Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: a systematic review and meta-analysis


Objective: The purpose of this meta-analysis is to evaluate the effectiveness of different systemic antibiotics in combination with scaling and root planing (SRP) compared to SRP alone in patients with untreated aggressive periodontitis.

Background: In patients with aggressive periodontitis, SRP is often combined with the use of systemic antibiotics. However, the effectiveness of these antibiotics over time and differences in effectiveness between different antibiotics are hardly known.

Material and Methods: The MEDLINE-PubMed database was searched from their earliest records until January 20, 2014. Several journals were hand searched and some authors were contacted for additional information. The following outcome measures were analysed: mean probing pocket depth reduction, mean clinical attachment level gain and mean bleeding on probing change. Extracted data were pooled using a random effect model. Weighted mean differences were calculated and heterogeneity was assessed.

Results: The search yielded 296 abstracts. Ultimately, 101 articles were selected of which 14 articles met the eligibility criteria. Systemic antibiotics showed a significant ($p < 0.05$) additional pocket depth reduction for moderate (0.36 ± 0.22 mm at 3 mo, 6 mo 0.42 ± 0.22 mm and 12 mo 0.88 ± 0.27 mm) and deep pockets (0.74 ± 0.36 mm at 3 mo, 6 mo 0.85 ± 0.55 mm and 12 mo 1.26 ± 0.81 mm) and a significant clinical attachment gain for moderate (0.26 ± 0.18 at 3 mo, 6 mo 0.52 ± 0.15 and 12 mo 0.83 ± 0.38) and deep pockets (0.59 ± 0.18 at 3 mo, 0.96 ± 0.21 at 6 mo and 1.00 ± 0.80 at 12 mo).

Conclusion: For the treatment of patients with aggressive periodontitis, systemic antibiotics combined with non-surgical periodontal therapy resulted in
Introduction

Periodontitis is an inflammatory disorder that leads to the destruction of the tooth supporting structures. This destruction is caused by an imbalance between a wide range of microorganisms, host response and essential modifying factors (1). Inflammation, loss of connective tissue attachment and loss of alveolar bone support are the clinical signs. Periodontitis is divided into aggressive periodontitis (characterized by a rapid loss of clinical attachment and alveolar bone) and chronic periodontitis (characterized by a progressive loss of clinical attachment and alveolar bone) (2). Today the treatment goals are to resolve inflammation and reduce the infection so that a clinical condition is created, which is compatible with periodontal health (3).

Aggressive periodontitis is characterized by a rapid loss of clinical attachment and alveolar bone affecting adolescents and young adults (4). It is subclassified as localized or generalized in relation to the extent of the periodontal destruction. In a recent article, Albandar proposed a new case definition for patients with aggressive periodontitis (5). The following distinctive criteria are recommended:

1. An early age onset, usually before 25 years of age. The age of onset might be a predictor of the disease’s severity.
2. Loss of periodontal tissue occurs at multiple permanent teeth. The tissue loss occurs because of a microbial infection.
3. The periodontal destruction is detectable clinically and radiographically. Typically, the lesions are depicted radiographically as a horizontal loss of the alveolar bone.
4. There is a relatively high progression rate of periodontal tissue loss.
5. The primary teeth may also be affected.
6. Clinically healthy except for the presence of periodontitis.

The major differences with respect to the classification of Armitage (2) are that some primary and secondary features, such as familial aggregation, elevated proportions of Aggregatibacter actinomycetemcomitans or Porphyromonas gingivalis, hypersensitive macrophage phenotypes and phagocyte abnormalities, are not considered anymore.

The treatment and maintenance for aggressive periodontitis are challenging for periodontists. There are still no established protocols and guidelines (6). The first step in the treatment of aggressive periodontitis is a non-surgical periodontal therapy. This therapy consists of scaling and root planing (SRP) and oral hygiene instructions combined with the adjunctive use of systemic antibiotics. This SRP can be done within 24 h or within 1 wk, which is called full mouth disinfection. The SRP can also be done over a longer period, which is called staged SRP. Systemic antibiotics help the immune system by suppressing the target microbial species. It is currently well established that systemic antibiotics should not be administered without previous disruption of the biofilm (7). The possible antibiotic regimens for aggressive periodontitis that have been reported in the literature are penicillins (amoxicillin, AMOX), tetracyclines (doxycycline [DOX], tetracycline, TET), macrolides (azithromycin, AZI) and nitroimidazole (metronidazole, MET). Evidently, the ultimate goal in the treatment of aggressive periodontitis is to create a clinical condition, which is necessary to save and maintain as many teeth as possible (6).

The reason why systemic antibiotics are given in combination with the initial non-surgical periodontal therapy is to suppress pathogenic bacteria and create a health-associated biofilm. If the use of systemic antibiotics is considered, the clinician needs to take into account the patient’s compliance, adverse effects and bacterial resistance (8–11). The EU (12,13) and WHO (14) have made some recommendations to prevent bacterial resistance worldwide. The key points are, avoid antibiotics whenever possible and use narrow-spectrum antibiotics if possible (11). It is highly necessary to develop evidence-based clinical protocols that will help and guide the clinician in his decision when and what kind of systemic antibiotic regimen should be used. As a step towards this protocol, this meta-analysis evaluates if there are differences between the effectiveness of the different types of systemic antibiotics in combination with SRP vs. SRP alone in patients with untreated aggressive periodontitis and whether the effect is consistent over time.

Material and methods

The following systematic review was conducted in agreement with the recommendations of the Cochrane Collaboration (15) and the principles of the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) statement (16).

Focused question (PICO)

The focused question that has been used was: “Do systemic antibiotics combined with SRP vs. SRP alone in untreated aggressive periodontitis patients have an additional effect on the clinical outcomes”.
Search strategy
The MEDLINE-PubMed database was searched from their earliest records until January 20, 2014. The following search terms were used: Periodontal diseases [MESH] AND Anti-Infective Agents [MESH] and Metronidazole [MESH] AND Periodontal diseases [MESH]. In addition, a manual search was performed of issues from the past 10 years of the Journal of Clinical Periodontology, Journal of Periodontal Research and Journal of Periodontology.

Study inclusion and exclusion criteria
The selection process was performed by two masked reviewers (I.G. and J.K.). The studies were analysed according to inclusion criteria:
1. Studies were limited to randomized controlled clinical trials of at least more than 1 mo duration.
2. The population was limited to subjects with aggressive periodontitis (2).
3. The interventions of interest were full mouth SRP (SRP within 1 wk) or staged SRP (SRP more than a week apart) with or without the use of systematic antibiotics.
4. No specific systemic antibiotics were excluded.
5. Only papers in the English language were included.

Only studies that met all inclusion criteria were analysed according to the exclusion criteria:
1. History of refractory periodontitis.
2. Combination of local and systemic antibiotics.
3. Primary outcome of interest were not analysed.
4. Duplicated studies.

Outcome variables
The primary outcomes were probing pocket depth (PPD) reduction and clinical attachment level change. Clinical attachment level change and PPD reduction were if possible divided into moderate (4–6 mm) and deep pockets (>6 mm). The secondary outcome was bleeding on probing (BOP) change.

Data extraction
The title and abstract of studies of possible relevance for the review were obtained and screened independently by two masked reviewers (I.G. and J.K.). Papers without abstracts but with titles suggesting relevance to the subject of the review were selected for full text screening. The selected full text papers were independently read in detail to check whether they passed the inclusion/exclusion criteria. The references of full text articles were searched for any relevant additional articles. The papers that fulfilled all the selection criteria were processed for data extraction. Discrepancies with regard to the inclusion or exclusion of studies were resolved by discussion between the reviewers (I.G. and J.K.). The extracted data included year of publication, design of the study, number of patients per study arm, length of follow-up, type of antibiotic, dosage of the antibiotic, duration of the antibiotic regimen, timing of the antibiotic in relation to SRP and primary and secondary outcome measures at 3, 6, 9 and 12 mo.

Quality assessment
A quality assessment of the methodologies of all included studies was conducted. It was based on the randomized controlled trial checklist of the Cochrane Center, the CONSORT guidelines (17), the Delphi list (18) and the checklist as proposed by Van der Weijden et al. (19). The following seven criteria were used: selection bias, allocation bias, performance bias, detection bias, defined inclusion/exclusion criteria, attrition bias and reporting bias. When all these criteria were fulfilled, the article was classified as a low risk of bias (L). When one or two of these criteria were assessed as high risk of bias or unclear, the study was regarded to have a moderate potential risk of bias (M). The risk of potential bias was high, when three or more criteria had a high or unclear risk of bias (H). The risk of bias was evaluated independently by two masked reviewers (I.G. and J.K.). If there was any disagreement, it was resolved by discussion.

Statistical analyses
Data of the included studies were extracted and entered into a database. Mean values and SDs were extracted from the data. If no SD was available it was recalculated by the formula \( SE = SD/\sqrt{n} \) with \( n \) the sample size. When intermediate assessments were performed, the 3, 6, 9 or 12 mo data were considered. If there were insufficient data available, the corresponding authors were contacted for additional data. The available data were recalculated to present data such as mean BOP change, mean clinical attachment level gain and mean PPD reduction. Clinical attachment level gain and PPD reduction were also presented for moderate (4–6 mm) and deep pockets (>6 mm). The \( F \) statistic was used to assess the heterogeneity between the studies. Because of observed heterogeneity mean differences were combined for continuous data using random effects models meta-analysis. Study weights were determined by the sample size (20).

Results
The initial search resulted in a total of 6738 articles (Fig. 1). After screening the titles, 296 abstracts were included for further analysis. Analysis of the abstracts resulted in 101 potential articles. In the third phase, the full text articles of the remaining 101 articles were evaluated, of which 44 articles (21–64) did not pass the inclusion criteria (Table 1). Another 43 articles (65–107) were excluded because they were about patients with chronic periodontitis. Screening of the reference lists of full text articles did not result in any additional articles. In Table 2 the main characteristics of the 14 included articles (108–121) are summarized. Four authors have provided additional results, which were
not present in the articles (111,117–119). These 14 included articles represent 13 studies. These studies were divided in to the following groups: azithromycin (AZI; two studies), DOX (two studies), MET (one study), MET+AMOX (10 studies) and TET one study. The quality evaluation was based on seven criteria (17–19). The potential risk of bias in the 13 studies included was low in eight, moderate in two and high in four studies (Table 2).

Probing pocket depth reduction

At 3 mo, 386 patients out of 13 studies could be analysed (Fig. 2 and Table S1). A statistically significant mean difference of 0.34 ± 0.11 mm and heterogeneity $I^2 = 26\%$, in favour of the use of a systemic antibiotic was observed. AZI (0.36 ± 0.33 mm, one study, 32 patients and $I^2 = \text{NA}$) and MET+AMOX (0.39 ± 0.16 mm, eight studies, 248 patients and $I^2 = 38\%$) showed a statistically significant mean difference when compared to the control group. DOX and AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for DOX, AZI and MET only one study was available. At 9 mo, no studies could be analysed.

At 12 mo, 65 patients out of two studies could be analysed. A statistically significant mean difference of 0.51 ± 0.38 mm and heterogeneity $I^2 = 42\%$, in favour of the use of a systemic antibiotic was observed. At 12 mo, only results for MET+AMOX were available.

Probing pocket depth reduction moderate pockets

At 3 mo, 191 patients out of six studies could be analysed (Fig. 3 and Table S2). A statistically significant mean difference of 0.36 ± 0.22 mm and heterogeneity $I^2 = 81\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.43 ± 0.22 mm, four studies, 135 patients and $I^2 = 76\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group.

At 6 mo, 190 patients out of six studies could be analysed. A statistically significant mean difference of 0.42 ± 0.22 mm and heterogeneity $I^2 = 55\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.50 ± 0.21 mm, four studies, 134 patients and $I^2 = 45\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group.

At 9 mo, 24 patients out of one study could be analysed. No statistically significant mean difference (0.65 ± 0.94 mm, one study, 24 patients and $I^2 = \text{NA}$), in favour of the use of a systemic antibiotic (AZI) was observed.

At 12 mo 54 patients out of two studies could be analysed. A statistically significant mean difference of 0.88 ± 0.27 mm and heterogeneity $I^2 = 0\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.89 ± 0.28 mm, one study, 30 patients and $I^2 = \text{NA}$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for both antibiotics only one study was available.

Probing pocket depth reduction deep pockets

At 3 mo, 191 patients out of six studies could be analysed (Fig. 4 and Table S3). A statistically significant mean difference of 0.74 ± 0.36 mm and heterogeneity $I^2 = 73\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.88 ± 0.27 mm, four studies, 135 patients and $I^2 = 42\%$) showed a statistically significant mean difference when com-
pared to the control group. AZI did not show a statistically significant mean difference when compared to the control group.

At 6 mo, 190 patients out of six studies could be analysed. A statistically significant mean difference of 0.85 ± 0.55 mm and heterogeneity $I^2 = 58\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (1.09 ± 0.39 mm, four studies, 134 patients and $I^2 = 66\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group.

At 9 mo, 24 patients out of one study could be analysed. No statistically significant mean difference (0.62 ± 1.65 mm, one study, 24 patients and $I^2 = NA$), in favour of the use of a systemic antibiotic (AZI) was observed.

At 12 mo, 54 patients out of two could be analysed. A statistically significant mean difference of 1.26 ± 0.81 mm and heterogeneity $I^2 = 0\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (1.40 ± 0.91 mm, one study, 30 patients and $I^2 = NA$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for both antibiotics only one study was available.
### Table 2. Characteristics of the 14 included articles

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Comparison</th>
<th>Follow-up</th>
<th>Treatment</th>
<th>Timing antibiotics</th>
<th>Antibiotics</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silva-senem et al. (2013) (108)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>12 mo</td>
<td>SSRP</td>
<td>Before SSRP</td>
<td>Amoxicillin 500 mg 3× for 10 d, Metronidazole 250 mg 3× for 10 d</td>
<td>L</td>
</tr>
<tr>
<td>Helle et al. (2011) (116)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Emingil et al. (2012) (109)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>6 mo</td>
<td>SSRP</td>
<td>After SSRP</td>
<td>Azithromycin 500 mg 3× for 3 d</td>
<td>L</td>
</tr>
<tr>
<td>Beliveau et al. (2012) (110)</td>
<td>Single-blind University</td>
<td>No placebo vs. antibiotics</td>
<td>3 mo</td>
<td>SSRP</td>
<td>After SSRP</td>
<td>Amoxicillin 500 mg 3× for 7 d, Metronidazole 250 mg 3× for 7 d</td>
<td>H</td>
</tr>
<tr>
<td>Mestnik et al. (2012) (111)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>12 mo</td>
<td>SSRP</td>
<td>After 1st SSRP</td>
<td>Amoxicillin 500 mg 3× for 14 d, Metronidazole 400 mg 3× for 14 d</td>
<td>L</td>
</tr>
<tr>
<td>Casarin et al. (2012) (112)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>6 mo</td>
<td>FMSRP</td>
<td>After FMSRP</td>
<td>Amoxicillin 375 mg 3× for 7 d, Metronidazole 250 mg 3× for 7 d</td>
<td>L</td>
</tr>
<tr>
<td>Aimetti et al. (2012) (113)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>6 mo</td>
<td>FMSRP</td>
<td>After 1st FMSRP</td>
<td>Amoxicillin 500 mg 3× for 7 d, Metronidazole 500 mg 3× for 7 d</td>
<td>L</td>
</tr>
<tr>
<td>Oliveira et al. (2012) (114)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>6 mo</td>
<td>SSRP</td>
<td>After 1st SSRP</td>
<td>Amoxicillin 500 mg 3× for 14 d, Metronidazole 400 mg 3× for 14 d</td>
<td>H</td>
</tr>
<tr>
<td>Baltacioglu et al. (2011) (115)</td>
<td>Blinding? University</td>
<td>No placebo vs. antibiotics</td>
<td>2 mo</td>
<td>FMSRP</td>
<td>After FMSRP</td>
<td>Amoxicillin 250 mg 3× for 10 d, Metronidazole 250 mg 3× for 10 d, Doxycycline 200 mg + 100 mg 1× for 13 d</td>
<td>H</td>
</tr>
<tr>
<td>Griffiths et al. (2011) (117)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>6 mo</td>
<td>FMSRP</td>
<td>After FMSRP</td>
<td>Amoxicillin 500 mg 3× for 7 d</td>
<td>L</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>Comparison</td>
<td>Follow-up</td>
<td>Treatment</td>
<td>Timing antibiotics</td>
<td>Antibiotics</td>
<td>Quality assessment</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------------</td>
<td>------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Yek et al. (2010) (118)</td>
<td>Double-blind University</td>
<td>No placebo vs. antibiotics</td>
<td>6 mo</td>
<td>FMSRP</td>
<td>After 1st FMSRP</td>
<td>Metronidazole 500 mg 3× for 7 d Amoxicillin 500 mg 3× for 7 d Metronidazole 500 mg for 7 d</td>
<td>M</td>
</tr>
<tr>
<td>Haas et al. (2008) (119)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>12 mo</td>
<td>SSRP</td>
<td>After 1st SSRP</td>
<td>Azithromycin 500 mg 1× for 3 d</td>
<td>L</td>
</tr>
<tr>
<td>Xajigeorgiou et al. (2006) (120)</td>
<td>Single-blind University</td>
<td>No placebo vs. antibiotics</td>
<td>6 mo</td>
<td>SSRP</td>
<td>After SSRP</td>
<td>Amoxicillin 500 mg 3× for 7 d Metronidazole 500 mg 3× for 7 d Doxycycline 200 mg + 100 mg 1× for 13 d</td>
<td>M</td>
</tr>
<tr>
<td>Palmer et al. (1996) (121)</td>
<td>Double-blind University</td>
<td>Placebo vs. antibiotics</td>
<td>3 mo</td>
<td>FMSRP</td>
<td>After FMSRP</td>
<td>Tetracycline 250 mg 4× for 14 d</td>
<td>H</td>
</tr>
</tbody>
</table>

(■) low risk of bias; (□) unclear risk of bias; (■■) high risk of bias.
Clinical attachment level gain

At 3 mo, 386 patients out of 13 studies could be analysed (Fig. 5 and Table S4). A statistically significant mean difference of 0.40 ± 0.30 mm and heterogeneity $I^2 = 85\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.50 ± 0.40 mm, eight studies, 248 patients and $I^2 = 91\%$) showed a statistically significant mean difference when compared to the control group. AZI, DOX, MET and TET did not show a statistically significant mean difference when compared to the control group. AZI, DOX and MET did not show a statistically significant mean difference when compared to the control group. AZI, DOX and MET did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI, MET and TET only one study was available.

At 6 mo, 290 patients out of 10 studies could be analysed. A statistically significant mean difference of 0.36 ± 0.10 mm and heterogeneity $I^2 = 0\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.36 ± 0.10 mm, seven studies, 214 patients and $I^2 = 0\%$) showed a statistically significant mean difference when compared to the control group. AZI, DOX and MET did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI, DOX and MET only one study was available. At 9 mo, no studies could be analysed.

At 12 mo, 65 patients out of two studies could be analysed. A statistically significant mean difference of 0.46 ± 0.37 mm and heterogeneity $I^2 = 60\%$, in favour of the use of a systemic antibiotic was observed. At

![Fig. 2. Probing pocket depth reduction.](image1)

![Fig. 3. Probing pocket depth reduction moderate pockets.](image2)
12 mo, only results for MET + AMOX were available.

### Clinical attachment level gain moderate pockets

At 3 mo, 159 patients out of five studies could be analysed (Fig. 6 and Table S5). A statistically significant mean difference of 0.26 ± 0.18 mm and heterogeneity $I^2 = 43\%$, in favour of the use of a systemic antibiotic was observed. MET + AMOX (0.27 ± 0.19 mm, four studies, 135 patients and $I^2 = 57\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI only one study was available.

At 6 mo, 158 patients out of five studies could be analysed. A statistically significant mean difference of 0.52 ± 0.12 mm and heterogeneity $I^2 = 14\%$, in favour of the use of a systemic antibiotic was observed. MET + AMOX (0.52 ± 0.15 mm, four studies, 134 patients and $I^2 = 32\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI only one study was available.

At 9 mo, 24 patients out of one study could be analysed. No statistically significant mean difference (0.41 ± 1.75 mm, one study, 24 patients and $I^2 = NA$), in favour of the use of a systemic antibiotic (AZI) was observed.

---

**Fig. 4.** Probing pocket depth reduction deep pockets.

**Fig. 5.** Clinical attachment level gain.
At 12 mo, 54 patients out of two studies could be analysed. A statistically significant mean difference of 1.00 ± 0.80 mm and heterogeneity $I^2 = 0\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (1.03 ± 0.84 mm, one study, 30 patients and $I^2 = NA$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for both antibiotics only one study was available.

Clinical attachment level gain deep pockets

At 3 mo, 159 patients out of five studies could be analysed (Fig. 7 and Table S6). A statistically significant mean difference of 0.59 ± 0.21 mm and heterogeneity $I^2 = 14\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.94 ± 0.28 mm, four studies, 134 patients and $I^2 = 34\%$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI only one study was available.

Bleeding on probing change

At 3 mo, 333 patients out of 11 studies could be analysed (Fig. 8 and Table S7). A statistically significant mean difference (0.52 ± 2.71 mm, one study, 24 patients and $I^2 = NA$), in favour of the use of a systemic antibiotic (AZI) was observed.

At 12 mo, 54 patients out of two studies could be analysed. A statistically significant mean difference of 0.83 ± 0.38 mm and heterogeneity $I^2 = 0\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (0.85 ± 0.39 mm, one study, 30 patients and $I^2 = NA$) showed a statistically significant mean difference when compared to the control group. AZI did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for both antibiotics only one study was available.
cant mean difference of $9.38 \pm 4.70\%$ and heterogeneity $I^2 = 81\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (10.07 ± 5.85\%, seven studies, 219 patients and $I^2 = 89\%$) showed a statistically significant mean difference when compared to the control group. AZI, DOX, MET and TET did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI, DOX, MET and TET only one study was available. At 6 mo, 266 patients out of nine studies could be analysed. A statistically significant mean difference of $6.84 \pm 3.81\%$ and heterogeneity $I^2 = 18\%$, in favour of the use of a systemic antibiotic was observed. MET+AMOX (8.85 ± 5.51 mm, six studies, 190 patients and $I^2 = 43\%$) showed a statistically significant mean difference when compared to the control group. AZI, DOX and MET did not show a statistically significant mean difference when compared to the control group. However, it should be noted that for AZI, DOX and MET only one study was available. At 9 mo, no studies could be analysed. At 12 mo, 65 patients out of two studies could be analysed. A statistically significant mean difference of $12.76 \pm 10.35\%$ and heterogeneity $I^2 = 32\%$, in favour of the use of a systemic antibiotic was observed. At 12 mo, only results for MET+AMOX were available.

**Discussion**

In the literature, evidence is available about the additional effect of systemic antibiotics in combination with SRP for the treatment of patients with aggressive periodontitis when compared to only SRP. This review has tried to evaluate systematically the current available evidence and has tried to compare the effectiveness of different types of systemic antibiotics as well as their long-term effects (up to 1 year). Thirteen clinical studies could be included from which the data were obtained and used to calculate the mean difference in clinical improvement for PPD, clinical attachment level and BOP change. PPD and clinical attachment level difference were additionally analysed for initially moderate pockets (4–6 mm) and deep pockets (> 6 mm).

The meta-analysis for the mean PPD difference showed statistically significant differences when compared to SRP at 3, 6 and 12 mo in favour of the adjunctive use of systemic antibiotics (0.34 ± 0.11, 0.51 ± 0.11 and 0.51 ± 0.38 mm). The analysis was hampered by the fact that the follow-up period from most of the studies was only 3–6 mo. When analysing only the studies that had results at 3, 6 and 12 mo (108,111,116), the clinical additional difference of these studies was similar at 3 mo (0.33 ± 0.33 mm), higher at 6 mo (0.63 ± 0.27 mm) and similar at 12 mo (0.51 ± 0.38 mm) when compared to the overall effect. Overall, it seems that the initial effect of the adjunctive systemic antibiotics on the mean PPD difference remains stable for at least 1 year. Additionally only two studies of MET+AMOX were available at 12 mo and unfortunately no other systemic antibiotic regimen was available. It became clear that only for MET+A-
MOX there is evidence that the mean PPD difference when compared to SRP could be obtained for up to 1 year.

The meta-analysis for the mean PPD difference in moderate and deep pockets showed a similar outcome as for mean whole mouth PPD reduction albeit more pronounced. When analysing only the studies that had results at 3, 6 and 12 mo (111,119), the clinical additional difference for the moderate pockets in these studies was higher at 3 mo (0.73 ± 0.32 mm) and 6 mo (0.74 ± 0.28 mm) and similar at 12 mo (0.88 ± 0.27 mm), for the deep pockets in these studies was higher at 3 mo (1.28 ± 0.90 mm) and 6 mo (1.35 ± 0.71 mm) and similar at 12 mo (1.26 ± 0.81 mm) when compared to the overall effect. Based on these studies, it seems that the initial effect of the systemic antibiotics on the mean PPD difference of moderate and deep pockets remains stable for at least 1 year. Additionally only one study using AMOX (111) were available at 12 mo. It became clear that only for MET+AMOX the mean clinical attachment level difference when compared to SRP could be obtained for up to 1 year.

The meta-analysis for the mean clinical attachment level difference showed statistically significant differences when compared to SRP at 3, 6 and 12 mo in favour of the use of antibiotics (0.41 ± 0.32, 0.36 ± 0.11 and 0.46 ± 0.37 mm). The analysis was also hampered by the fact that the follow-up period from most of the studies was only 3–6 mo. When analysing only the studies that had results at 3, 6 and 12 mo (108,111), the clinical additional difference of these studies was higher at 3 mo (0.63 ± 0.35 mm) and 6 mo (0.49 ± 0.27 mm), and similar at 12 mo (0.46 ± 0.37 mm) when compared to the overall effect. Overall, it seems that the initial effect of the systemic antibiotics on the mean clinical attachment level difference remains stable for at least 1 year. Additionally, only two studies using MET+AMOX were available at 12 mo and unfortunately no other antibiotics were available. It became clear that for MET+AMOX the mean clinical attachment level difference when compared to SRP could be obtained for up to 1 year.

The meta-analysis for the mean clinical attachment level difference in moderate and deep pockets showed a similar outcome as for mean whole mouth clinical attachment level difference albeit more pronounced. When analysing only the studies that had results at 3, 6 and 12 mo (111,119), the clinical additional difference for the moderate pockets in these studies was higher at 3 mo (0.61 ± 0.36 mm) and 6 mo (0.58 ± 0.32 mm) and similar at 12 mo (0.83 ± 0.38 mm), for the deep pockets in these studies was higher at 3 mo (1.09 ± 0.66 mm) and 6 mo (1.05 ± 0.69 mm) and similar at 12 mo (1.00 ± 0.80 mm) when compared to the overall effect. Based on these studies, it seems that the initial effect of the systemic antibiotics on the mean clinical attachment level difference of moderate and deep pockets remains stable for at least 1 year. Additionally only one study using AMOX (111) and one using MET+AMOX (111) were available at 12 mo. It became clear that only for MET+AMOX the mean clinical attachment level difference when compared to SRP could be obtained for up to 1 year.

The meta-analysis for the mean BOP difference showed statistically significant differences when compared to SRP at 3, 6 and 12 mo in favour of the use of antibiotics (9.38 ± 4.70%, 6.84 ± 3.81% and 12.76 ± 10.35%). The analysis was hampered by the fact that the follow-up period from most of the studies was only 3–6 mo. When analysing only the studies that had results at 3, 6 and 12 mo (108,111), the clinical additional difference of these studies was higher at 3 mo (10.30 ± 6.98%), 6 mo (7.30 ± 4.23%) and 12 mo (12.76 ± 10.35%). For the overall PPD difference, clinical attachment level difference and BOP difference, the difference was initially less but at 12 mo almost the same as the results with none of the studies excluded. Overall, the studies with a high risk of bias could bias the results. However, more studies will give more conclusive results.

The findings of this meta-analysis should be interpreted with caution because the meta-analysis had some limitations. There were no restrictions for the study population made. In addition, there was only a limited amount of data (13 studies) available. In the 13 studies there were only four different antibiotics used. For AMOX (109,119), DOX (115,120), MET (120) and TET (121) just one or two studies were available compared with 10 studies (108,110–118,120) for the combination MET+AMOX. As yet there is no general consensus on which specific systemic antibiotic should be used. Nearly all the studies had a follow-up period of 6 mo. Unfortu-
nately, just three studies (108,111,116,119) showed the results at 12 mo. As only three studies had a 12 mo follow-up period and because of the previous discussed limited availability of data it is dangerous to give long-term conclusions about the effect of antibiotics.

Since the data of our previous study Keestra et al. (122) were available it was possible to compare the effectiveness of MET+AMOX in chronic vs. patients with aggressive periodontitis. When analysing the data, the PPD difference for moderate pockets in patients with chronic periodontitis was 0.60 ± 0.15 mm at 3 mo, 0.50 ± 0.23 mm at 6 mo and 0.60 ± 0.24 mm at 12 mo. While in patients with aggressive periodontitis, it was 0.43 ± 0.22 mm at 3 mo, 0.50 ± 0.21 mm at 6 mo and 0.89 ± 0.28 mm at 12 mo. The PPD difference for deep pockets in patients with chronic periodontitis was 0.92 ± 0.49 mm at 3 mo, 0.79 ± 0.27 mm at 6 mo and 1.00 ± 0.53 mm at 12 mo. In patients with aggressive periodontitis, the results were 0.88 ± 0.27 mm at 3 mo, 1.09 ± 0.39 mm at 6 mo and 1.40 ± 0.91 mm at 12 mo. The clinical attachment level difference for moderate pockets in patients with chronic periodontitis was 0.42 ± 0.18 mm at 3 mo, 0.33 ± 0.14 mm at 6 mo and 0.40 ± 0.22 mm at 12 mo. While in patients with aggressive periodontitis, it was 0.27 ± 0.19 mm at 3 mo, 0.52 ± 0.15 mm at 6 mo and 0.85 ± 0.39 mm at 12 mo. The clinical attachment level difference for deep pockets in patients with chronic periodontitis was 0.67 ± 0.55 mm at 3 mo, 0.48 ± 0.53 mm at 6 mo and 0.80 ± 0.48 mm at 12 mo. In patients with aggressive periodontitis the results were 0.63 ± 0.25 mm at 3 mo, 0.94 ± 0.28 mm at 6 mo and 1.03 ± 0.84 mm at 12 mo. The number of studies on which these data are based was similar for both periodontal conditions. Based on these data it seems that the effect of MET+AMOX in patients with aggressive periodontitis is lower at 3 mo compared to the effect in patients with chronic periodontitis. However, the effect of MET+AMOX is higher at 6 and 12 mo in patients with aggressive periodontitis than in patients with chronic periodontitis.

In the past 3 years, four systematic reviews have been published about systemic antibiotics in combination with SRP for the treatment of patients with periodontitis. The systematic review from Zanbergen et al. (123) focused on the effect of MET+AMOX in combination with SRP without making the distinction between patients with aggressive periodontitis and patients with chronic periodontitis. Two other reviews from Sgolastra et al. (124) dealt with DOX and MET+AMOX (125) in combination with SRP for the treatment of patients with chronic periodontitis. Only one other review, also from Sgolastra et al. (10), focused on systemic antibiotics in combination with SRP for the treatment of patients with aggressive periodontitis. However, only MET+AMOX was included in the meta-analysis. A disadvantage of the latter meta-analysis is that for calculating the PPD, clinical attachment level and BOP, 3 and 6 mo follow-up data were pooled and used for the meta-analysis. As far as the data of the current meta-analysis can be compared to this meta-analysis, the data appear similar.

In 2014 Preus et al. (11) emphasized that extreme care should be taken when the usage of systemic antibiotics in patients with periodontitis is considered. These authors addressed four items that might be potential caveats in recent reviews (10,123–125). One of these was the overall treatment strategy. In the literature, many different non-surgical periodontal treatment options are available. In Table 2 a subdivision has been made between studies using a full mouth SRP and staged SRP approach. A subanalysis was tried to see if there is a difference in outcome depending on the SRP approach. Regrettably, too few studies were available to make a reasonable conclusion. Additionally, there are no studies available that compared a full mouth SRP and systemic antibiotics to staged SRP and systemic antibiotics. Perhaps further research should focus on the most effective non-surgical periodontal therapy instead of the most effective systemic antibiotic regimen.

The results of this meta-analysis support the additional effect of the usage of systemic antibiotics in patients with aggressive periodontitis. These systemic antibiotics support the immune system by suppressing the target microbial species and causes a delayed microbial infection, better infection control and, in the end, an improved periodontal healing. The widespread usage of systemic antibiotics in the dental practice is not something that should be promoted. Therefore, the clinical additional benefit should be balanced against the side effects such as bacterial resistance, nausea, thrust, gastrointestinal intolerance, antibiotic hypersensitivity, vomiting and diarrhoea. As mentioned in the introduction the WHO (14) and EU (12,13) made some recommendations to prevent bacterial resistance. The bacterial resistance may be a neglected problem, which was already proven in 2005 by Van Winkelhoff. The study showed a major susceptibility difference profile between periodontal pathogens isolated from patients with periodontitis in Spain and the Netherlands (126). Currently it is impossible to define which microbiological profiles would necessitate the use of adjunctive systemic antimicrobials. At the fourth European Workshop on Periodontology, Herrera et al. in 2002 defined these specific clinical situations, as patients with deep pockets, patients with progressive or “active” disease, or with specific microbiological profiles (127). In the consensus statement of the sixth European Workshop on Periodontology, it was posed that the use of systemic antibiotics in periodontitis should be restricted to certain patients and certain periodontal conditions such as in aggressive periodontitis or in severe and progressing forms of periodontitis (9).

Based on the findings of this meta-analysis, systemic antibiotics combined with non-surgical periodontal therapy resulted in a significant additional effect for the treatment of
patients with aggressive periodontitis. Because of the limited availability of different antibiotic regimens with an adequate quantity of studies, there remains only one antibiotic regimen, MET+AMOX. Therefore, it is not possible to draw the conclusion that MET+AMOX is the best performing, but there is a visible trend. The antibiotic regimens AZI, DOX, MET, TET did not show any significant additional effect. The effect of MET+AMOX on patients with aggressive periodontitis is lower at 3 mo but higher at 6 and 12 mo compared to the patients with chronic periodontitis. For long-term stability, more long-term studies are needed to prove the firmness of the additional effect. However, based on currently available data, the clinical benefit of MET+AMOX is not lost over a period of 1 year and even seems to increase. Their prescription, however, should be considered on a case-by-case basis and limited as much as possible, considering the risks of indiscriminate use of systemic antibiotics in the world.

Acknowledgements

This paper has been prepared without any sources of institutional, private or corporate financial support, and there are no potential conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1 PPD reduction.
Table S2 PPD reduction moderate pockets.
Table S3 PPD reduction deep pockets.
Table S4 CAL gain.
Table S5 CAL gain moderate pockets.
Table S6 CAL gain deep pockets.
Table S7 BOP change.

References

Non-surgical periodontal therapy with systemic antibiotics


60. Lindhe J, Liljenberg B, Adielson B et al. Use of metronidazole as a probe in the study of human periodontal dis-
126. van Winkelhoff AJ, Herrera D, Oteo A et al. Antimicrobial profiles of periodontal pathogens isolated from peri-