing attachment loss is therefore the most reasonable parameter next to tooth loss, because it reflects periodontal disease progression and may be assessed within reasonable periods of observation (Claffey & Egelberg 1995, Hujoel et al. 1999). Therefore, this parameter could be chosen to appraise the efficacy of a clinical procedure (Herrera et al. 2002). Former studies showed that the rate of attachment loss is low in patients with moderate to severe periodontal disease participating in a stringent maintenance programme, and this makes this factor difficult to interpret in prospective studies with reasonable observation periods (Lindhe et al. 1983). The dilemma is that very small differences in the proportions of sites with further attachment loss may be interpreted as negligible or may be interpreted as

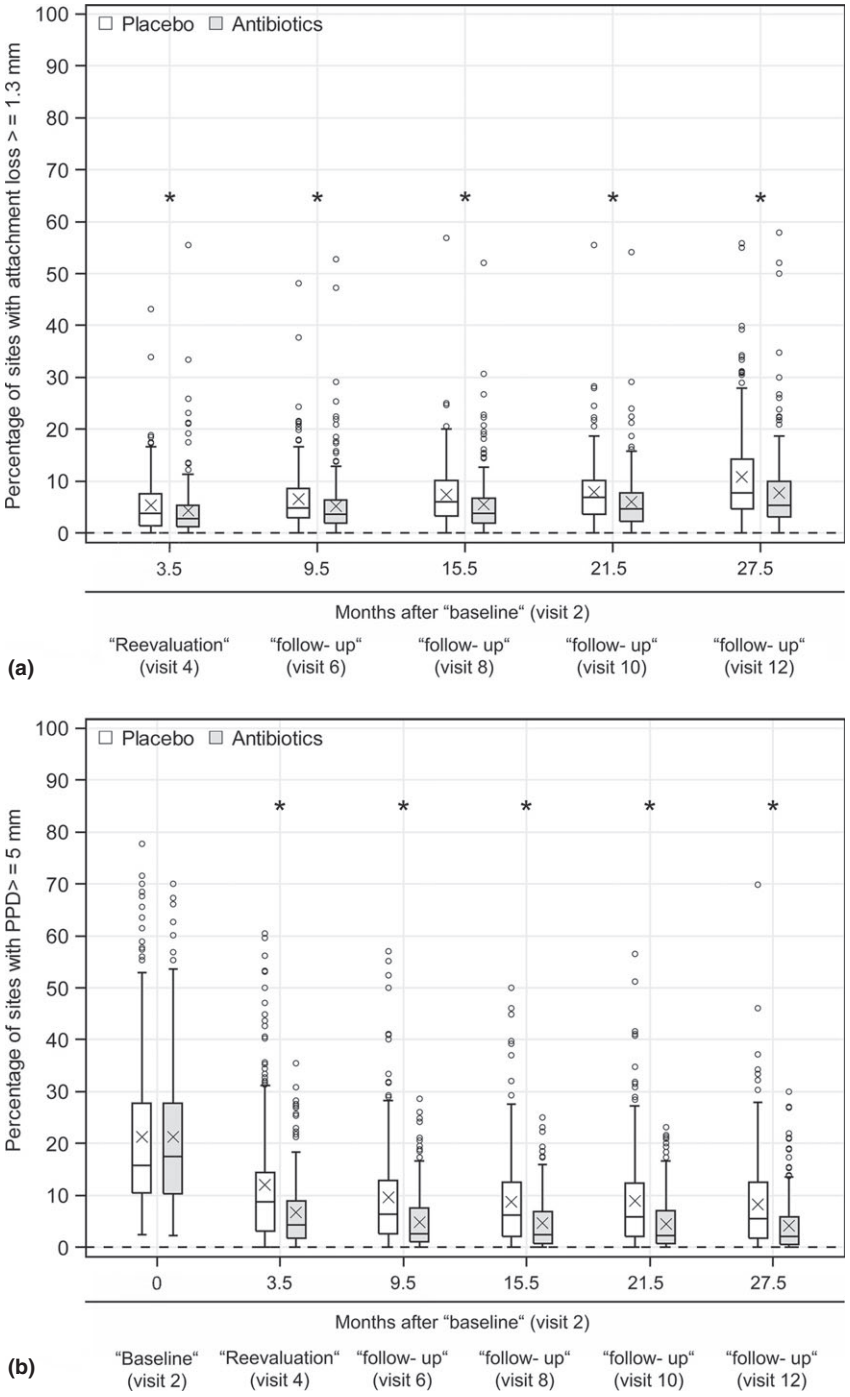

Fig. 2. Changes in main clinical parameters over the course of the study. (a) Percentage of sites with attachment loss (PSAL) ≥1.3 mm displayed for the placebo and antibiotics (amoxicillin/metronidazole) group over the course of the study. *$p < 0.001$, from stratified van Elteren tests. (b) The percentage of sites with pocket probing depth (PPD) ≥5 mm are displayed for the placebo and antibiotics (amoxicillin/metronidazole) group over the course of the study. At baseline (visit 2), the percentage of PPD ≥5 mm was not different in both groups ($p = 0.66$, stratified van Elteren test). Beginning with visit 4, although both groups achieved clinically favourable levels, the antibiotics group patients showed statistically noticeable lower presence of PPD ≥5 mm compared to placebo patients. *$p < 0.001$.

meaningful, because also small differences could add up to clinically relevant amounts over a certain period of time. However, it is questionable if the small differences found between the placebo and the antibiotics group in this study can be extrapolate in a linear way for, i.e., a decade.

So the question still remains: How clinically relevant are the findings of the present trial for the use of adjunctive systemic antibiotics in

Table 4. The proportion (%) of sites per patient with new clinical attachment loss (PSAL) ≥1.3 mm between baseline (visit 2) and the 27.5 months follow-up (visit 12). PSAL is also analysed according to the baseline probing depth category (≤3.4 mm, 3.5–6.4 mm, ≥6.5 mm) of the site. PSAL is described by median (25% quantile Q25/75% quantile Q75)

Initial pocket probing depths	Placebo group		Antibiotics group		*p*-value
	PSAL ≥1.3 mm (%)	Q 25/Q75	PSAL ≥1.3 mm (%)	Q 25/Q75	
Intention to Treat Collective					
All	7.8	4.7/14.1	5.3	3.1/9.9	<0.001
≤3.4 mm	7.2	3.9/14.5	5.8	2.8/11.5	0.026
3.5–6.4 mm	8.7	4.4/15.5	4.8	1.8/9.6	<0.001
≥6.5 mm	2.2	0.0/20.0	0.0	0.0/6.7	<0.001
Per-Protocol Collective					
All	7.5	4.5/14.4	5.3	3.2/9.7	<0.001
≤3.4 mm	7.1	3.8/14.5	5.8	3.1/10.7	0.053
3.5–6.4 mm	8.6	4.3/15.6	4.6	1.9/8.8	<0.001
≥6.5 mm	0.0	0.0/20.0	0.0	0.0/7.7	0.004

p-values are from the van Elteren tests comparing the differences in PSAL ≥1.3 mm between placebo and antibiotic patients overall and in each subgroup.

Table 5. The proportion (%) of sites per patient with new clinical attachment loss (PSAL) ≥2 mm between baseline (visit 2) and the 27.5 months follow-up (visit 12). PSAL is also analysed according to the baseline probing depth category (≤3.4 mm, 3.5–6.4 mm, ≥6.5 mm) of the site. PSAL is described by median (25% quantile Q25/75% quantile Q75)

Initial pocket probing depths	Placebo group		Antibiotics group		*p*-value
	PSAL ≥2 mm (%)	Q 25/Q75	PSAL ≥2 mm (%)	Q 25/Q75	
Intention to Treat Collective					
All	3.3	1.5/6.7	2.1	0.7/4.0	<0.001
≤3.4 mm	2.7	0.9/6.5	2.0	0.0/4.4	0.040
3.5–6.4 mm	3.7	1.4/8.3	2.0	0.0/4.5	<0.001
≥6.5 mm	0.0	0.0/9.1	0.0	0.0/0.0	0.006
Per-Protocol Collective					
All	3.2	1.4/6.7	2.2	0.8/3.9	<0.001
≤3.4 mm	2.6	0.9/6.4	2.0	0.7/4.2	0.068
3.5–6.4 mm	3.6	1.5/8.3	2.0	0.0/4.3	<0.001
≥6.5 mm	0.0	0.0/9.1	0.0	0.0/2.0	0.037

p-values are from the van Elteren tests comparing the differences in PSAL ≥1.3 mm between placebo and antibiotic patients overall and in each subgroup.

Table 6. Proportions (%) and absolute numbers (*n*) of patients showing ≤4sites with pocket probing depth ≥5 mm (yes/no) at baseline (visit 2), 2 months re-evaluation (visit 4) and 27.5 months follow-up (visit 12)

Intention to Treat Collective	Baseline		Re-evaluation 2 months		Follow-up 27.5 months	
	Yes	No	Yes*	No	Yes*	No
Placebo group – % (*n*)	0.4 (1)	99.6 (254)	24.9 (60)	75.1 (181)	36.5 (73)	63.5 (127)
Antibiotics group – % (*n*)	0.8 (2)	99.2 (248)	39.9 (95)	60.1 (143)	63.1 (130)	36.9 (76)

Statistically noticeable differences*, Fisher's exact test, $p < 0.001$.

periodontal therapy? The patients' subjective perception of both regimes, for example OHIP score change, and the appearances of serious adverse events during the course of the study were similar in both groups. The overall low incidence of attachment loss and its small absolute difference between the groups would not really influence routine daily treatment. In contrast to that, the higher number of teeth with residual PPD ≥5 mm in the placebo group could require a more laborious maintenance therapy. However, it is of crucial importance to consider the use of systemic antibiotics in non-life threatening but widespread diseases in relation to the development of general antibiotic resistance. The increased appearance of bacterial resistance is strongly related to the frequency of antibiotic drug consumption (Costelloe et al. 2010, Laxminarayan et al. 2014). The Standing Medical Advisory Committee has recommended using the lowest number of systemic antibiotic courses possible (United Kingdom Department of Health 1998).

After weighing up the pros and cons of adjunctive administration amoxicillin and metronidazole in the treatment of moderate or severe chronic periodontitis, we found that a simple clinical cut off, from where this treatment regimen should be prescribed and is accompanied by reasonably foreseeable benefits for the patient, is obviously hard to define. Because there is no easy way out, obviously the clinical relevance of a therapeutic option like the prescription of systemic antibiotics must be estimated on different levels. For patients suffering from aggressive periodontitis, generalized severe chronic periodontitis, or disease progression despite proper mechanical therapy, antibiotic drug prescription as an adjunct to initial mechanical therapy is a relevant therapeutic option and may have additive effects (Goodson et al. 2012). But besides such diagnosis-related treatment decision making, a risk-related therapeutic approach considered by the periodontist may be even more important (Wennström et al. 1990). A risk-related approach could mean that, for example younger patients may benefit more from adjunctive amoxicillin and metronidazole than older patients showing a comparable severity of periodontal disease as expressed by clinical measurements. Similar clinical signs at not similar ages may express different susceptibilities to the disease and may lead to a diverging appraisal of the clinical relevance of therapeutic approaches. Therefore, the 40-year-old patient with 50% attachment loss and 50% PPDs ≥5 mm at 28 teeth may require a different extend of therapy than a 65-year-old patient

Table 7. The proportion (%) of sites per patient with new clinical attachment loss (PSAL) ≥1.3 mm between baseline (visit 2) or re-evaluation (visit 4) and the 27.5 months follow-up (visit 12). The PSAL was analysed separately for patients according to the presence or not of ≤4 sites with pocket probing depth ≥5 mm at 27.5 months follow-up (visit 12). PSAL is described by median (25% quantile Q25/75% quantile Q75)

Intention to treat collective		Placebo group		Antibiotics group		*p*-values
		PSAL ≥1.3 mm (%)	Q 25/Q75	PSAL ≥1.3 mm (%)	Q 25/Q75	
Baseline visit 2	≤4 sites with PPD ≥5 mm	5.1	2.6/9.0	4.3	2.4/8.3	0.246
	>4 sites with PPD ≥5 mm	10.0	5.9/16.3	8.1	4.1/12.3	0.024
Re-evaluation visit 4	≤4 sites with PPD ≥5 mm	7.7	4.2/12.8	7.7	4.2/11.9	0.667
	>4 sites with PPD ≥5 mm	11.1	7.1/18.5	9.1	5.9/15.6	0.109

p-values are from the van Elteren tests comparing the differences in PSAL ≥1.3 mm between placebo and antibiotic patients in each subgroup.

with identical clinical signs and amount of teeth, because the risks of both patients for further disease progression may be different. In this example, the younger patient may have a better chance retaining more teeth in his lifetime due to the more reduced PPDs and the slight reduction in further attachment loss after adjunctive antibiotics, whereas the older patient probably will not lose more teeth, if no antibiotics were prescribed. In other words, the clinical relevance of reducing PPDs or avoiding small amounts of further attachment loss with the help of adjunctive amoxicillin and metronidazole may be related to the patient's individual risks for periodontal disease. So it will remain the therapist's decision to prescribe adjunctive amoxicillin and metronidazole and judge the effect on periodontal disease progression in patients undergoing periodontal maintenance and against the background of antibiotic resistance as clinically relevant or not.

In conclusion, mechanical debridement is highly effective in the prevention of new attachment loss and improves the majority of other clinical parameters. Results of mechanical therapy were statistically significant improved by the prescription of adjunctive antibiotics, but these improvements depend on the outcome parameter and are of conflicting clinical relevance in real life. Against the background and danger of increasing microbiological resistance, it seems even more reasonable that for routine treatment of periodontitis therapists should consider the patient's overall risk for periodontal disease when making a decision for or against antibiotic prescription, and should be careful not to underestimate the effect of proper mechanical debridement and modification of behavioural risk factors. In the present trial, compared to placebo, the prescription of empiric adjunctive systemic amoxicillin plus metronidazole was highly effective in terms of PPD reduction, but showed little absolute, although statistical significant, reduction in further attachment loss in formerly untreated patients with moderate or severe chronic periodontitis.

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Clinical Relevance

Scientific rationale for the study: Systemic antibiotics are established adjuncts for periodontal therapy. The uncritical use of antibiotics increases bacterial resistances. It is mandatory, that prescription of systemic antibiotics undergoes a critical appraisal of its clinical relevance on the course of periodontal disease.

Principal findings: In the present trial, compared to placebo, the prescription of empiric adjunctive systemic amoxicillin plus metronidazole was highly effective in terms of PPD reduction, but showed small absolute, although statistical significant, reduction in further attachment loss in formerly untreated patients with moderate or severe chronic periodontitis.

Practical implications: Therapists should consider the patient's overall risk for periodontitis when making a decision for or against antibiotic prescription, and should be careful not to underestimate the effect of proper mechanical debridement and modification of behavioural risk factors.