

# DUAL ANTIBIOTIC SYSTEMIC THERAPY IN THE TREATMENT OF PERIODONTAL DISEASES AND THE ROLE OF METRONIDAZOLE

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## Abstract

**INTRODUCTION:** Periodontitis is an inflammatory disease of bacterial origin, which affects the supporting tissues of the tooth. There are a number of procedures and protocols aimed at the prevention of the progression of the lesion and maintaining current status of periodontal tissues. To support such procedures, in addition to monotherapy with antibiotics, dentists frequently use a combination of antibiotics, known as the dual antibiotic therapy. Among the pharmacological therapeutic options, with metronidazole and its combinations with other antibiotics, positive results are obtained in managing the disease.

**OBJECTIVE:** This study aims to assess the role and advantages of dual systemic antibiotic therapy, one of the antibiotics being Metronidazole, in the treatment of periodontal disease, compared with other treatment options.

**MATERIALS AND METHODS:** A retrieval of on-line scientific literature up to 31 January 2017 was conducted in the US National Library of Medicine (PubMed) on clinical studies for periodontitis. Inclusion criteria for the selection of studies were: published in English, controlled clinical trials in humans, and cohort studies of > 1 month duration with a comparison group; subjects with aggressive or chronic periodontitis who received two antibiotics. The final selection was independently completed by the two reviewers reading the selected articles, and their results were compared.

**RESULTS:** After an initial selection, 79 papers were identified by the electronic search; 18 papers met the inclusion criteria. Total study population was 1261; 1086 with ChP and 175 with AgP. The most common parameter evaluated was pocket depth (PD) assessed in 13 studies, followed by bleeding on probing in 9 studies and clinical attachment level (CAL) in 8 studies. In almost all of the studies, systemically administered antibiotics exhibited a more positive attachment level change than the control group in the study. The shortest therapy regimen was determined 3 days and the longest regimen was 4 weeks.

**CONCLUSIONS:** Analyzed data showed that systemically administered adjunctive antibiotics with and without SRP and/or surgery appeared to provide a greater clinical improvement in attachment levels than therapies not employing these agents. The use of metronidazole and amoxicillin in patients with aggressive periodontitis showed statistically significantly higher PD reduction and lower number of pockets  $\geq 7$  mm compared to only SRP (Scaling and Root Planning). Administration immediately after initial SRP provides more PD reduction and CAL "gain" in initially deep sites than late administration of SPT (Supportive Periodontal Therapy) with reinstrumentation after 3 months. Literature suggests that metronidazole can also be used in combination with ciprofloxacin. This is a very powerful combination against mixed and resistant infections.

**KEYWORDS:** metronidazole, periodontitis, dual therapy.

## Introduction

Periodontitis is an inflammatory disease of bacterial origin, which affects the supporting tissues of the tooth. It constitutes one of the most frequent bacterial infections in adults. There are hundreds of bacterial species associated with this disease, and this fact makes it more complicated the achievement of a successful specific therapy for periodontitis (Paster et al, 2001). Among these, the most relevant are Aggregate bacter *Actinomyces comitans* (A.a.), *Porphyromonas gingivalis*, *Treponema Denticola*, *Fusobacterium Nucleatum*, *Prevotella Intermedia*, *Campylobacterium Rectus* and *Eikenella Corodens* (Nishihara et al, 2004, Feng et al, 2006). *P. Gingivalis* is considered as the main cause of chronic periodontitis, though no less important is the A.a., which is recognized as the leading cause of aggressive periodontitis (Nishihara et al, 2004, Slots et al, 1999). The difficulties faced by periodontists lie in the fact that the restoration of normality for the periodontal tissues becomes difficult with time, and if left untreated, it can progress into an irreversible

situation (Lindhe 2008). There are a number of procedures and protocols aimed to prevent the progression of the lesion and maintaining current status of periodontal tissues. To succeed in these procedures, in addition to manual curettage, the systemic antibiotic therapy plays an important role. There is evidence that manual mechanical removal of supra and subgingival plaque, without the use of antibiotic therapy, is incapable to eliminate pathogenic bacterial species and thus to maintain gingival levels of adhesion (Seiler, AAP 1966). To support such procedures, except monotherapy with antibiotics, which consists in the use of only one type of antibiotic, dentists frequently use a combination of antibiotics known as a combined therapy or dual antibiotic therapy (Herrera et al, 2008, Ciancio 2002). Among the pharmacological therapeutic options, metronidazole, and its combination with other antibiotics, has had positive results in managing the disease.

## Materials And Methods

The purpose of this systematic review is to determine whether systemically dual therapy with antibiotics improves primary clinical outcomes and the role of Metronidazole in the combined therapy regimen. A computerized search of the literature of clinical studies for Periodontitis was conducted independently by two reviewers up to 31 January 2017 in the US National Library of Medicine (PubMed), using the search terms and combinations presented in Table 1. Inclusion criteria for the studies selection were: published in English, controlled clinical trials in humans, and cohort studies of > 1 month duration with a comparison group; subjects with aggressive or chronic periodontitis who received two antibiotics, when one of them was Metronidazole and that compared the

effectiveness of the therapy either with placebo, or with another pharmacologic therapy, or another intervention (surgical or non-surgical intervention). Studies involving systemic reviews in vitro experiments, combinations of locally plus systemic antibiotics, were excluded. Initially (phase 1), the search encompassed published abstracts with the following combination of keywords: (*periodontitis, metronidazole, two, anti-bacterial agents*). Eligibility of potential studies was determined by reading the title and abstracts of each article identified by the search engine. All the articles that appeared to meet the inclusion criteria on the basis of their abstracts were selected and collected. Secondly, the full-text articles were obtained for manuscripts with missing abstracts or those in which insufficient

relevant information was included in the published abstract. The final selection was independently completed by the two reviewers reading the complete articles and their results were compared. Disagreements were resolved by discussion between the two review authors. Excel worksheets were

designed to list the selected articles and the specific parameters for each case. These parameters included the authors and year of publication, type of study, therapy used in the two groups, parameters evaluated for measuring clinical outcomes and main conclusion of the studies.

Term used	Number of studies
periodontitis OR periodontal infection OR chronic periodontitis OR aggressive periodontitis OR periodontal disease	59,354
And ("periodontitis"[MeSH Terms] OR "periodontitis"[All Fields]) AND ("metronidazole"[MeSH Terms] OR "metronidazole"[All Fields]) AND two[All Fields] AND ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])	79
<i>*MESH: Medical Subject Heading</i>	

Figure 1. Search strategy stages in PubMed.

## Results

After an initial selection, 79 papers were identified by the electronic searches; 18 papers met the inclusion criteria. Thirteen for chronic periodontitis and 5 for aggressive periodontitis. Total study population, for both control and test groups, was 1261;1086 with ChP and 175 with AgP. The most common parameter evaluated was pocket depth (PD) assessed in 13 studies, followed by bleeding on probing in 9 studies and clinical attachment level (CAL) in 8 studies. Seven out of 18 studies involved comparison of placebo with the combined dual

antibacterial therapies, from which 6 conducted on patients with ChP and 1 on patients with AgP. In almost all of the studies, systemically administered antibiotics exhibited a more positive attachment level change than the control group in the study. The shortest therapy regimen was determined 3 days and the longest regimen was 4 weeks. Overall, scaling and root planning (SRP) plus systemic antimicrobial groups demonstrated better results in CAL and PD change than SRP alone, or in placebo groups.



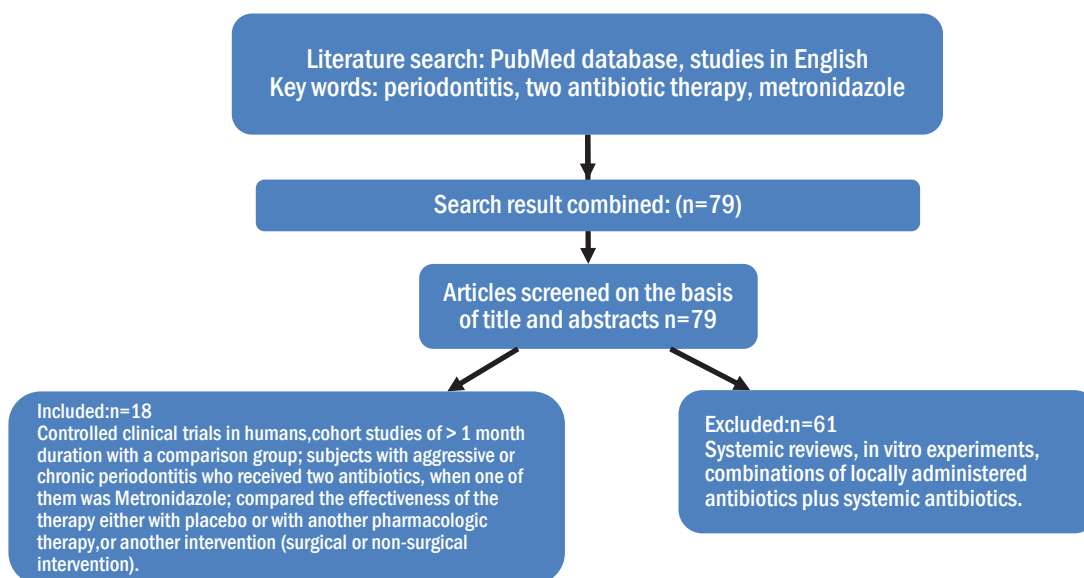


Figure 2. Scheme of search strategy.

Table 1. Information relating to 18 papers selected from the search.

Author	Type of study	Nr. of patients	Type	Therapy	Parameters evaluated	Conclusions
Cosgarea et al (2016)	placebo-controlled, randomized clinical study	102	ChP	SRP + placebo or SRP + AMX + MET (both 500 mg × 3 times daily) for 3 days or SRP + AMX + MET (both 500 mg × 3 times daily) for 7 days	PD, CAL, BOP, FMPS, GBI prior to treatment and at 3, 6 months post-treatment.	3 or 7 days' systemic administration of AMX + MET may lead to significantly greater clinical improvements compared to non-surgical therapy alone
Mombelli et al (2016)	group control, randomized clinical trial	80	ChP	375 mg AMX and 500 mg MTZ three times per day for 7 days during the non-surgical treatment phase/ during surgical phase.	Resistance of VGS to penicillin and erythromycin	Amoxicillin plus metronidazole did not significantly affect the resistance pattern of the VGS to penicillin or erythromycin.
Ercan et al (2015)	group control, retrospective record study	45	AgP	SRP only; SRP plus azithromycin (AZT group); and SRP plus MTZ and AMX (M+A group)	PD, CAL, GI, PI, BOP recorded at baseline and 3-month post therapy.	Nonsurgical therapy reduces PD, CAL and clinical inflammation findings. The scores were decreased more in the AZT and M+A groups than the controls, but this difference did not reach significance.
Yang et al (2015)	group control, randomized clinical trial	138	ChP	Minocycline hydrochloride; MTZ sustained-release film with minocycline hydrochloride, 4 weeks	therapeutic effect, adverse reaction and relapse situation of patients	Metronidazole sustained-release film combined minocycline hydrochloride can evidently improve patients' periodontal status, enhance drug therapeutic effect. It has less adverse reaction and low relapse rate, thus is worthy of clinical promotion.
Mombelli et al (2015)	single-center, randomized placebo-controlled crossover clinical trial	80	ChP	Group A, 500 mg MTZ plus 375 mg AMX three times per day for 7 days during the first, non-surgical phase of periodontal therapy (T1) and placebo during the second, surgical phase (T2); and group B, placebo during T1 and antibiotics during T2	PD, BOP	Giving the antibiotics during T1 or T2 yielded similar long-term outcomes, but antibiotics in T1 resolved the disease quicker and thus reduced the need for additional surgical intervention.
Arweiler et al (2014)	group control, randomized clinical trial	36	AgP	SRP and either systemic administration of AMX+MTZ or 7 days or with two episodes of PDT.	PI, BOP, PD, GR, CAL	Both treatments resulted in statistically significant clinical improvements, AB showed statistically significantly higher PD reduction and lower number of pockets

Table 1. Information relating to 18 papers selected from the search.

Author	Type of study	Nr. of patients	Type	Therapy	Parameters evaluated	Conclusions
						≥7 mm compared to PDT.
Almaghlouth et al (2014)	placebo-controlled, randomized clinical study	40	ChP	Full-mouth SRP within 48 h with either adjunctive systemic AMX and MTZ or placebo	Serum cytokines, acute-phase proteins	Subjects with untreated periodontitis may show high peaks for several inflammatory markers in serum simultaneously. Nonsurgical periodontal treatment with or without antibiotics reduced most of these peak levels.
Arweiler et al (2013)	randomized, group control clinical trial	36	AgP	Full-mouth SRP, then randomly divided into two groups: Group AB received AMX and MTZ 3 times a day for 7 days. Group PDT received two applications of PDT on the day of SRP as well as at follow-up after 7 days	PI, BOP, PD, GR, CAL	Both treatments led to statistically significant clinical improvements. The systemic administration of antibiotics, however, resulted in significantly higher reduction of PD and a lower number of deep pockets compared to PDT.
Faveri et al (2014)	group control, clinical trial	64	ChP	SRP combined with MTZ (400 mg 3 times daily) + AMX (500 mg 3 times daily for 14 days applied in 32 smokers and 32 non-smokers	PD	Smokers with CP benefit less than non-smokers from treatment by the combination of SRP, MTZ, and AMX.
Feres et al (2012)	group control, clinical trial	118	ChP	SRP only or with MTZ 400 mg/3 a day or MTZ+AMX (500 mg 3 times day) for 14 days. Half of the subjects in each group rinsed with 0.12% chlorhexidine twice a day (BID) for 2 months	PD	Treatment of generalized ChP is significantly improved by the adjunctive use of MTZ+AMX and MTZ.
Goodson et al (2012)	group control, randomized clinical trial	187	ChP	SRP plus none, SRP + Systemic amoxicillin + metronidazole (SMA), local tetracycline delivery (LTC) and periodontal surgery (SURG)	CAL, PD	Patients receiving adjunctive therapies generally exhibited improved CAL gain and/or PPD reduction when compared with the outcome of SRP alone. Only additive, not synergistic effects of the various adjunctive therapies were observed
Mendonça et al (2012)	group control, randomized clinical trial	21	ChP	MTZ + AMX for 10 days with SD; MTZ + AMX for 10 days with NSD;	INF-γ, IL-17, IL-23 and IL-4	SD and NSD associated with systemic antimicrobials did not differ in terms of clinical benefits for RP in diabetics up to 6 months post-therapies. RP treated by SD presented increased levels of cytokines.
Casarin et al (2012)	randomized placebo controlled clinical trial	24	AgP	FMUD plus placebo, FMUD plus 375 mg AMX plus 250 mg MTZ for 7 days	PI, BOP, PD, GMP, CAL	amoxicillin/metronidazole improves clinical and microbiologic results of FMUD in AgP treatment.
López et al (2012)	parallel-arm, double-blind, randomized clinical trial	165	ChP	plaque control and root planning plus AMX and MTZ; plaque control instructions, supra-gingival scaling, and two placebos	Risk factors for cardiovascular disease, serum lipoprotein cholesterol, glucose, BMI, CRP, fibrinogen concentrations, PD	Reduction of periodontal inflammation either with root planning and systemic antibiotics or with plaque control and subgingival scaling significantly reduces CRP levels after 9 months in patients with MetS.
Dannewitz et al (2007)	post-operative follow up group control trial	53	ChP	amoxicillin/metronidazole or ciprofloxacin/metronidazole	A.a. test, PD	No differences were found between the subjects that were tested positive and negative for A.a in the postoperative period
Kaner et al (2007)	group control, clinical trial	34	AgP	SRP+AMX/MTZ, SRP +AMX/MTZ after 3 months	PD, CAL, BOP	administration of amoxicillin/metronidazole immediately after initial SRP provides more PD reduction and RAL "gain" in initially deep sites than late administration at SPT with

Table 1. Information relating to 18 papers selected from the search.

Author	Type of study	Nr. of patients	Type	Therapy	Parameters evaluated	Conclusions
						reinstrumentation after 3 months.
López et al (2006)	randomized, placebo controlled clinical trial	22	ChP	M+A for 7 days; (SRP) and two placebos	BOP, PD, CAL	Changes in clinical and microbiological parameters were similar after receiving systemically administered M+A as the sole therapy or after receiving SRP only
Giannopoulou et al (2006)	randomized, placebo-controlled, clinical trial	16	ChP	Half of the subjects received 250 mg MTZ and 375 mg AMX three times a day for 7 days; the other half received a placebo	GCF	Improved healing of the soft tissues has been noted clinically in non-surgically treated sites in subjects treated with antibiotics
<i>*Abbreviations</i>						

ChP - chronic periodontitis	GBI - gingival bleeding index (GBI)	CRP - C-reactive protein	AMX - Amoxicillin
AgP - aggressive periodontitis	AdvP - Advanced Periodontitis	GCF - gingival crevicular fluid	MTZ - Metronidazole
SRP - scaling and root planning	SD - surgical debridement	GR - gingival recession	BOP - bleeding on probing
GMP - gingival margin position	NSD - non-surgical debridement	CAL - clinical attachment level	PD - Pocked depth
FMPS - full-mouth plaque scores	FMUD - full mouth ultrasonic debridement	PDT - photodynamic therapy	

## Discussions

Analyzed data showed that systemically administered adjunctive antibiotics with and without SRP and/or surgery appeared to provide a greater clinical improvement in attachment levels than therapies not employing these agents. Selection for an individual patient has to be made on other clinical factors. Systemically administered metronidazole, and especially the combination of metronidazole, amoxicillin and SRP leads to a beneficial change in the composition of the subgingival microbiota by reducing pathogens and allowing the growth of host-compatible species. In addition, the combination of systemic antibiotics and a strict control of supragingival plaque during the active phase of therapy has shown promising results in the treatment of chronic periodontitis. Furthermore, the use of metronidazole and amoxicillin in patients with aggressive periodontitis showed statistically significantly higher PD reduction and lower number of pockets  $\geq 7$  mm compared to only SRP. Administration

immediately after initial SRP provides more PD reduction and CAL "gain" in initially deep sites than late administration at SPT with reinstrumentation after 3 months. Overall, systemic antimicrobials in conjunction with SRP, can offer an additional benefit over SRP alone in the treatment of periodontitis, in terms of CAL and PD change, and reduced risk of additional CAL loss. However, it is difficult to provide guidance to the more effective ones, since studies presented insufficient sample size for many of the antibiotics tested and very few of them were cross-over studies. Although, literature shows that metronidazole has a prominent effect on periodontitis, but alone it's not the drug of choice for treating A.a. infections. Instead, its combination with other antibiotics shows to be effective against these bacteria (Rams 1992). Also, it is effective against anaerobes such as P.Gingivalis and P.Intermedia (Jorgensen 2000).

Metronidazole combined with Amoxicillin may have a great impact in the management of patients with aggressive periodontitis (Abinaya et al, 2012 ). Amoxicillin is found to be useful in the management of patients with aggressive periodontitis, in both localized and generalized forms (Weinstein 1975). Literature suggests that metronidazole can be used in combination with ciprofloxacin. Actually, ciprofloxacin is the only antibiotic in periodontal therapy to which all strains of A.a. are susceptible. Metronidazole targets obligate anaerobes, and Ciprofloxacin targets facultative anaerobes. This is a very powerful combination against mixed infections. This combination provides a therapeutic benefit by reducing or eliminating pathogenic microorganisms and offers a prophylactic benefit by giving rise to predominantly streptococcal microflora (Rams et al, 1992). Periodontal infections contain a wide diversity of bacteria; hence, no single antibiotic can be effective against all putative pathogens (Walker et al, 1993). This "mixed infection" can include a variety of aerobic, microaerophilic, and anaerobic bacteria, both gram negative and gram positive. This scenario makes it mandatory to use more than one antibiotic, either serially or in combination (Jorgensen et al, 2000).

In addition to issues that arise from the inappropriate choice of the antibiotic prescribed, the duration of the treatment shows to be a problem itself. A short-term therapy may pose a risk in terms of antibiotic resistance rather than a treatment for the disease. This is true especially in cases of a chronic periodontitis where the presence of periodontal pathogens, specifically A.a., is known to endure in tissues after therapy and re-infect the pocket. Thus, the use of systemic antibiotics was thought to be necessary to eliminate pathogenic bacteria from the tissues. It is suggested that therapy in these cases should be at least 8 days or more for most of the antibiotics, which if greater than the data we found in our study (Christersson et al, 1987).

In practice, antibiotics are often used empirically without microbial testing. Studies conducted to evaluate the effectiveness of microbial testing

concluded that the usefulness of microbial testing may be limited and that empirical use of antibiotics, such as a combination of amoxicillin and metronidazole, may be more clinically and cost effective than bacterial identification and antibiotic-sensitivity testing. The practice of such measures can still be considered whenever a case of aggressive periodontitis is not responding or if the destruction continues despite good therapeutic efforts (Abinaya et al, 2012).

While the use of antibiotics in periodontal treatment will probably always be controversial, reports from both the American Academy of Periodontology and the European Federation of Periodontology contain valuable guidance for their use (Rams et al, 1992). Both these reports, following exhaustive literature searches, determined that patients with aggressive periodontitis appear to benefit from the adjunctive use of systemic antibiotics during treatment. The mechanical curettage without the addition of systemic antibiotics would probably be a failure considering the rapid bacterial colonization of periodontal pockets (Ciancio 2002). Systemic antibiotic therapy helps the manual curettage and improves immune response to eliminate subgingival bacteria, which are not affected by manual therapy (7???, Ciancio 2002). Based on WHO reports, bacterial resistance to antibiotics poses a "major global threat" to public health. Additionally, in some countries such as Norway, there is a national policy for the use of antibiotics with narrow spectrum in dental clinics to limit antibiotic-resistance (Mohammed et al 2007). Consequently, we must limit their use and prescribe the right dosage and duration of therapy to prevent further resistance.

## Conclusions

From all the antibiotics available to dentists for periodontal diseases, metronidazole has a limited practice and it's not a first choice drug. A combined therapy with metronidazole and amoxicillin can be of great benefit for the patient because periodontal



infections contain a wide diversity of bacteria; hence, no single antibiotic can be effective against all putative pathogens. For this purpose, we would suggest the combination of metronidazole and ciprofloxacin.

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