



# Administration of systemic antibiotics during non-surgical periodontal therapy—a consensus report

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## Abstract

**Aim** The aim of this meta-review was to evaluate whether there is a meaningful clinical benefit regarding the use of systemic adjunctive antibiotics in the treatment of patients with periodontitis. Additionally, a consensus regarding possible recommendations for future administration of antibiotics should be reached.

**Methods** A structured literature search was performed by two independent investigators focusing on systematic reviews (SR) covering adjunctive systemic antibiotics during non-surgical periodontal therapy. Additionally, recent randomized clinical trials (RCT, July 2015 to July 2017) were searched systematically to update the latest SR. Results were summarized and discussed in a plenary to reach a consensus.

**Results** Mostly, systematic reviews and RCTs showed a significant positive effect of adjunctive systematic antibiotics compared to controls. These positive effects gain clinical relevance in patients with severe periodontal disease aged 55 years and younger.

**Conclusion** Systemic antibiotics as an adjunct to non-surgical periodontal therapy should be sensibly administered and restrictively used. Only certain groups of periodontitis patients show a significant and clinically relevant benefit after intake of systemic antibiotics during periodontal therapy.

**Clinical relevance** Avoiding antibiotic resistance and possible side effects on the human microbiome should be a focus of dentists and physicians. Thus, a sensible administration of antibiotics is mandatory. This manuscript suggests guidelines for a reasonable use.

**Keywords** Periodontal therapy · Antibiotic · Adjunctive systemic antibiotics · Non-surgical therapy

## Introduction

Periodontal disease is one of the most common chronic inflammatory diseases in the population [1]. In Germany, 10 to

12 million people are affected by severe cases of periodontitis requiring periodontal treatment [2]. The latest data from the 5th German Oral Health Study revealed prevalence of severe or moderate periodontitis in 64.6% of the younger seniors (65

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B. Pretzl and S. Sälzer contributed equally to this work.

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to 74 years). Even every second (52%) younger adult (35–44 years) is affected by periodontal disease [3]. If periodontitis remains untreated, it leads to a loss of tooth-bearing tissue, an apical migration of the junctional epithelium and ultimately can result in tooth loss [4]. Periodontal diseases cause considerable restrictions of the chewing function, phonetics, and esthetics of the patient and might even be accompanied by impairment in participation of social life [5, 6].

Periodontal inflammation effects not only the integrity and functions of the periodontium locally, but also leads to a significant increase in the systemic inflammatory burden [7]. Epidemiologically, links between presence of periodontal disease and earlier/more frequent occurrence of diabetes mellitus [8, 9], cardiovascular diseases (e.g., coronary heart disease and stroke) [10, 11], chronic respiratory diseases [12], and rheumatoid arthritis [13, 14] have been established. In all these diseases, the pathophysiological correlate is the chronic-systemic inflammatory reaction, the transfer of potentially pathogenic bacteria into the vascular pathway, and the interaction of these pathogens, e.g., with vascular endothelial cells (invasion, inflammation, and endothelial dysfunction). Additionally, an increased concentration of inflammatory mediators in the blood is discussed.

The etiology of periodontitis is closely linked to the manifestation of proinflammatory bacterial dysbiosis [15] through the overgrowth of specific, mostly gram-negative, germs in bacterial biofilms. Therefore, the reduction of the bacterial biofilm must be the aim of any established systematic periodontal therapy. According to general consensus, the treatment of periodontitis comprises the non-surgical, mechanical removal of the inflammation-associated bacterial biofilms from all supra- as well as subgingivally exposed surfaces (teeth and/or direct or indirect restorations) accompanied by a regular domestic cleaning executed by the patient and a recurring professional maintenance care [16]. The vast majority of clinical intervention studies demonstrate a statistically verifiable added benefit for the use of adjuvant administration of systemic antibiotics to increase the effectiveness of mechanical therapy, but their clinical relevance is controversially discussed. However, due to the risk of microbial resistance and the influence on the entire microbiome of the human organism, which is inextricably linked with systemic antibiotic administration, the empiric use of antibiotics has to be critically questioned, especially in view of the added benefit and possible adverse drug reactions possibly arising for the patient. So far, there is no concrete guideline that translates the indication and implementation of the adjunctive systemic antibiotic treatment into evidence-based instructions adapted to clinical requirements based on available data.

The aim of this consensus report is to provide decision guidance on adjunctive administration of systemically effective antibiotics in periodontal therapy. It should be answered, if evidence from studies for the benefit of systemic antibiotics

after mechanical biofilm removal is available and, if so, if information on indication regarding disease severity, antibiotic selection, and comorbidities exists.

## Methods

The methodology for this review follows the criteria of the German Guideline Assessment Instrument (DELBI [17]).

The following focused question should be answered:

Are there differences in the outcome of subgingival scaling and root planning during systematic periodontal therapy in patients with periodontitis (P) with adjunctive systemic antibiotic therapy (I) as compared to controls without adjunctive systemic antibiotic therapy (C) regarding

- the primary outcome: reduction of probing pocket depths (PPD) (O)
- secondary outcomes:

Attachment gain/loss

Bleeding on probing (BOP)

Periodontal inflamed surface area (PISA) [18]

And subjective parameters like oral health-related quality of life (OHRQoL)

To answer this question, existing guidelines as well as systematic reviews (SR) were searched. Furthermore, randomized clinical trials (RCT) were searched to update the latest SR.

Guidelines were searched internationally. Using the terms “periodontitis” or “periodontal” or “periodont” or “antibiotics” in the Guideline International Network (GIN), Scottish Intercollegiate Guideline Network (SIGN), National Institute for Health and Clinical Excellence (NICE), National Guideline Clearinghouse (NGC), or German Council for International Organizations of Medical Sciences (AWMF) revealed three guidelines addressing periodontitis and antibiotics:

1. American Academy of Periodontology (AAP): Position Paper “Systemic antibiotics in periodontics” (2005)
2. American Dental Association (ADA):
  - a. “The use of systemic antibiotics in the treatment of refractory periodontitis” (2016)
  - b. “Evidence based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planning with or without adjuncts” (2015)

None of them focused on reduction of periodontal probing depths. Thus, in September 2017, no existing guideline had to be taken into account.

Two electronic databases (PubMed, Web of Knowledge) were searched without any restriction of language by two independent reviewers (BP, SS). The following search term was used to identify relevant meta-analyses:

(((((((((“Periodontitis”[Mesh]) OR “Periodontal Diseases”[Mesh]) OR “Chronic Periodontitis”[Mesh]) OR “Aggressive Periodontitis”[Mesh] OR periodontitis) OR periodontal disease)))) AND (((((((“Debridement”[Mesh]) OR “Dental Scaling”[Mesh]) OR “Root Planing”[Mesh]) OR “debridement” OR “Scaling” OR “root planing”))) AND (((((((((((((((“Anti-Infective Agents”[Mesh]) OR “Anti-Bacterial Agents”[Mesh]) OR “Amoxicillin”[Mesh]) OR “Metronidazole”[Mesh]) OR “Doxycycline”[Mesh]) OR “Penicillins”[Mesh]) OR “Ampicillin”[Mesh]) OR “Clindamycin”[Mesh]) OR “Ciprofloxacin”[Mesh]) OR “antibiotic” OR “Anti-Infective Agents”) OR “Anti-Bacterial Agents”) OR “Amoxicillin”) OR “Metronidazole”) OR “Doxycycline”) OR “Penicillins”) OR “Ampicillin”) OR “Clindamycin”) OR “Ciprofloxacin”)))))) AND (Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb]).

In order to detect relevant randomized clinical studies, the following search term was applied:

(((((((((((((“Periodontitis”[Mesh]) OR “Periodontal Diseases”[Mesh]) OR “Chronic Periodontitis”[Mesh]) OR “Aggressive Periodontitis”[Mesh] OR periodontitis) OR periodontal disease)))) AND (((((((“Debridement”[Mesh]) OR “Dental Scaling”[Mesh]) OR “Root Planing”[Mesh]) OR “debridement” OR “Scaling” OR “root planing”))) AND (((((((((((((((((((“Anti-Infective Agents”[Mesh]) OR “Anti-Bacterial Agents”[Mesh]) OR “Amoxicillin”[Mesh]) OR “Metronidazole”[Mesh]) OR “Doxycycline”[Mesh]) OR “Penicillin”[Mesh]) OR “Ampicillin”[Mesh]) OR “Clindamycin”[Mesh]) OR “Ciprofloxacin”[Mesh]) OR “antibiotic” OR “Anti-Infective Agents”) OR “Anti-Bacterial Agents”) OR “Amoxicillin”) OR “Metronidazole”) OR “Doxycycline”) OR “Penicillins”) OR “Ampicillin”) OR “Clindamycin”) OR “Ciprofloxacin”)))))))) AND (“2017”[Date-Publication]: “2015”[Date-Publication])) AND randomized controlled clinical trial).

The following inclusion criteria, which had been defined in advance, had to be fulfilled:

- Patients with periodontitis
- Adjunctive systemic antibiotics
- Control group that did not receive adjunctive antibiotics
- Randomization
- Focusing on primary and secondary outcomes as mentioned above
- Blinded examiners
- Meta-analysis conducted (in reviews)

Research on patients, who had received *only* surgical therapy, was excluded.

In case one of these criteria was missing, the respective meta-analysis or clinical study was excluded. If multiple manuscripts on the same study population were published, only the first publication was included.

All publications fulfilling the inclusion criteria were screened independently by two individuals (BP and SS) according to the *Scottish Intercollegiate Guidelines Network (SIGN)* ([http://www.sign.ac.uk/assets/checklist\\_for\\_controlled\\_trials.doc](http://www.sign.ac.uk/assets/checklist_for_controlled_trials.doc)). Then, a methodological evaluation followed and a meta-review was prepared. Using this information, a first draft of the guideline was prepared by another author (YJS) and circulated before the consensus conference took place.

A peer review panel by periodontal as well as statistical experts (among them: PE) examined the consensus paper, revised it, and judged it according to the DELBI criteria [17].

The draft was circulated in the consensus group prior to the consensus conference and discussed there. Changes and suggestions of the panel were incorporated, if the majority agreed. Finally, the draft was presented to the entire consensus conference and a voting on each item took place.

## Results

### Systematic reviews

Figure 1 shows a flow chart of the search strategy. Two hundred ninety-six manuscripts could be identified. After exclusion of 222 papers by title and 46 by abstract, 28 manuscripts were fully read by two authors (BP and SS). Then, further nine publications were dismissed. Of the 19 selected manuscripts, seven focused on chronic periodontitis (ChP), four on aggressive periodontitis (AgP), and eight on both ChP and AgP. Two papers centered on smokers, two on diabetic subjects.

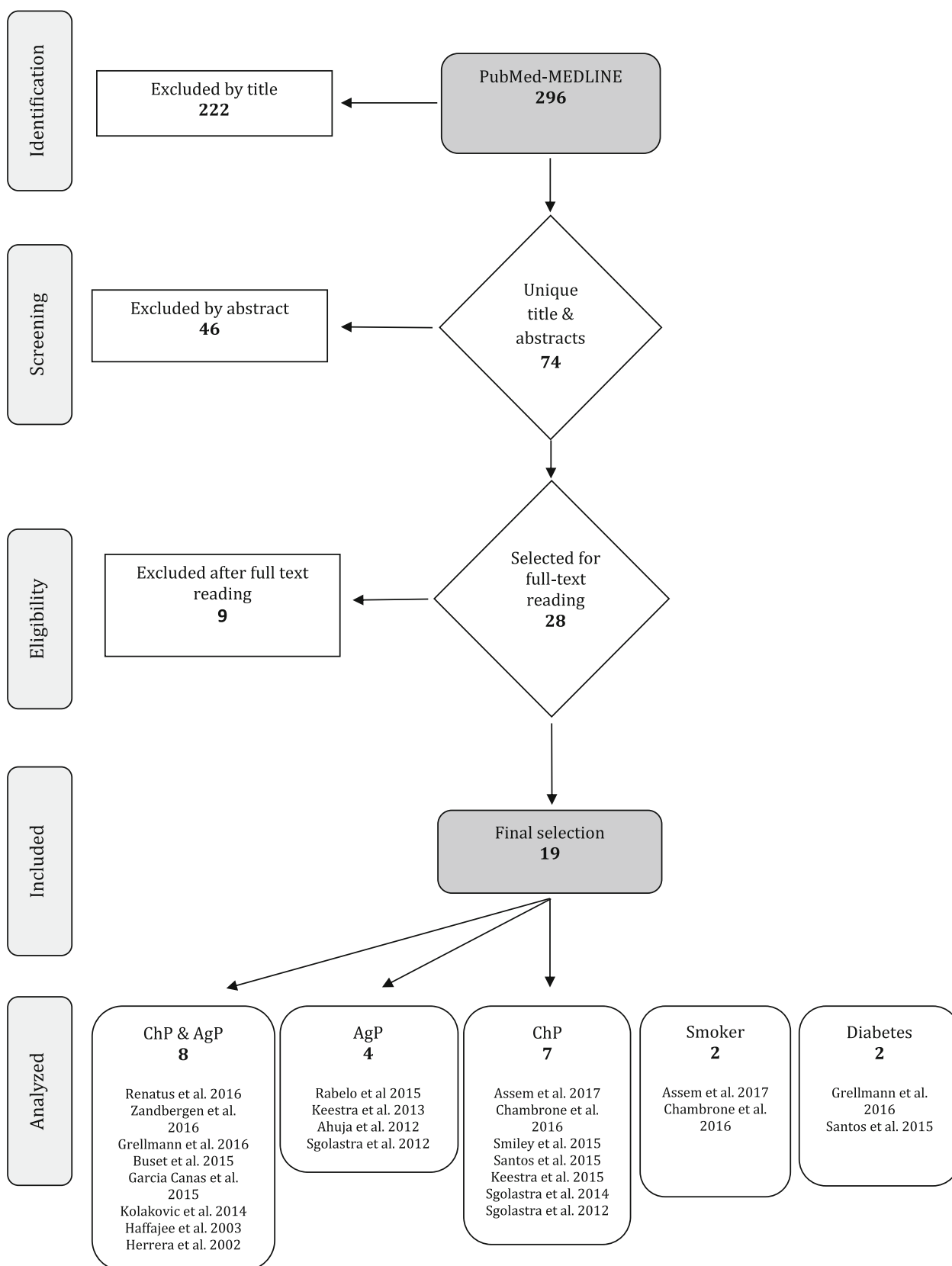
Study selection by title screening reached an accordance of  $\kappa = 0.94$ , selection by abstract an accordance of 100%. Differences were resolved via discussion. All selected systematic reviews are listed in Table 1 [19–36].

In the included reviews, additional reductions in PPD and CAL due to supplementary systemic antibiotics could not be detected or were rather small and reached (weighted) mean differences ranging from 0.18 to 1.26 mm (PPD) and 0.08 to 1.0 mm (CAL). A positive effect of systemic antibiotic use regarding BOP could not be detected in some analyses, and reached 1.9 to 12.76% in others.

Table 2 lists the excluded manuscripts and reasons for exclusion.

### Randomized clinical trials

Figure 2 illustrates the search strategy. Out of 50 potential manuscripts (published between November 2015 and



**Fig. 1** Flow chart of search strategy (systematic reviews)

**Table 1** Overview of included systematic reviews

Focus	Author (year)	Participants # Antibiotics	Mode of analysis	PPD	CAL	BOP	Other
AgP and ChP	Renatus et al. 2016	178 ChP and AgP patients Azithromycin	Descriptive statistics	Treatment group (TG, SRP + AZM) and control group (CG, SRP) both exhibited significant improvements in the values recorded with a greater clinical improvement in TG compared with CG		PI values improved in all studies in 2 studies CG achieved better values, in 3 studies TG recorded better values	
AgP and ChP	Zandbergen et al. 2016	776 ChP and AgP patients Amox/Met	Meta-analysis with WMD	Mean additional reduction of PPD, (DiffM $-0.47$ mm, $p < 0.00001$ ) Sites with baseline PPD $\geq 6$ mm also showed significant difference (DiffM $-0.86$ , $p < 0.00001$ )	Mean CAL gain (DiffM $+0.33$ mm, $p < 0.00001$ )	Significantly better outcomes at end trial regarding full-mouth BOP (DiffM $-6.98\%$ , $p = 0.0001$ )	No major side effects associated with the intake of Amox/Met were reported
AgP and ChP	Buset et al. 2015	338 ChP and AgP patients Azithromycin	Descriptive analysis with vote counting	In contrast to aggressive periodontitis patients, data from this analysis indicate a potential benefit of systemic azithromycin as adjunctive to non-surgical periodontal therapy in chronic periodontitis patients		Minor adverse events were reported in 5 studies	
AgP and ChP	Garcia Canas et al. 2015	1297 ChP and AgP patients Amox/Met, AZM, Clarithromycin, Doxycycline, Met, Moxifloxacin	Descriptive analysis with vote counting	Owing to the high level of heterogeneity of the studies included in this review, the authors could not establish definitive conclusions and guidelines regarding the use of adjunctive systemic antibiotics. However, within the limitations of this review, the use of systemic antibiotics with SRP may be beneficial for specific populations. Standardized clinical disease diagnostic criteria and additional randomized controlled clinical trials are necessary to verify the effectiveness of the use of adjunctive systemic antimicrobials with SRP			
AgP and ChP	Kolakovic et al. 2014	703 ChP and AgP patients Amox/Met	Meta-analysis with WMD	We observed the most significant improvement in CAL in studies whose investigators used AZM and a combination of Amox with Met The best improvement in PPD was reported with the use of AZM, and, in the case of BOP, the best improvement was reported with the use of AM with M. In this review, we noted an optimum effect in deep pockets (greater than 6 mm) in patients with ChP and in all cases of AgP			
AgP and ChP	Haffajee et al. 2003	763 ChP and 239 AgP patients, abscesses Amox, Met, Amox/Met, C.A., Clindamycin, Doxycycline, Tetracycline	Meta-analysis	Amox/Met with SRP increased the chance of pocket closure by a factor of 3.55 3 months after therapy and a 4.43-fold chance 6 months after treatment, but failed to show a benefit regarding the possible avoidance of surgical interventions Mean PPD changes favored test over control in 78%	Mean AL changes favored test over control in shallow ( $< 4$ mm), intermediate (4 and 5 mm or 4 to 6 mm), and deep pockets (87%, 80%, and 83%, respectively)		
AgP and ChP	Herrera et al. 2002	AgP and ChP Tetracycline, Spiramycin, Amox/Met, Met	Meta-analysis	Statistically significant additional effect of Spiramycin with regard to PPD change for initial PPD $> 6$ mm	Significant effect of Amox/Met with regard to CAL change, for initial PPD $> 6$ mm	No differences for BOP or GI between test and control groups	
AgP	Rabelo et al. 2015	388 AgP patients Doxycycline, Met, Clindamycin, Amox/Met, Azithromycin	Bayesian network meta-analysis with WMD	SRP plus systemic antibiotics led to an additional clinical effect compared with SRP alone in the treatment of AgP Most consistent advantages—reduction in PPD and CAL gain—were attained with the use of Met and Amox/Met	Effect of Met close to significance		
AgP	Keestra et al. 2015	386 AgP patients AZM, Doxycycline, Met, Amox/Met, Tetracycline	Meta-analysis	Significant ( $p < 0.05$ ) additional reduction for moderate (0.36 mm at 3 mo, 6 mo 0.42 mm, and 12 mo 0.88 mm) and deep pockets (0.74 mm at 3 mo, 6 mo 0.85 mm, and 12 mo 1.26 mm). It seems that the effect of	Significant gain for moderate (0.26 mm at 3 mo, 0.52 mm at 6 mo, and 0.83 mm at 12 mo) and deep pockets (0.59 mm at 3 mo,	Significant mean difference of 9.38% in 219 patients at 3 mo and of 12.76% in 65 patients at 12 mo	

**Table 1** (continued)

Focus	Author (year)	Participants # Antibiotics	Mode of analysis	PPD	CAL	BOP	Other
AgP	Ahuja et al. 2012	107 gAgP patients Amox/Met	3 RCTs	the antibiotics on PPD remains stable for at least 1 year	0.96 mm at 6 mo, and 1.00 mm at 12 mo) Effect of antibiotics on CAL seems stable for at least 1 year	Effect of antibiotics on BOP seems stable for at least 1 year	
AgP	Sgolastra et al. 2012	181 gAgP patients Amox/Met	Meta-analysis	No study data could be pooled for statistical process to decipher the efficacy of antibiotics prescribed along with SRP against aggressive periodontitis in human beings Significant PPD reduction (MD, 0.58; 95% CI, 0.39 to 0.77; $p < 0.05$ )	Significant CAL gain (MD, 0.42; 95% CI, 0.23 to 0.61; $p < 0.05$ )		No significant occurrence of adverse events (RD, 0.01; 95% CI, -0.02 to 0.04; $p > 0.05$ )
Diabetes	Santos et al. 2015	776 ChP and AgP patients with diabetes Doxycycline, AZM, Amox/Met	Meta-analysis WMD	Significant effect favoring SRP plus antibiotic for reductions in mean PPD (-0.22 mm [-0.34, -0.11])	No significant effect for CAL gain and plaque index reduction	Significant effect favoring SRP plus antibiotic for reductions in mean percentage of BoP (4% [-7, -1])	No significant effect for CAL gain and plaque index reduction
ChP and diabetes	Grellmann et al. 2016	ChP patients with diabetes Amox, Clavulanic Acid, Doxycycline, AZM, Amox/Met	Meta-analysis WMD	End-of-trial PPD and CAL values showed statistically significant differences in reduction between the test and control groups [-0.19 mm, $n = 12$ , $p = 0.002$ , 95% CI, -0.31 to -0.07 and -0.24 mm, $n = 10$ , $p = 0.04$ , 95% CI, -0.47 to 0.02, respectively] favoring adjunctive systemic antibiotic therapy over SRP alone		WMDs in BOP and PI reductions of -1.91% ( $n = 7$ , $p = 0.39$ , 95% CI, -6.32 to 2.51) and 4.01% ( $n = 7$ , $p = 0.05$ , 95% CI, -0.04 to 8.07), respectively, did not favor adjunctive systemic antibiotics	
ChP	Smiley et al. 2015	1086 ChP patients Amox/Met, Met, AZM, Carithromycin, Moxifloxacin, Fluoroquinolone, Tetracycline, Doxycycline	Meta-analysis WMD	Panel found approximately 0.5-mm average improvement in CAL with SRP. SRP plus systemic antimicrobials resulted in a 0.35-mm mean gain in CAL (95% CI, 0.20-0.51)			
ChP	Keestra et al. 2015	1506 untreated chP patients Amox, Met, Tetracycline, Clavulanic Acid, Doxycycline, Moxifloxacin, AZM	Meta-analysis of 43 RCTs	Significant ( $p < 0.05$ ) additional reduction for moderate (at 3 mo 0.27 mm; at 6 mo 0.23 mm, and at 12 mo 0.25 mm) and deep pockets (at 3 mo 0.62 mm, at 6 mo 0.58 mm, and at 12 mo 0.74 mm) Effect of antibiotics on PPD seems stable for at least 1 year	Statistically significant gain of 0.20 mm at 3 mo, and of 0.10 mm at 12 mo Effect of antibiotics on CAL was relatively low and almost lost over 1 year	Statistically significant mean difference of 5.39% at 3 mo; statistically significant mean difference of 3.80% at 12 mo Initial effect of antibiotics on BOP difference was relatively low but remained stable over a 1-year period	
ChP Met	Sgolastra et al. 2014	450 ChP patients Met	Meta-analysis of 6 RCTs	Significant reduction in PPD present in favor of SRP + Met when compared to SRP alone (MD, 0.18; 95% CI, 0.09-0.28; $p < 0.05$ )	Significant difference in favor of SRP + Met observed in terms of CAL gain (MD, 0.10; 95% CI, 0.08-0.12; $p < 0.05$ )	Significant reduction in BOP present in favor of SRP + Met when compared to SRP alone (MD, 8.74; 95% CI, 3.23-14.24; $p < 0.05$ )	No significant difference in reduction of suppuration (MD, 0.69; 95% CI, -0.96 to 2.34; $p > 0.05$ )



**Table 1** (continued)

Focus	Author (year)	Participants # Antibiotics	Mode of analysis	PPD	CAL	BOP	Other
ChP Amox/Met	Sgolastra et al. 2012	414 ChP patients Amox/Met	Meta-analysis	PPD reduction (WMD = 0.43; 95% CI = 0.24 to 0.63; $p < 0.05$ ) in favor of SRP + Amox/Met	Significant CAL gain (WMD = 0.21; 95% CI = 0.02 to 0.4; $p < 0.05$ )	No significant differences found for BOP (WMD = 10.77; 95% CI = -3.43 to 24.97; $p > 0.05$ )	No significant differences were found for suppuration (WMD = 1.77; 95% CI = -1.7 to 5.24; $p > 0.05$ )
ChP and smokin-g	Assem et al. 2017	127 ChP patients, smokers Met, Amox/Met, AZM	Meta-analysis WMD	Statistically significant PPD reduction in favor of systemic antibiotics (-0.21 mm vs. -0.42 mm MD, $p < 0.05$ )	Statistically significant CAL gain (-0.22 mm vs. -0.39 mm MD, $p < 0.05$ )	No statistically significant difference in BOP between treatments (-4% vs. -0.13% MD, $p > 0.05$ )	
ChP and smokin-g	Chambrone et al. 2016	148 ChP patients, smokers AZM, Met, Doxycycline	Meta-analysis WMD	No significant differences for PPD reduction (WMD 0.18; 95% CI, -0.02 to 0.37; $p = 0.07$ , I <sup>2</sup> = 0%)	No significant differences for CAL gain (WMD 0.08; 95% CI, -0.21 to 0.36; $p = 0.60$ , I <sup>2</sup> = 0%)		

AgP, aggressive periodontitis; gAgP, generalized aggressive periodontitis; ChP, chronic periodontitis; PPD, probing pocket depth; (C)AL, (clinical) attachment level; BOP, bleeding on probing; AZM, Azithromycin; Amox, Amoxicillin; Met, Metronidazole; WMD, weighted mean difference; CI, confidence interval; mo, months

**Table 2** Excluded systematic reviews and reasons for exclusion

John et al. 2017	Complementary to Smiley et al. 2015
Fritoli et al. 2015	Only comparison of different time points of administration
Faggion et al. 2014	Meta-review
Gomez Muniz et al. 2013	Control group in some cases Amox/Met Narrative review
Zandbergen et al. 2013	Complementary to Zandbergen et al. 2016
Moreno Villagrana et al. 2012	Prophylactic antibiotics as well as host modulation therapy
Herrera et al. 2012	Narrative review
Angaji et al. 2010	4 RCTs with antimicrobials, low-dose antibiotics, at least 1 with surgery
Bonito et al. 2004	Surgery included

July 2017), 35 were excluded by title, and a further four by abstract. Five publications were dismissed after full-text reading. Of the six selected randomized clinical trials (RCTs), two focused on ChP, three on AgP, and one on both ChP and AgP. None centered on smokers or diabetics.

Reviewer agreement reached 100% in each step of selection.

All selected RCTs are shown in Table 3 [37–42], excluded RCTs as well as reasons for exclusion are listed in Table 4.

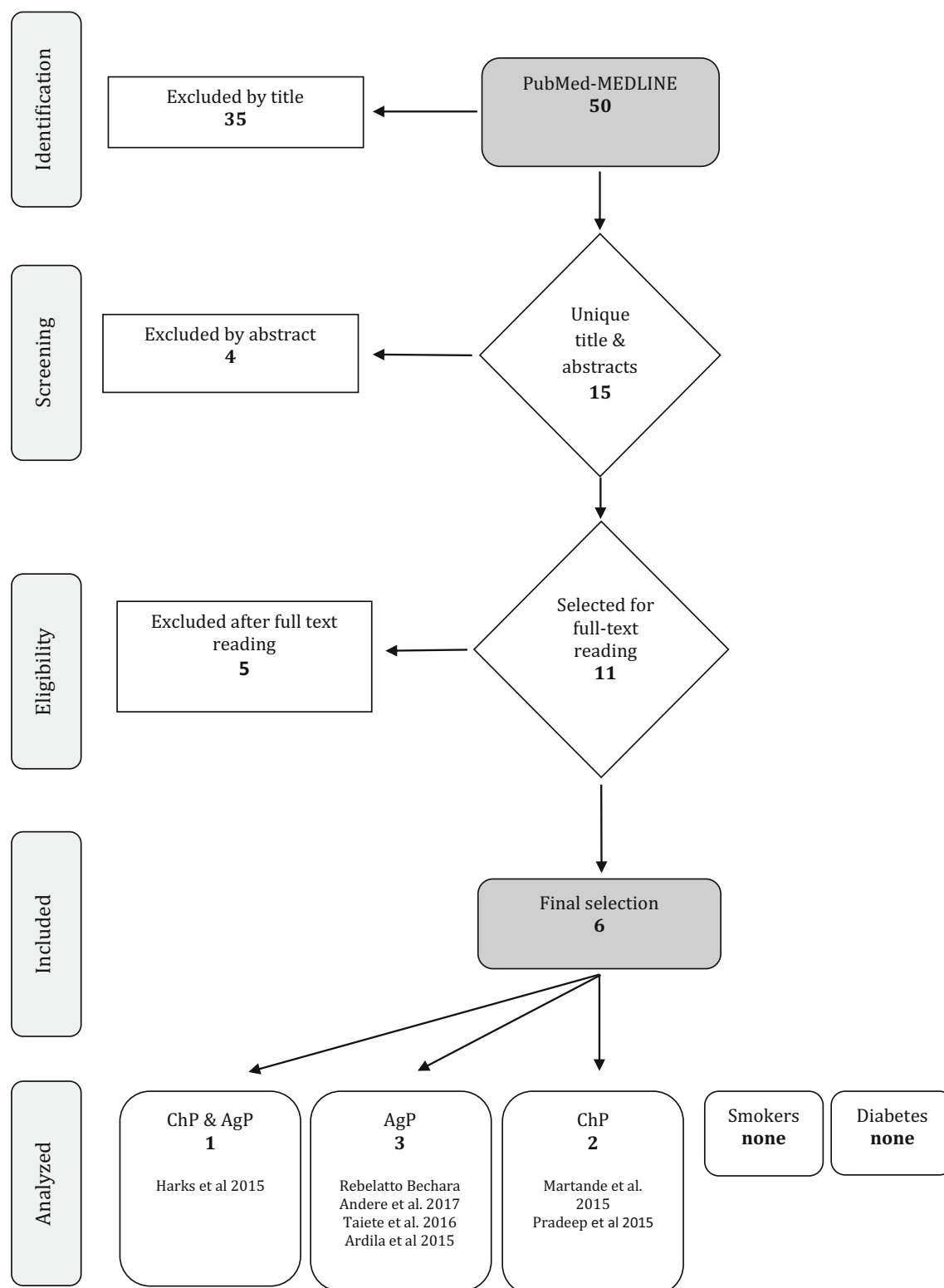
## Recommendations and statements

In order to diagnose a periodontal disease, an adequate anamnesis as well as periodontal status including PPD, clinical attachment levels (CAL), and BOP shall be performed. Adjunctive systemic antibiotics shall only be considered, if severity and extent of the disease as well as history of medication are taken into account.

Adjunctive systemic antibiotics shall only be taken simultaneous to mechanical removal of supra- and especially subgingival bacterial biofilms. There is indirect evidence that adjunctive systemic antibiotics should be initiated in direct context with mechanical debridement (full-mouth scaling) [26, 44].

In periodontitis patients younger than 56 years of age exhibiting PPDs  $\geq 5$  mm in at least 35% of sites, systemic antibiotics can be administered parallel to non-surgical periodontal therapy. Patients with periodontitis aged 56 or more should not take systemic antibiotics, a priori. In patients showing no PPDs  $> 4$  mm or PPDs  $> 4$  mm in less than 35% of sites, a primary systemic antibiotics should not be considered [27, 33–35, 38].

In patients younger than 36 years of age or patients formerly diagnosed with AgP, a systemic antibiotics in the context of mechanical subgingival plaque removal should be performed [21, 23, 28, 30, 34, 37, 41]. It has to be kept in mind that all included systematic reviews and RCTs used the classification of 1999 (or even the one before that). Thus, patients diagnosed with AgP had to have attachment or radiographic bone loss at



**Fig. 2** Flow chart of search strategy (randomized and controlled clinical trials) from July 2015 to July 2017

more than two non-adjacent sites. Using the new classification of 2017 [43], patients 36 years or younger should at least exhibit at least a periodontitis stage II.

Administration of systemic adjunctive antibiotics in the context of full-mouth scaling is not to be based on BOP incidence, alone [20, 24, 26–28, 32–34, 36, 37].



**Table 3** Overview of included randomized and controlled clinical trials

Authors (year) Periodontal disease Patients	Study design, Duration	Subject baseline (end) Gender Age in years	Intervention, type of antibiotics, and application + time point	PPD	CAL	BOP	Other
Rebelatto Bechara Andare 2017 AgP Non-smokers	Parallel, randomized double-blind, placebo--controlled	40 Male and female 31.12 years At least 20 teeth familiar aggregation	Test (20) one-stage FM ultrasonic debridement + clarithromycin 2/d for 3 days Control (20) + placebo	Clarithromycin group showed a mean PPD reduction of $0.81 \pm 0.4$ , (placebo group of $0.67 \pm 0.4$ ) after 6 mo ( $p = 0.7$ ) and lower means of pocket depth at 6 mo ( $4.0 \pm 1.7$ ) when compared to placebo ( $4.7 \pm 1.3$ ) ( $p = 0.04$ )	Both groups showed full-mouth CAL gain (no additional benefits in CLM) Mean CAL gain in CLM group compared to control group were $0.77 \pm 0.4$ and $0.60 \pm 0.4$ ( $p = 0.3$ ), respectively	No statistically significant difference regarding BOP	FMPI for both groups low during the entire study period 2 from CLM group reported gastrointestinal discomfort Optimum dosage of CLM questionable
Taiete 2016 AgP	Double-blind placebo--controlled RT 6 mo	48 (39) Female (69%) 28 years At least 20 teeth	Test (24/21) SRP + Amox (375 mg) and Met (250 mg) 3/d 7 days Control (24/18) SRP + placebo	Significant improvement at 6 mo with no significant differences between groups apart from PPD in deep pockets (at least 6 mm)			No adverse events reported Statistics?
Harks 2015 Moderate to severe ChP and AgP	Prospective double-blind, placebo--controlled Multi-center RT 27.5 mo	506 (445) Male and female At least 10 teeth	Test (251/215) Amox 500 mg plus MET 400 mg (3 $\times$ /day, 7 days) Control (255/230) placebo Supra- and subgingival debridement within 24 h	Median percentage of sites showing attachment loss (PSAL) $\geq 1.3$ mm was 7.8% (Q254, 7% Q75 14.1%) in placebo versus 5.3% (quartile 25 3.1% quartile 75 9.9%) in antibiotic group Oral health impact profile (OHIP) scores decreased in course of study to $32.2 \pm 29.4$ and $32.9 \pm 29.4$ for placebo and antibiotic patients with mean changes of $-5.5 \pm 21.3$ and $-11.0 \pm 26.1$ , respectively Both treatments were effective in preventing disease progression. Compared to placebo, prescription of empiric adjunctive systemic antibiotics showed a small absolute, although statistically significant, additional reduction in further attachment loss Both therapeutic approaches were very effective and absolute clinical differences between placebo and antibiotic groups were small 90 serious adverse events (SAE), 39 in the placebo and 43 in the antibiotic group reported. 8 SAE occurred prior to medication intake. 7 patients dropped out due to un-blinding following an SAE occurrence. 1 case of anaphylactic reaction related to the study medication (antibiotic group) reported			
Ardila 2015 gAgP Non-smokers	Tripleblind placebo--controlled RT 6 mo	40 17 m/ 23 f 28.4 years (test) 26.4 (control) At least 20 teeth Familiar aggregation	Test (20) one-stage SRP combined with systemically administered moxifloxacin 400 mg once daily for 7 days Control (20) one-stage SRP + placebo	Both groups resulted in significant reduction of PPD and CAL compared with baseline, this was maintained at 6 months. Differences between treatments were statistically significant at 3 and 6 mo, favoring Moxifloxacin.			No adverse event reported Results suggest that Moxifloxacin as an adjunct to one-stage full-mouth SRP leads to better clinical and microbiological advantages
Martande et al. 2015 chP Non-smokers	Placebo-controlled RT 6 mo	70 38 m/32 f 36.4 years (test) 37.2 years (control)	Test (32) one-stage SRP combined with systemically administered roxithromycin 300 mg once daily for 5 days	Both groups showed improved clinical parameters over 6 months Roxithromycin group showed a statistically significant gain in PPD and CAL compared to test			Both groups showed improved clinical parameters over 6 months No significant differences regarding BOP, PI, or GI at any time point

**Table 3** (continued)

Authors (year) Periodontal disease Patients	Study design, Duration	Subject baseline (end) Gender Age in years	Intervention, type of antibiotics, and application + time point	PPD	CAL	BOP	Other
Pradeep et al. 2015 ChP Non-smokers	Double-blind placebo--controlled RT 6 mo	70 patients (65) Male and female 35.78 years At least 15 teeth At least 30% of the sites with PPD, CAL $\geq 5$ mm, BoP	Control (30) one-stage SRP + placebo Test (33) SRP and Levofloxacin 500 mg, once daily [o.d.] Control (32) SRP and placebo, o.d. 10 days	Patients receiving LFX showed statistically significant improvements in mean PPD and CAL		The intergroup difference in PI, GI, and %BoP not significant at any interval	Difference in PI, GI, and %BoP not significant at any interval 3 participants (1 male and 2 female) in test group reported dizziness, 1 reported diarrhea and lightheadedness Discrepancies regarding age and gender in M&M and Results section—reliability?

AgP, aggressive periodontitis; Amox, Amoxicillin; ChP, chronic periodontitis; Met, Metronidazole; PPD, probing pocket depth (TST); CAL, clinical attachment level; BOP, bleeding on probing; mo, months

**Table 4** Excluded randomized and controlled clinical trials and reasons for exclusion

Li et al. 2017	No randomization
Haas et al. 2016	Secondary analysis of a previously published randomized controlled trial (Haas et al. 2008)
Tamashiro et al. 2016	Follow-up of Miranda et al. 2014
Ardila & Guzman 2016	Multi-level analysis of Ardila et al. 2015
Preus et al. 2015	Clinical results already published in 2013

No specific recommendations can be given for patients with diabetes regarding adjunctive systemic antibiotics during non-surgical anti-infective therapy. The above-mentioned recommendations should be applied [24, 32].

For periodontitis patients regularly consuming tobacco (smoking, chewing), no specific recommendations can be given. In these patients, the guidelines mentioned above can be followed [20, 22].

The strongest favorable evidence regarding intake of systemic antibiotics in the context of subgingival mechanical plaque removal and their safety exists for the combination of Amoxicillin and Metronidazole [19, 23, 25–27, 29, 30, 32–36, 38, 45]. Alternatively, systemic antibiotics adjunctive to mechanical subgingival plaque removal can be provided with Metronidazole only [23, 25, 26, 28, 30, 32, 33, 35, 45].

A possible effect of adjunctive systemic antibiotics could neither be found regarding an impact on oral health-related quality of life nor on the reduction of the periodontally inflamed surfaces area quantified by the PISA index.

## Discussion

In general, health professionals should always be aware of the possibility of antibiotic resistance and potential negative effects of antibiotics on the human microbiome. Thus, a sensible and restricted use of antibiotics is called for. Compared to planktonic cells, the effectiveness of antibiotics is significantly reduced in biofilms. An essential prerequisite for the use of adjunctive systemic antibiotics during periodontal therapy is the mechanic disruption of the integrity of the subgingival biofilm and its reduction during full-mouth scaling. In addition, the necessary effect concentration in periodontal pockets can hardly be reached without disaggregating subgingival plaque mechanically [44].

Regarding the time point of systemic antibiotic administration, in vitro data suggest a rise of antibiotic tolerance in biofilms 24 h after initial colonization calling for adjunctive systemic antibiotics within hours after full-mouth scaling.

In the majority, data from meta-analyses and RCTs showed a significant additional benefit with regard to PPD reduction and CAL gain when adjunctive systemic antibiotics were administered in addition to mechanical biofilm removal compared to

non-surgical therapy alone. But the clinical relevance of this gain should be questioned especially in mild and moderate disease. Thus, diagnosis of periodontitis alone should not indicate administration of systemic antibiotics [27, 33–35, 38].

A sub-analysis of data from Harks et al. [38] shows a clinically relevant adjunctive effect of systemic antibiotics parallel to full-mouth scaling in certain age and severity groups: 27.5 months after subgingival debridement in patients exhibiting PPDs  $\geq 5$  mm in 35% or more of sites, administration of adjunctive systemic antibiotics showed a clinically relevant reduction in percentage of sites with further attachment loss compared to controls. Additionally, patient's age proved to impact upon further attachment loss in the test compared to the placebo group: in patients 55 years or younger, adjunctive systemic antibiotics combined with full-mouth scaling leads to a significant and clinically relevant reduction of sites with further attachment loss 27.5 months after therapy.

In patients aged 35 years and younger (formerly diagnosed with aggressive periodontitis), all meta-analyses, RCTs, and CCTs showed a relevant additional benefit of adjunctive systemic antibiotics compared to subgingival debridement alone [21, 23, 30, 34, 37, 41]. This conforms to data in patients with diagnosis of chronic periodontitis, showing a relevant benefit in younger patients with severe forms of periodontitis [38].

Choosing the correct antibiotic as an adjunct to full-mouth scaling is not an easy task: out of more than 700 phylotypes living in the oral cavity, some species are detected more often in periodontitis patients [46]. Only few of these species can routinely be identified via commercially available test kits, whereas the pathogenic relevance of other bacteria is unclear. Thus, choosing an adjunctive systemic antibiotic based on microbial testing does currently not seem reasonable [47–49]. The evaluated systematic reviews and RCTs cover multiple antibiotics in different study designs showing mostly a small positive effect of test versus control group. Due to the plurality of the trials and the numerous antibiotic agents used, no specific recommendation for any antibiotic or combination of antibiotics can be given. But, most evidence exists for the combination of Amoxicillin and Metronidazole, Metronidazole alone, and Azithromycin.

## Conclusion

Systemic antibiotics as an adjunct to non-surgical periodontal therapy should be sensibly administered and restrictively used. Only certain groups of periodontitis patients show a significant and clinically relevant benefit after intake of systemic antibiotics during periodontal therapy.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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