# Analysis of the Effectiveness of Periodontitis Treatment Using Antimicrobial Agents

Oleksandr Korniichuk[1,*], Vasyl Humeniuk[2], Olha Isakova[3], Borys Shchepanskyi[4] and Vasyl Antoniv[5]

[1]*Department of Therapeutic Dentistry and FPE Dentistry, Faculty of Postgraduate Education, Dnipro State Medical University, 9 Volodimir Vernadsky street, 49044, Dnipro, Ukraine*

[2]*Department of Disaster Medicine and Military Medicine, Medical Faculty No. 2, Danylo Halytsky Lviv National Medical University, 69, Pekarska street, 79010, Lviv, Ukraine*

[3]*Department of Pediatric Dentistry, Faculty of Dentistry, Danylo Halytsky Lviv National Medical University, 69, Pekarska street, 79010, Lviv, Ukraine*

[4]*Department of Prosthodontic Dentistry, Faculty of Dentistry, Lviv Medical University, 76 V. Polishchuka street, 79018, Lviv, Ukraine*

[5]*Department of General Surgery № 2 of Faculty for training of doctors for the Armed Forces of Ukraine of Bogomolets National Medical University, 13 T. Shevchenko blvd, 01601, Kyiv, Ukraine*

**Abstract:** A combination of systemic antibiotics with scaling may provide an additional advantage over scaling alone in the periodontitis treatment in terms of clinical loss of attachment and change in pocket depth. The use of antibiotics should be justified by a determined need and should not replace adequate local treatment. Different treatment protocols have been proposed, but their indications and efficacy remain controversial. The study aims to analyse the literature on the use of antimicrobial agents for non-surgical periodontal therapy and to compare different protocols for prescribing antimicrobial agents. A search in MEDLINE and EBSCOhost electronic databases was conducted using relevant MeSH words. Targeted studies had to be published within the last five years. Studies were selected based on inclusion and exclusion criteria. Data from selected studies were extracted and analysed. Ten randomized clinical trials were included in the review. The general conclusions of this review indicate a positive effect of antibiotics as an adjunct to non-surgical treatment of chronic periodontitis, regardless of antimicrobial drugs used in the reviewed studies. A prospect for further research is a comparative analysis of the effectiveness of the use of antimicrobial agents and probiotics as an adjunct to the non-surgical treatment of chronic periodontitis.

**Keywords:** Antimicrobial agents, Chronic periodontitis, Non-surgical treatment of chronic periodontitis, Periodontal pocket, Systemic antibiotics.

## 1. INTRODUCTION

Nowadays periodontal disease is a global health problem. Recently the incidence rate of periodontal disease worldwide has increased dramatically, more than that a large number of cases point to the fact that it is associated with systemic diseases [1]. Periodontitis is a multicausal chronic inflammatory disease that affects 11% of the population all over the world [2]. Specific microorganisms or their groups destroy the soft and hard periodontal tissues, leading to the progressive impairment, chronic periodontitis takes place when the pathogenic microbial load in the periodontal pocket exceeds the host immune response, when the imbalance between the subgingival microbiome and the host immune system develops [3].

The periodontitis treatment is aimed at the elimination or suppression of periodontopathogenic microorganisms. The first step of periodontal treatment is a non-surgical therapy, which means mechanical removal of microbial biofilm and tartar combined with oral hygiene, which usually yields good clinical improvement in most patients [4]. Mechanical scaling and root scaling form the gold standard of periodontitis treatment. In most patients, mechanical and surgical periodontitis treatment combined with proper oral hygiene can halt or prevent further loss of periodontal attachment. Nevertheless, they do not constantly provide stable clinical improvements. Periodontal pathogens such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Treponema denticola persistence is frequently found after scaling and can lead to microbial re-colonization and further destruction of periodontal tissues [3].

The use of systemic antibiotics as an adjunctive therapy in the treatment of periodontal diseases after mechanical periodontal treatment provides a significant therapeutic effect [5, 6]. These results were obtained

*Address correspondence to this author at the Department of Therapeutic Dentistry and FPE Dentistry, Faculty of Postgraduate Education, Dnipro State Medical University, 9 Volodimir Vernadsky street, 49044, Dnipro, Ukraine; E-mail: med.23dent@gmail.com

E-ISSN: 1929-6029/23

with different antibiotics such as Amoxicillin/ Metronidazole, Azithromycin, Clindamycin, and Clarithromycin, and others [5, 7]. The prescribing of antibiotics for non-surgical treatment is usually based on the dantist's personal experience as soon as the universally accepted recommendations are absent [8].

The study aims to analyse the literature on the use of antimicrobial agents for non-surgical periodontal therapy and to compare different protocols for prescribing antimicrobial agents proposed over the past five years.

## 2. LITERATURE REVIEW

The frequency of periodontal diseases among people of different countries, and of different social status remains an important public health problem all over the world. In the United States, one in five adults suffers from some form of periodontitis [9]. The main risk factor for the development of periodontitis is still smoking [9]. Periodontitis is revealed nearly in all adults in China, India, Germany, Taiwan, and the Republic of Belarus. The highest frequency of periodontitis in adults is in Belarus (76%), Germany (73%), and Nepal (64%). And more than half of the adult population of Poland (62%), Malaysia (60%), Libya (56%), Iran (53%), and Taiwan (53%) suffer from periodontitis[1]. The Global Burden of Disease Study (1990-2010) found that: severe periodontitis takes the 6th place among the most common diseases all over the world (743 million people are affected) with an overall frequency of 11.2%; the global frequency of periodontal disease increased by 57.3% from 1990 to 2010 [10]. The global incidence rate of chronic periodontitis is constantly fluctuating (Figure **1**). The data varies because of the complexity of data collection in different countries.

Chronic periodontitis is an inflammatory periodontal disease induced by plaque microorganisms. Infiltration of gingival tissue by mononuclear cells is one of the morphological characteristics of chronic periodontites. It may lead to the destruction of the tooth-supporting apparatus, represented by connective tissue and resorption of alveolar bone, which can ultimately lead to tooth loss, which potentially influences the stability of the maxillofacial system. Smoking, diabetes, cardiovascular diseases, or chronic stress usually facilitate the development of chronic periodontitis, which increases with age (Figure **2**) [16]. The main etiological factor of periodontal diseases is dental plaque biofilm - an organized complex accumulation of bacteria and their waste products on the tooth surface [18]. When a certain type of bacteria grows in the subgingival space, it can cause inflammation and destruction of the periodontium with loss of attachment and loss of bone tissue [19]. One of the main prerequisites for the emergence of a potentially pathogenic complex is the ability of so-called "key pathogens", to modulate the reaction of the patient's organism in such a way as to impair immune control and pull the balance from homeostasis to dysbacteriosis. However, the latter enhances the immune response, creating a vicious circle [3, 8]. Interactions between co-pathogens and key pathogens enhance the virulence of the microbial complex as a whole, the expression of different molecules, including relevant adhesins, cognate receptors, proteolytic enzymes, and proinflammatory surface structures/ ligands on the surface of the host cells and virulent microbiota also enhances the virulence factors of the whole complex to provide a heterotypic, compatible, and proinflammatory microbial effect that leads to the irreversible tissue-destructive reaction of the host organism [20].

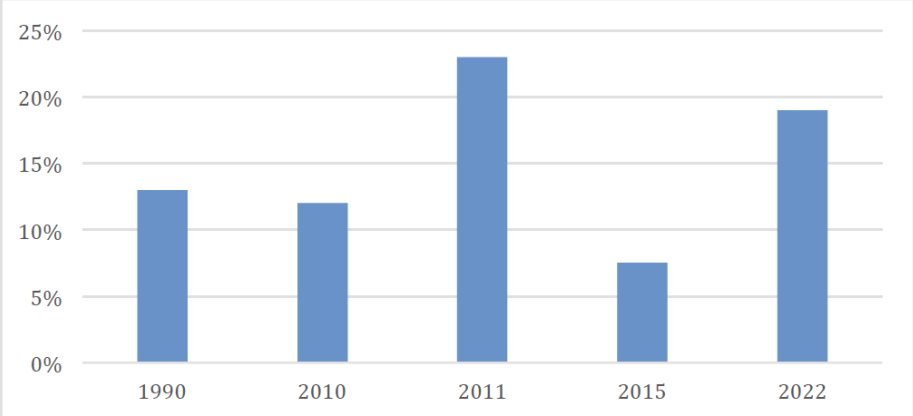


**Figure 1:** The incidence rate of chronic severe periodontitis in the world: 1990 [11]; 2010 [11]; 2011 [12]; 2015 [13]; 2022 [14].

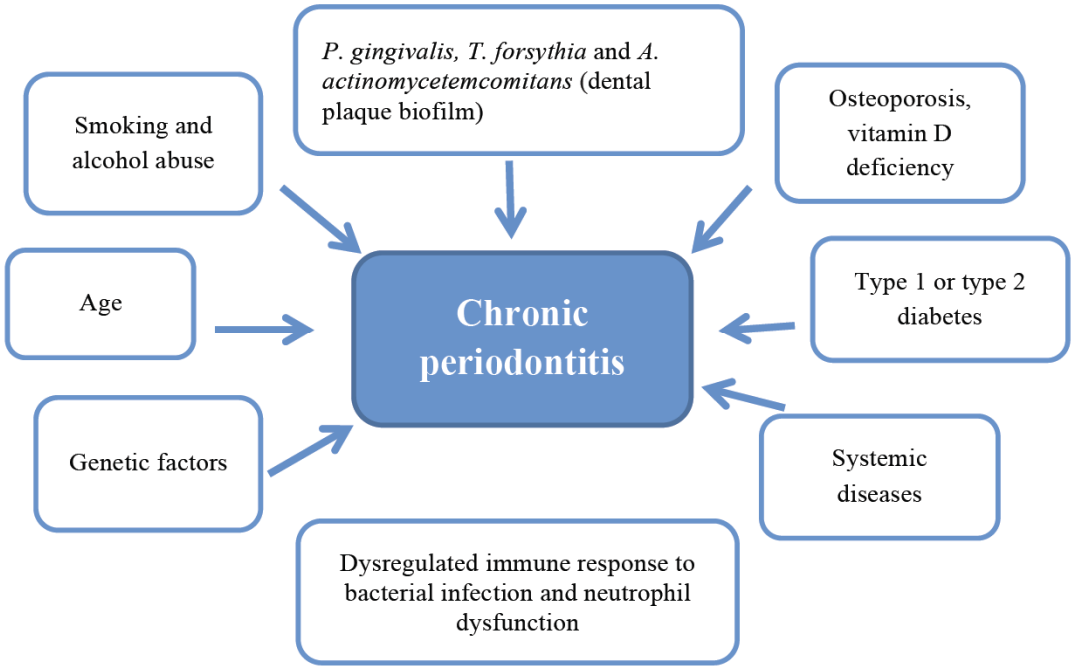


**Figure 2:** The main etiological factors of the development of chronic periodontitis.

Effective periodontitis treatment means reducing the bacterial load in order to increase the self-repair ability of periodontal tissues. Successful root surface debridement by scaling and root scaling is followed by the primary goals of treatment: reduce inflammation and close the pockets [21]. Clinically, decreasing of inflammation leads to tissue compression and recession, and a decreased probing depth is also revealed [21].

Mechanical debridement is a very complex therapeutic procedure, but it does not remove all periodontopathogenic bacteria from the subgingival environment, especially those in hard-to-reach areas such as furcations, grooves, concavities, and tortuous pockets [4, 18]. Mechanical plaque removal by scaling and root scaling alone is not capable of causing sufficiently profound changes in the microbial ecology of the oral cavity to create a new stable biofilm symbiosis compatible with periodontal health [22].

It is generally approved that only 10 to 15 species of approximately 700 different bacterial species living in periodontal pockets may cause periodontitis, but there are still ongoing debates about the exact mechanisms of periodontal tissue destruction [18]. Some bacterial species, such as Aggregatibacter actinomycetemcomitans [23], Porphyromonas gingivalis [24], Treponema denticola, and Tannerella forsythia [25], cause local inflammation and provide damaging and destruction of periodontal tissues. Persistence of periodontal pathogens such as Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis, which are often found after scaling, can lead to microbial recolonization and subsequent destruction of periodontal tissues [3]. Other Gram-negative anaerobic bacilli, some Gram-positive bacteria, and even Escherichia coli/Pseudomonas may also cause periodontitis development [18].

Nonsurgical calculus removal and root preparation can eliminate some bacteria, such as subgingival Campylobacter rectus, but it is usually ineffective against Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythus, and *E. coli*. It can neither significantly reduce the amount of Aggregatibacter actinomycetemcomitans nor Peptostreptococcus. During the second stage of periodontiitis treatment, periodontal surgery can be performed to clean and eliminate deep residual pockets to achieve long-term stable treatment results [8].

The use of adjunctive systemic antimicrobial remedies is approved in exact cases to ameliorate clinical outcomes and periodontal repairment by reducing inflammation in the periodontal pocket [18]. It is usually recommended as an adjunctive therapy in exact situations, such as progressive periodontitis, aggressive periodontitis, necrotizing periodontitis, and periodontal abscesses even after conducting of conventional mechanical treatment [18]. As soon as the evidence for the bacterial specifics of periodontitis has

accumulated and strengthened during the past two decades, dentists and microbiologists use additional periodontal antibiotic therapy as an effective complement to traditional mechanical tooth treatment for the therapeutic influence on periodontal disease. Antibiotics are natural or synthetic organic substances that at low concentrations depress or eliminate selected microorganisms [6]. The antibiotics administration is restrictive and in general, is aimed at diminishing the development of microorganisms antibiotic resistance [18].

Aggressive periodontitis is often associated with high levels of A. actinomycetemcomitans and/or Porphyromonas gingivalis, bacteria that can invade periodontal tissues. A. actinomycetemcomitans is most susceptible to Amoxicillin but resistant to Metronidazole, while other gram-negative but strictly anaerobic bacteria (eg, P. gingivalis) are most susceptible to Metronidazole [7]. There is a great number of antibiotics that can be used to treat periodontal infections, but it is often unclear which antibiotic will be more effective in an exact patient with a particular periodontal infection with minimal side effects [5].

## 3. MATERIALS AND RESEARCH METHODS

Search strategy. A comprehensive search of relevant articles was conducted in the MEDLINE-PubMed, Embase, and Cochrane databases starting from 2018 studies. A selection of MeSH terms was created to remove a large number of irrelevant papers from the manual search: “Periodontal Pocket/Drug Therapy”[Mesh], or “Periodontal Pocket/Therapy” [Mesh], or “Calculus/Methods”[Mesh]), or “Periodontitis/ Drug Therapy”[Mesh], or “Periodontitis/Therapy”[Mesh], or “Gingival Loss/Drug Therapy”[Mesh], or “Antibacterials/Periodontitis.” The search terms and strategies were similar WHEN searching IN another database (EBSCOhost).

Two reviewers performed independent data collection and then compared their results to avoid data extraction errors. Data included participant characteristics (age, gender), and duration of observation. Data from each included study were recorded using a standardized data extraction form, including author names, year of publication, definition, and diagnosis of periodontitis, research design, intervention (antibiotic/placebo regimen), sample size, demographics, inclusion criteria, and duration of observation.

## 4. RESULTS

A total of 394 studies were identified during the initial search; 164 PubMed, 136 Embase, and 94 from the Cochrane Library database. Ten papers were selected during the manual search. After removing duplicates (n = 197), 217 articles were included in the title and abstract selection phase. A total of 183 articles were excluded and 34 articles were selected for full reading. Only 10 articles were considered acceptable for review (Table **1**). All included studies were randomized clinical trials; 100% of the included articles were studies with a high level of scientific evidence, with interesting recommendations.

A 6-month randomized controlled trial by authors [27], included 14 people with severe periodontitis (Table **1**). It was settled that the advantages of systemic use of Amoxicillin and Metronidazole together with scaling over only mechanical treatment of chronic periodontitis resulted in clinical improvement and abolition of infection both in the subgingival area and in saliva 3 months after treatment. The microbiological advantage almost disappeared after 6 months, but the clinical advantage persisted longer [27].

A randomized controlled trial on thirty-eight patients with previously untreated generalized moderate to severe chronic periodontitis was conducted by authors [26]. It was settled that in patients of all groups with moderate to severe periodontitis additional administration of systemic antibiotics after periodontal mechanical treatment, especially in patients with a more generalized distribution of periodontal areas with moderate and severe periodontitis may show clinical benefits compared to scaling alone. However, the authors insist on the prescription of antibiotics only to patients who may get the maximum therapeutic benefit from it. Even though simultaneous administration of Amoxicillin and Metronidazole after scaling shows benefits over Azithromycin monotherapy in reducing periodontal pocket depth for areas with moderate periodontitis, the authors didn’t find out an exact definitive conclusion concerning the antibiotic regimen is better to use and insist on the need for further research to clarify the results [26].

Researchers [28, 29], evaluated the clinical effects for patients with generalized aggressive periodontitis, and [28], — also with chronic severe periodontitis. The obtained results of both studies demonstrated that the addition of antibiotics caused additional clinical advantages regardless of the antimicrobial agent.

**Table 1: Brief Description of Academic Studies Selected for Analysis**

| Source | Number of examinees | The main diagnosis | Accompanying diagnosis | Groups and schemes of antibiotic therapy |
|---|---|---|---|---|
| Liaw, Miller and Nimmo (2019), [26] | 38 | Generalized medium-severe and severe chronic periodontitis | - | 1 — only scaling; 2 – scaling + 500 mg of Amoxicillin plus 400 mg of Metronidazole three times a day for 7 days; 3 - 500 mg of Azithromycin for 3 days |
| Lu, *et al*. (2022), [27] | 14 | Severe chronic periodontitis | - | Group 1 — scaling followed by prescribing Amoxicillin (500 mg) and Metronidazole (200 mg) three times a day for 7 days; Group 2 - scaling + placebo |
| Suryaprasanna, *et al*. (2018), [28] | 30 | Aggressive periodontitis | - | Group 1 (n=15) – scaling and root planing + placebo; Group 2 (n=15) - scaling and root planing + Clarithromycin 500 mg three times a day for 7 days |
| Ardila, *et al*. (2020), [29] | 36 | Aggressive periodontitis | - | Scaling + Group 1: Moxifloxacin 400 mg/day for 7 days; Group 2 Amoxicillin + Metronidazole 500 mg/day for 7 days |
| Ramiro, *et al*. (2018), [30] | 59 | Chronic periodontitis | - | Group 1: scaling and root planning; Group 2: scaling and root planing + Amoxicillin + Metronidazole 500 mg for 14 days; Group 3: scaling and root planing + Metronidazole 400 mg for 14 days |
| Cosgarea, *et al*. (2022), [31] | 50 | Aggressive periodontitis | | Scaling +: 1 group (n = 25): 500 mg of antibiotics (Amoxicillin and Metronidazole) 3 times a day for 3 days, followed by placebo 3 times a day for 4 days; Group 2 (n = 25): 500 mg of antibiotics (Amoxicillin and Metronidazole) 3 times a day for 7 days |
| Jentsch, Dietrich and Eick (2020), [32] | 58 | Chronic periodontitis | - | Complete probing of the oral cavity +: 1 group (n = 29): Metronidazole; Group 2 (n = 29): Amoxicillin/Metronidazole |
| Čuk, *et al*. (2020), [33] | 40 | Chronic periodontitis | - | Non-surgical periodontal treatment (scaling and root planing) in two sessions within 7 days, followed by: Group 1 (n = 20) - Azithromycin 500 mg/day for 3 days; Group 2 (n = 20) - placebo |
| Gómez-Sandoval, *et al*. (2020) [34] | 42 | Chronic periodontitis | diabetes mellitus type 2 | Group 1 – Clindamycin 300 mg three times a day for 7 days; Group 2 – Amoxicillin 500 mg + Metronidazole 250 mg three times a day for 7 days |
| Lecio, *et al*. (2020) [35] | | Severe and generalized chronic periodontitis | diabetes mellitus type 2 | One-moment full oral ultrasonic debridement + Group 1 (n = 20): placebo in the form of nanospheres of polylactic co-glycolic acid; Group 2 (n = 20): nanospheres loaded with Doxycycline |

According to [29], this statistically significant reduction was observed in periodontal depth ≥ 6 mm after 6 months of initial therapy. In both studies, a significant decrease in the reduction of Aggregatibacter actinomycetemcomitans index was approved by comparison with the results of the control group [28, 29]. Researcher [29] stated a significant reduction in Aggregatibacter actinomycetemcomitans even after 6 months of using Amoxicillin or Amoxicillin in combination with Metronidazole. Researcher [28] found out that this significant difference between experimental and control groups was observed up to month 3 but was not significant (p = 0.774) in 6 months after therapy began.

Another group of scientists [30], estimates areas colonized by Archaea and their levels after 6 months of antimicrobial treatment administration. Groups of patients who received Amoxicillin in combination with Metronidazole or Metronidazole alone showed a significantly lower percentage of areas colonized by Archaea and lower mean levels of this species in initially deep pockets (PD ≥ 5 mm) compared to the control group of patients, who received placebo. Authors [29, 30], studied the efficacy of the Aamoxicillin/Metronidazole combination (Table **1**). It was settled that, notwithstanding the dose of Metronidazole in both studies, significant improvements in clinical and/or microbiological indexes were

observed. The duration of taking was from 7 to 14 days and it was settled that 14 days were more effective than 7 days. The author [28], used Clarithromycin 500 mg three times daily for 7 days as an adjunct to scaling and showed that the reduction in periodontal pocket depth was significant in all areas without exception.

Researchers [31], in a randomized controlled trial, investigated fifty systemically healthy patients (32.7 ± 4.3 years old) with aggressive periodontitis (Table **1**). In general, it was settled that there were no general benefits of the administration of antimicrobial treatment (combination of Amoxicillin and Metronidazole) for 7 days compared to the three-days treatment protocol [31].

A comparison of two different regimens of systemic antibiotic therapy adjunct to non-surgical periodontal therapy when Aggregatibacter actinomycetemcomitans was not detected in the subgingival biofilm was conducted by authors [32]. It was a randomized clinical trial, which involved 58 patients with periodontitis and the absence of A. actinomycetemcomitans in the subgingival biofilm (Table **1**). Subgingival biofilm and crevicular fluid were collected for major periodontal pathogens and biomarkers analysis. It was revealed that with no difference between groups, all three indexes (probing depth, clinical attachment level, and probing bleeding) and areas with an initial measurement of periodontal pocket depth ≥ 6 mm had been improved during 3 and 6 months (each $p<0.001$ compared to baseline). The level of T. forsythia was lower in the Amoxicillin/Metronidazole group at 3 months ($p < 0.05$). In the case of the absence of A. actinomycetemcomitans in the subgingival biofilm, additional systemic administration of Amoxicillin/ Metronidazole provides beneficial clinical and microbiological results of non-surgical periodontal treatment [32].

A double-blind randomized parallel placebo-controlled trial, conducted by researchers [33], included 40 patients with periodontitis. All of them received non-surgical periodontal treatment in two sessions, and after that, they received systemic antibiotic therapy (Table **1**). It was revealed that administration of Azithromycin as an additional treatment, compared to non-surgical periodontal treatment only, resulted in a more effective eradication of A. actinomycetemcomitans ($p = 0.013$) and C. rectus ($p = 0.029$), a decreased proportion ($p = 0.006$) and the total number ($p = 0.003$) of P. gingivalis, as well as a decreased share of C. rectus ($p = 0.012$). Both groups demonstrated crucial but equivalent improvement in periodontal parameters, with no differences in between groups in initially shallow and deep areas. Despite significant changes in the number of A. actinomycetemcomitans, P. gingivalis, and C. rectus, the authors guess that patients with periodontitis have no benefit from additional administration of systemic Azithromycin in terms of the number of persistent areas with periodontal pocket depth ≥5 mm [33].

42 patients with chronic periodontitis and Type 2 diabetes took part in a double-blind randomized clinical trial conducted by researchers in [34] (Table **1**). Two groups of patients were randomly formed: the first one got Clindamycin 300 mg + placebo three times a day for 7 days; the second group got Amoxicillin (500 mg) + Metronidazole (250 mg) through the same period. At the end of a trial, no differences were found between clinical indicators, probing depth, plaque index, and bleeding during probing, respectively, after 7 days of taking Clindamycin or Amoxicillin-Metronidazole. The authors guessed that 7 days of Clindamycin or Amoxicillin/Metronidazole were equally effective in reducing of clinical indexes in patients with periodontitis and Type 2 diabetes [34].

Author [35], in a parallel double-blind randomized placebo-controlled clinical trial, evaluated the clinical, microbiological, and immunological results of polylactic co-glycolic acid nanospheres containing 20% Doxycycline in the treatment of Type 2 diabetes with severe and generalized chronic periodontitis. A significant decrease in periodontopathogenic microorganisms, and clinical improvement in all parameters after treatment was observed in the group of patients, who received nanospheres loaded with Doxycycline ($p<0.05$) compared to the control group. The authors believe that Doxycycline-loaded nanospheres could be considered as a potential adjunct to mechanical cleaning in the treatment of periodontitis in patients with Type 2 diabetes [35].

## 5. DISCUSSION

The obtained data from analysed scientific reports have shown that the additional administration of systemic antibiotics in the active phase of periodontal treatment helps to improve clinical, microbiological, and/or biological indexes, such as increased attachment and reduction of periodontal depth, even if it does not lead to a reduction compared to placebo groups. The ten included randomized clinical trials differed in the study population, sample size, risk of

bias, statistical methods used, primary result, placebo use, start of treatment, antimicrobial classes, dosing, and/or sequence of non-surgical treatment, so it was difficult to compare different protocols.

The combination of Metronidazole and Amoxicillin is a benefical combination with the greatest clinical and microbiological effects compared to other systemic antibiotics used for the treatment of periodontitis. Their additional use improves the results of scaling, including a reduction in the number of deep pockets after treatment and, as a result, the need for surgical interventions. It also reduces the number of major periodontal pathogens such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans in periodontal pockets and other oral surfaces [22]. Empirical administration of antimicrobial treatment in dentistry without investigating the composition of the subgingival biofilm mostly leads to prescribing a combination of Amoxicillin and Metronidazole [5]. Most studies settled that the combination of Amoxicillin + Metronidazole after scaling in initial areas with moderate to severe disease provides an improvement in all clinical parameters, compared to scaling alone [26, 27, 29, 32]. These benefits in initial deep areas are likely due to the broad spectrum of action targeting heterogeneous pathogen populations [36].

Researchers [26] concluded that scaling + Amoxicillin + Metronidazole or scaling + Azithromycin do not provide significantly greater improvements compared to scaling alone in oral clinical indexes, including reducing areas with periodontal pocket depth ≥5 mm. That was also approved by [36, 37]. The residual areas with a periodontal pocket depth of ≥5 mm is one of the main risk factors for prolonged and sometimes ineffective periodontal treatment and predict disease recurrence. It is consistent with data that indicated a positive effect of antibiotic therapy regardless of the combination or duration of antibiotic use [28, 30, 36] [37].

Authors [30], observed a decrease in the total number of cultured microbiota at all stages of observation in patients who used Azithromycin, they demonstrated a significantly greater reduction in periodontal pocket depth in comparison with patients after scaling alone. This does not exactly coincide with the data confirmed by [33], who indicated that patients with periodontitis do not benefit significantly from the additional use of Azithromycin in terms of the number of persistent areas with periodontal pocket depth ≥ 5 mm. However it is consistent with the data of [38] in which the use of Azithromycin improves the clinical and microbiological indexes of patients with chronic periodontitis after mechanical scaling and root scaling.

Researchers [31] focused on the relationship between the effectiveness of the combination of Amoxicillin + Metronidazole and the pathogen. The patients initially negative for T. Denticola had significantly fewer deep areas after 6 and 12 months in the 3-day antimicrobial group compared with placebo, whereas significantly fewer areas were found in the 7-day antimicrobial group after only 6 months. Patients positive for T. Denticola after 6 months had significantly fewer deep areas in both antimicrobial treatment groups than in the placebo group, whereas patients positive after 12 months showed borderline significance ($p = 0.05$) for the 3 days of antimicrobial therapy [31]. These results support the data of other studies in which the use of the combination of Amoxicillin + Metronidazole resulted in a statistically significant reduction in the number of P. gingivalis, T. forsythia, or T. denticola bacteria after 3, 6, and/or 12 months [25, 39]. Researchers [31], indicate the almost complete ineffectiveness of the combination of Amoxicillin + Metronidazole against A. actinomycetemcomitans, which is consistent with the data [40]. The latter did not reveal a statistically significant reduction of A. actinomycetemcomitans in 3-6 months after scaling with the systemic use of the combination of Amoxicillin + Metronidazole (500 mg 3 times a day for 7 days) neither in patients with chronic nor with aggressive periodontal disease [40]. Some studies compared the effectiveness of the combination of Amoxicillin + Metronidazole for different durations [30, 31], or the advantages of monotherapy with Amoxicillin over the combination of Amoxicillin + Metronidazole [29], or the advantages of monotherapy with Metronidazole over the combination of Amoxicillin + Metronidazole [30, 32]. Almost all studies proved that there is no difference in the use of monotherapy or the combination of Amoxicillin + Metronidazole in the non-surgical adjuvant treatment of chronic periodontitis after previous scaling. The authors also found no significant difference between three- or seven-day treatment, except researchers [30], who demonstrated the effectiveness of long-term (14 days) antibiotic therapy.

Only three studies [28, 34, 35], two of which involved patients with Type 2 diabetes [34] [35], dealt with the effectiveness of other antimicrobial agents for the treatment of chronic periodontitis: Doxycycline [35], Clarithromycin [28], and Clindomycin [34]. Researchers [34] compared the efficacy of Clindomycin and the

combination of Amoxicillin + Metronidazole, but found no significant advantages. Researchers [35], settled that the use of locally applied Doxycycline nanospheres may be an additional therapeutic approach in the treatment of periodontitis in patients with Type 2 diabetes, achieving additional benefits in the improvement of clinical parameters, especially in deep pockets.

## 6. CONCLUSION

The results of all selected studies confirm the additional effect of systemic antibiotics after non-surgical periodontal treatment, especially in patients with more generalized moderate to severe lesions of periodontal areas. Additional use of specific systemic antibiotics may be considered for certain categories of patients, for example, with stage III generalized periodontitis in young people or refractory periodontitis. Although the protocol based on the prescription of Amoxicillin + Metronidazole seems to be more effective and has shown better results, the dose and duration are still controversial. Therefore, further research is needed to clarify these results.

## REFERENCES


[1] Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global Prevalence of Periodontal Disease and Lack of Its Surveillance. Scientific World J 2020; Article ID 2146160. https://doi.org/10.1155/2020/2146160

[2] Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, Murray CJ. Global burden of oral conditions in 1990-2010: a systematic analysis. J Dent Res 2013; 92(7): 592-597. https://doi.org/10.1177/0022034513490168

[3] Zhao H, Hu J, Zhao L. Adjunctive subgingival application of Chlorhexidine gel in nonsurgical periodontal treatment for chronic periodontitis: a systematic review and meta-analysis. BMC Oral Health 2020; 20: 34. https://doi.org/10.1186/s12903-020-1021-0

[4] Drisko C. Periodontal Debridement, Still the Treatment of Choice. J Evid Based Dent Pract 2014; 14. https://doi.org/10.1016/j.jebdp.2014.02.007

[5] Hagenfeld D, Koch R, Jünemann S, Prior K, Harks IP, Eickholz P, Hoffmann T, Kim TS, Kocher T, Meyle J, Kaner D, Schlagenhauf U, Ehmke B, Harmsen D. Do we treat our patients or rather periodontal microbes with adjunctive antibiotics in periodontal therapy? A 16S rDNA microbial community analysis. PLoS One 2018; 13(4): e0195534. https://doi.org/10.1371/journal.pone.0195534

[6] Borges I, Faveri M, Figueiredo LC, Duarte PM, Retamal-Valdes B., Montenegro, SCL, Feres M. Different antibiotic protocols in the treatment of severe chronic periodontitis: A 1-year randomized trial. J Clin Periodontol 2017; 44(8): 822-832. https://doi.org/10.1111/jcpe.12721

[7] Kunz EMK, Thurnheer T, Karygianni L, Walter C, Sculean A, Eick S. Antibiotic Susceptibility Patterns of Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis Strains from Different Decades. Antibiotics 2019; 8: 253. https://doi.org/10.3390/antibiotics8040253

[8] Delatola C, Loos BG, Laine ML. Three periodontitis phenotypes: Bone loss patterns, antibiotic-surgical treatment and the new classification. J Clin Periodontol 2020; 47(11): 1371-1378. https://doi.org/10.1111/jcpe.13356

[9] Chatzopoulos GS, Jiang Z, Marka N, Wolff LF. Association between Periodontitis Extent, Severity, and Progression Rate with Systemic Diseases and Smoking: A Retrospective Study. J Pers Med 2023; 13(5): 814. https://doi.org/10.3390/jpm13050814

[10] Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. J Clin Periodontol 2017; 44: 456-462. https://doi.org/10.1111/jcpe.12732

[11] Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global Burden of Severe Tooth Loss: A Systematic Review and Meta-analysis. J Dent Res 2014; 93(7 Suppl): 20S-28S. https://doi.org/10.1177/0022034514537828

[12] Trindade D, Carvalho R, Machado V, Chambrone L, Mendes JJ, Botelho J. Prevalence of periodontitis in dentate people between 2011 and 2020: A systematic review and meta-analysis of epidemiological studies. J Clin Periodontol 2023; 50(5): 604-626. https://doi.org/10.1111/jcpe.13769

[13] GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. London: Lancet 2017; 390(10100):1211-1259. https://doi.org/10.1016/S0140-6736(17)32154-2

[14] WHO. Oral health. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/oral-health

[15] Listl S, Galloway J, Mossey PA, Marcenes W. Global Economic Impact of Dental Diseases. J Dent Res 2015; 94(10): 1355-1361. https://doi.org/10.1177/0022034515602879

[16] Reynolds I, Duane B. Periodontal disease has an impact on patients' quality of life. Evid Based Dent 2018; 19: 14-15. https://doi.org/10.1038/sj.ebd.6401287

[17] Varma SV, Varghese S, Nair SV. Prevalence of Chronic Periodontitis and Chronic Stress in the South Indian Population. Cureus 2023; 15(1): e33215. https://doi.org/10.7759/cureus.33215

[18] Hashim NT. Use of Antibiotics Versus Probiotics in Periodontitis Therapy. Ann Dent Oral Health 2020; 3(1): 1019.

[19] Hajishengallis A, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. Mol Oral Microbiol 2013; 27(6): 409-419. https://doi.org/10.1111/j.2041-1014.2012.00663.x

[20] Monteiro AV, Ribeiro FV, Viana Casarin RC, Ribeiro Cirano F, Pimentel SP, Zaffalon Casati M. Evaluation of the use of systemic antimicrobial agents by professionals for the treatment of periodontal diseases. Braz J Oral Sci 2013; 12.

[21] Ribeiro FV, Mehta JJ, Monteiro MF, Moore J, Casati MZ, Nibali L. Minimal invasiveness in nonsurgical periodontal therapy. Periodontol 2000 2023; 91: 7-19. https://doi.org/10.1111/prd.12476

[22] Navarrete M, Oñate H, Loyola K, Olivares P. Effect of Periodontal Debridement plus Systemic Azithromycin in subjects with Stage III Periodontitis: A Randomized Controlled Clinical Trial. J Oral Res 2022; 11(5): 1-16. https://doi.org/10.17126/joralres.2022.051

[23] Åberg CH, Kelk P, Johansson A. Aggregatibacter actinomycetemcomitans: Virulence of its leukotoxin and

association with aggressive periodontitis. Virulence 2014; 6: 188-195.
https://doi.org/10.4161/21505594.2014.982428

[24] Rafiei M, Kiani F, Sayehmiri K, Sayehmiri F, Tavirani M, Dousti M, Sheikhi A. Prevalence of Anaerobic Bacteria (P.gingivalis) as Major Microbial Agent in the Incidence Periodontal Diseases by Meta-analysis. J Dent (Shiraz, Iran) 2018; 19: 232-242.

[25] Mombelli A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. Periodontol 2000 2017; 76: 85-96.
https://doi.org/10.1111/prd.12147

[26] Liaw A, Miller C, Nimmo A. Comparing the periodontal tissue response to non-surgical scaling and root planing alone, adjunctive azithromycin, or adjunctive amoxicillin plus metronidazole in generalized chronic moderate-to-severe periodontitis: a preliminary randomized controlled trial. Aust Dent J 2019; 64(2): 145-152.
https://doi.org/10.1111/adj.12674

[27] Lu H, He L, Jin D, Zhu Y, Meng H. Effect of adjunctive systemic antibiotics on microbial populations compared with scaling and root planing alone for the treatment of periodontitis: A pilot randomized clinical trial. J Periodontol 2022; 93(4): 570-583.
https://doi.org/10.1002/JPER.20-0764

[28] Suryaprasanna J, Radhika PL, Karunakar P, Rekharani K, Faizuddin U, Manojkumar MG, Jammula S. Evaluating the effectiveness of clarithromycin as an adjunct to scaling and root planing: a randomized clinical trial. J Indian Soc Periodontol 2018; 22(6): 529-534.
https://doi.org/10.4103/jisp.jisp_254_18

[29] Ardila CM, Flórez-Flórez J, Castañeda-Parra L-D, Guzmán IC, Bedoya-García JA. Moxifloxacin versus amoxicillin plus metronidazole as adjunctive therapy for generalized aggressive periodontitis: a pilot randomized controlled clinical trial. Quintessence Int 2020; 51(8): 612-621.
https://doi.org/10.3290/j.qi.a44715

[30] Ramiro F, de Lira E, Soares G, Retamal-Valdes B, Feres M, Figueiredo LC, Faveri M. Effects of different periodontal treatments in changing the prevalence and levels of Archaeapresent in the subgingival biofilm of subjects with periodontitis: a secondary analysis from a randomized controlled clinical trial. Int J Dent Hyg 2018; 16(4): 569-575.
https://doi.org/10.1111/idh.12347

[31] Cosgarea R, Jepsen S, Heumann C, Batori-Andronescu I, Rosu A, Bora R, Arweiler NB, Eick S, Sculean A. Clinical, microbiological, and immunological effects of 3- or 7-day systemic antibiotics adjunctive to subgingival instrumentation in patients with aggressive (Stage III/IV Grade C) periodontitis: A randomized placebo-controlled clinical trial. J Clin Periodontol 2022; 49(11): 1106-1120.
https://doi.org/10.1111/jcpe.13676

[32] Jentsch FR, Dietrich M, Eick S. Non-Surgical Periodontal Therapy with Adjunctive Amoxicillin/Metronidazole or Metronidazole When No Aggregatibacter actinomycetem-comitans Is Detected - A Randomized Clinical Trial. Antibiotics 2020; 9(10): 686.
https://doi.org/10.3390/antibiotics9100686

[33] Čuk K, Povšič K, Milavec S, Seme K, Gašperšič R. Influence of adjunctive azithromycin on microbiological and clinical outcomes in periodontitis patients: 6-month results of randomized controlled clinical trial. BMC Oral Health 2020; 20(1): 241.
https://doi.org/10.1186/s12903-020-01209-0

[34] Gómez-Sandoval JR, Robles-Cervantes JA, Hernández-González SO, Espinel-Bermudez, MC, Mariaud-Schmidt R, Martínez-Rodríguez V, Morgado-Castillo KC, Mercado-Sesma AR. Efficacy of clindamycin compared with amoxicillin-metronidazole after a 7-day regimen in the treatment of periodontitis in patients with diabetes: a randomized clinical trial. BMJ Open Diabetes Res Care 2020; 8: e000665.
https://doi.org/10.1136/bmjdrc-2019-000665

[35] Lecio G, Ribeiro FV, Pimentel SP, Reis AA, Clima da Silva RV, Nociti-Jr F, Moura L, Duek E, Casati M, Casarin RCV. Novel 20% doxycycline-loaded PLGA nanospheres as adjunctive therapy in chronic periodontitis in type-2 diabetics: randomized clinical, immune and microbiological trial. Clin Oral Invest 2020; 24: 1269-1279.
https://doi.org/10.1007/s00784-019-03005-9

[36] Saleh A, Rincon J, Tan A, Firth M. Comparison of adjunctive azithromycin and amoxicillin/metronidazole for patients with chronic periodontitis: preliminary randomized control trial. Aust Dent J 2016; 61(4): 469-481.
https://doi.org/10.1111/adj.12415

[37] Botero JE, Yepes FL, Ochoa SP, Hincapie JP, Roldan N, Ospina CA, Castrillon CA, Becerra MA. Effects of periodontal non-surgical therapy plus azithromycin on glycemic control in patients with diabetes: a randomized clinical trial. J Periodontal Res 2013; 48(6): 706-712.
https://doi.org/10.1111/jre.12058

[38] Martande SS, Pradeep AR, Singh SP, Kumari M, Naik SB, Kumar Suke D, Singh P. Clinical and microbiological effects of systemic azithromycin in adjunct to nonsurgical periodontal therapy in treatment of Aggregatibacter actinomycetemcomitans associated periodontitis: a randomized placebo-controlled clinical trial. J Investig Clin Dent 2016; 7(1): 72-80.
https://doi.org/10.1111/jicd.12115

[39] Nibali L, Koidou VP, Hamborg T, Donos N. Empirical or microbiologically guided systemic antimicrobials as adjuncts to non-surgical periodontal therapy? A systematic review. J Clin Periodontol 2019; 46: 999-1012.
https://doi.org/10.1111/jcpe.13164

[40] Eick S, Nydegger J, Bürgin W, Salvi GE, Sculean A, Ramseier C. Microbiological analysis and the outcomes of periodontal treatment with or without adjunctive systemic antibiotics-a retrospective study. Clin Oral Investig 2018; 22: 3031-3041.
https://doi.org/10.1007/s00784-018-2392-3

Received on 30-10-2023 Accepted on 27-11-2023 Published on 19-12-2023

https://doi.org/10.6000/1929-6029.2023.12.30