Archives of Current Research International

Volume 24, Issue 2, Page 50-69, 2024; Article no.ACRI.112867
ISSN: 2454-7077

Antimicrobial Sensitivity Associated with *Porphyromonas gingivalis* Present in Periodontitis Frameworks: An Integrative Review

Matéus Simplício Araújo [a], Antônio Evandro de Sousa Silva [a] and Júlio César Sousa Prado [b*]

[a] Universidade Federal do Ceará, Brazil.
[b] Universidade Estadual do Ceará, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. Authors MSA and JCSP designed the study. Mateus performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author JCSP managed and corrected the study analyzes. Author AEDSS managed the literature research and translated the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ACRI/2024/v24i2633

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/112867

Review Article

Received: 01/12/2023
Accepted: 06/02/2024
Published: 09/02/2024

ABSTRACT

Objectives: The Gram-negative anaerobic bacterium *Porphyromonas gingivalis* is identified as one of the most important causes of the chronic form of periodontitis. This work aimed to analyze the sensitivity of *P. gingivalis* to antibiotics and antimicrobial agents.
Study Design: Integrative literature review.
Methodology: Through a careful analysis of clinical trials published in the last 5 years. A bibliographic search was carried out in the PubMed, Scielo and Google Scholar databases. Three keywords were established and verified on the DeCs-Descritores em Ciências da Saúde website

**Corresponding author: Email: cesarprado55@gmail.com;*

for the literary search “Antimicrobial resistance”, “Periodontal biotherapy” and “*Porphyromonas gingivalis*”. 66 articles were found. Of these, animal studies, studies that did not involve patients diagnosed with periodontitis according to the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions, and studies on peri-implantitis were excluded. Studies that used only surgical therapy without association with at least one antibiotic or antimicrobial and duplicate studies were excluded.

Results: This integrative review presents the results of 19 studies. Amoxicillin, Metronidazole and Azithromycin are the most commonly used antibiotics. Photodynamic therapy has demonstrated benefits in reducing inflammation and *P. gingivalis* counts. It has been demonstrated that *P. gingivalis* is not sensitive to *Lactobacillus brevis* and *Lactobacillus plantarum*-ProlcSan probiotic gel and tablets, as no reductions in its proportion and total count were observed. Similar results were also observed in the study that investigated the effect of administering piperacillin plus Tazobactam gel and doxycycline gel.

Conclusion: Although most of the articles presented report the sensitivity of *P. gingivalis* to their protocols, microbiological reduction is not always accompanied by clinical benefit, since periodontal disease is multifactorial. Based on these findings, it is concluded that there are several antimicrobial agents capable of promoting the reduction of this key pathogen in periodontitis.

Keywords: Porphyromonas gingivalis; resistance; sensitivity and periodontal antibiotic therapy.

1. INTRODUCTION

The periodontal or periodontal apparatus consists of various types of tissue (epithelium, connective tissue, cement and bone), which has the function not only to anchor the dental element in the jawbone bones (mandibula and jawbones), but also to form a hermetic seal around the tooth to prevent the penetration of oral microorganisms in it, thus preventing infections in these tissues. Periodontal diseases are those that affect the health of the gums and are among the most common diseases worldwide, periodontitis and gingivitis are the ones with the greatest epidemiological impact [1]. Most of the affected individuals have a mild to moderate course of the disease. Severe forms of periodontitis occur mainly in older and older adults. In the 2015 Global Burden of Disease Study, the prevalence of severe periodontitis worldwide was estimated at 7.4% [2].

Periodontitis is an inflammatory disease that affects the cement, periodontal ligament and alveolar bone, resulting in the degradation of these tissues and, subsequently, if not treated in more severe consequences such as the loss of the dental element [3]. This disease has an important and complex microbiological role, since it is mediated by the action, mainly, of bacteria of anaerobic nature that are normally present in the oral cavity and that due to immune imbalance or lack of oral hygiene can proliferate in a complex arrangement of microorganisms, the subgingival biofilm, and induce constant inflammation in the tissues adjacent to the dental surface that has biofilm adhered, inducing a degeneration of the insertion apparatus (cement, periodontal ligament and alveolar bone). This picture is clinically reflected in loss of clinical insertion level (CIN), probe bleeding, formation of purulent secretion bags, aesthetic and functional defects, dental mobility, halitosis and in some cases painful episodes [4].

The subgingival accumulation of Gram-negative bacteria predominantly anaerobic as a result of periodontal destruction and installation of the disease. Among the various bacterial species associated with the biofilm present in the periodontal bolsas, a bacteria anaeróbia Gram-negativa *Porphyromonas gingivalis* is pointed out as one of the most important causes of the chronic form of the disease [5]. In this bias, Socransky et al. (1998) describes a group of bacteria but virulentas that possess but atuação no processo de destruição periodontal, bacterial species *Porphyromonas gingivalis, Tannerella forsythia e Treponema denticola* thus composing the so-called “microorganisms of the red complex”[6]. This group colonizes the biofilm subgingivally and is strongly associated with inflammation and progression of periodontal disease [6].

“After an initial periodontal therapeutic intervention, the periodontal bags should be treated mainly with scratching and root smoothing (RAR), to remove subgingival biofilms and dental calculus, which is the gold standard for achieving mechanical debridement” [7]. In this context, the treatment of *P. gingivalis* infections in periodontitis frames is based on the removal of retention factors from the dental biofilm and can

be surgical, such as removing of subgingival stone through scratching and radicular smoothing (RAR) or subgingival scratch, non-surgical, administration of antibiotics and oral rinse, or the combination of the two [8]. Evidence in the literature points out that the combination of the two forms is the best therapeutic conduct to obtain the decrease of the concentration of *P. gingivalis* in the periodontal tissues [8]. In this context, this work will aim to analyze the sensitivity of *Porphyromonas gingivalis*, one of the main and most studied agents involved in the etiopathogenesis of periodontal disease, to antibiotics and antimicrobial agents.

2. METHODOLOGY

2.1 Criteria to Consider Studies for this Analysis

Due to the constant therapeutic innovations related to periodontal therapy, a literary search was carried out limited to the last 5 years, therefore this work selected only studies published between July 2023 and June 2018. To this end, this search was carried out using the PubMed data bases, Scielo and Google Scholar. Three keywords were established and verified in the DeCs-Descriptors on the Health Sciences website.

2.1.1 Types of studies and inclusion criteria

The selection of articles for analysis in this study was based primarily on the inclusion of randomized clinical trials that had as a test group at least one antimicrobial agent and works published in the English, Portuguese and Spanish languages over the past 5 years.

2.1.2 Exclusion criteria

Animal studies, studies that did not involve patients diagnosed with periodontitis according to the 2017 World Workshop on the Classification of Periodontal and Perimplantal Diseases and Conditions, and studies on peri implantitis were excluded. Works using only surgical therapy without association with at least one antibiotic or antimicrobial agent were excluded.

3. RESULTS

After critical reading of titles and summaries, articles that appeared to meet the inclusion criteria were downloaded for full text review. This was done in the same way when there was not enough title, keyword or summary information. At the end of this stage, 66 items were obtained, as described in Table 1. In addition to the exclusion criteria already mentioned, duplicate studies were excluded, so this literature review was made using 18 articles. Table 1 shows how many articles were selected in the search for each descriptor.

Table 1. Relation of articles selected for integrative review

Keywords	Number of studies obtained	Number of selected studies
"Antimicrobial resistance"	170	02
"Periodontal antibiotic therapy"	82	15
"Porphyromonas gingivalis"	70	18

Source: Authors, 2023

The results found in the literature regarding the sensitivity and antimicrobial resistance of *P.gingivalis* are described and synthesized in Table 2.

4. DISCUSSION

"This integrative review of the literature was carried out with 18 articles, of which individuals were included in the clinical trials, among the results, this work allows to conclude that the use of antibiotics as a supplement to the standard protocol of scratching and root smoothing (RAR) has been a research topic in the treatment of periodontitis due to its effect on all niches occupied by bacteria associated with periodontitis, especially those of the red complex, such as *P. gingivalis"* [14]. However, excessive and inappropriate use has been associated with the problem of developing bacterial resistance [27]. Among the antibiotics used to reduce the population of *P. gingivalis* found in periodontal bags most described in the literature are Azithromycin (AZI), Amoxicillin (AMX) and Metronidazole (MET). Several clinical trials investigate the effects of these three antimicrobial agents ranging in combination, dosage and duration of treatment. It has been demonstrated that the uses of systemic MET+AMX after RAR during 3 and 7 days regimes do not cause significant differences, since the RAR+placebo protocol obtained similar results in reduction of *P. gingivalis* [24], similar conclusions have also been achieved in other studies with MET +AMX [20].

Table 2. Results of clinical trials selected for analysis

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
Nakao, et al. [9]	A double-blind controlled clinical trial was conducted with 24 subjects to investigate the effect of topical administration of propolis (a beekeeping product) or curry leaf (a plant-based product) on periodontal bags of patients with periodontitis	Inclusion criteria: (1) patients who had finished the initial periodontal therapy and were entering the therapy phase periodontal support; (2) patients who had at least one tooth with periodontal bags with PPD≥5 mm.	During periodontal therapy of support, four groups were submitted to the administration of different ointments; Placebo group n=06 [placebo ointment of CMC (carboxymethyl cellulose sodium salt)] Propolis group n= 06 (0,01 mg/mL of propolis extracted with ethanol in CMC ointment) Curry leaves group n=06 (1 mg/mL curry leaf extracted with water in CMC ointment) Minocycline group n=06 (minocycline hydrochloride ointment at 2%)	Ginger crevicular fluid samples (FGC) collected before and after the intervention were analyzed to quantify the total number of bacteria and the number of six main Real-time PCR periodontopathic bacteria. Clinical parameters related to periodontitis were also analyzed among six patients treated with propolis whose GCF samples were *P. gingivalis*-positive.	Propolis treatment caused a tendency to reduce *P. gingivalis* load on the GCF. Propolis therapy will likely become an alternative treatment option for chronic periodontitis during periodontal supportive therapy. In conclusion, *P. gingivalis* is sensitive to propolis.
Cosgarea, et al. [10]	This study was a prospective, randomized, placebo-controlled, double-blind clinical trial. The following hypothesis	One hundred and two individuals (average age 43.37 ± 9.85, 65 females, 35 smokers, n = 34/group) were included in the study	Placebo group n = 26 AMX + MET Group of 3	The detection of *P. gingivalis* was performed using the real-time PCR method.	Analysis of the present data from this work indicates that significant reductions in *P. gingivalis* pathogen

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	was tested “systemic use of Amoxicillin and Metronidazole administered for 3 or 7 days as a supplement to Radicular Debridement (DS) leads to superior clinical results compared to DS alone”.	and 27 patients dropped out of the 12-month evaluation. The reasons for excluding the final analysis were antibiotic intake by other medical reasons, non-compliance with the consultation schedule and change of city.	days n = 24 AMX + MET Group of 7 days n = 25.		concentration were achieved. Investigation of the two antibiotic protocols led to comparable microbiological and inflammatory results. In other words, *P. gingivalis* is sensitive to Amoxicillin and Metronidazole..
Kokak, et al. [11]	This parallel drawing study was a blind clinical trial, controlled and randomized. The study was approved by the Selcuk University Ethics for Human Beings (2013/57) (Registration number: TCTR20180901001). The study was conducted in Department of Periodontology of Selcuk University, Faculty of Dentistry, between April 2011 and October 2013.	The following inclusion criteria were used: be ≥30 years old, have at least 17 teeth and have≥8 periodontal bags with PD≥5 mm and CAL≥4mm	Sixty patients with type 2 diabetes mellitus (DM) with chronic periodontitis (PC) were distributed randomly in two parallel groups to receive root scratching (RAR,n =30) or RAR followed by laser irradiation 940 nm diode periodontal bag DL (RAR + DL, n = 30).	A commercial extraction kit (DNeasy Blood & Tissue Kit, Qiagen, Hilden, Germany) was used for DNA extraction bacterial of subgingival plaque samples, considering the instructions of the manufacturer. Quantities of *Porphyromonas gingivalis, Treponema dentistry,* and *Tannerella forsythia* were evaluated with RT-PCR quantitative.	Within its limits, the results of this study suggest that the use of a DL of 940 nm as an adjuvant to RAR did not promote additional effects in terms of reduction in *P. gingivalis* counts compared to RAR alone. However, although its clinical application is not advantageous, it is concluded that this agent has the ability to reduce the count of this pathogen.
Odor, et al. [12]	This study was designed as a randomized, controlled, single-blind, multicenter, with split mouth design to compare the antimicrobial effect of non-periodontal therapy	The inclusion criteria were the following: at least 16 natural teeth present in the cavity oral distributed in 4 squares, probe depth periodontal (PPD) minimum of 5 mm per square with reabsorption	Group 1 (control group): scraping and root smoothing (SRP) n=38; and the following experimental groups: Group 2: laser diode SRP	The microbiological tests were carried out by means of polymerase chain reaction (PCR) in real time by MIP Pharma Laboratory, for determination qualitative and quantitative of nine periodontal pathogens, including *P. gingivalis*	Within the limitations of this study, we can conclude that the synergistic effect of SRP and H2O2 photoactivation with a 940 nm diode laser offers an efficient and

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	surgical with SRP alone, 940 nm diode laser in combination with SRP and H2O2 photoactivation with 940 diode nm in combination with SRP. The study protocol was approved by the Ethics Committee of Ovidius University of Constanta, Faculty of Dental Medicine, under no 14533/22.09.2015 and conducted in accordance with the Declaration of Helsinki (revisada em 2013, Fortaleza, Brasil).	clinically and radiologically proven bone and bleeding to probe (BoP) in all 4 squares.	+940 nm n=38 ; Group 3: SRP+H2O2 photoactivation with 940 nm diode laser n = 38.	.In addition, the total count of bacteria (TBC) was evaluated by sample. The company stated that the detection limit for each bacterium was confirmed in 100 germs per milliliter.	reliable antimicrobial effect in the non-surgical periodontal treatment approach. Thus, it is concluded that the pathogen *P. gingivalis* is sensitive to said protocol.
Acharya, et al. [13]	This study was conducted as a double-blind, randomized clinical trial.	The inclusion criteria were as follows: (a) patients with diagnosis of periodontitis (CAL of 2 mm, PD of ≥ 4 mm and bone loss horizontal marginal [MBL] of at least 3 mm [21]).	The patients were randomly divided into 3 groups as follows: Group-1 – patients submitted to RAR with PDT only at the beginning of study n=15; Group 2 – patients were subjected to RAR and PDT at the beginning of the study, followed by a second PDT session after 1 month n=15; Group 3 – patients were subjected to	Dilutions of the samples were placed on a plaque of non-selective blood agar supplemented with menadione (1 mg/l), hemin (5 mg/L) and 5% sterile horse blood. After 7 days of anaerobic incubation total counts and representative colony counts were performed on plates containing between 30 and 300 colonies. colonies were identified by microscopy, studying Gram colouring and enzymatic activity (including α-galactosidase, α-glucosidase and α-fucosidaze, activity tripsin-like,N-acetyl-β-D-glucosaminidase, indol and sculin). The pigmented colonies of black *P. gingivalis* and intermediary P. were tested under red fluorescent light (360 nm): negative for *P. Gingivalis* and positive for	There was a statistically significant reduction in CFU/mL periodontopathogenic bacteria at 6 months of follow-up in groups 2 and 3. It was concluded that there is antimicrobial sensitivity of *P. gingivalis* to the protocols studied.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
			RAR and PDT at the beginning of the study, followed by 2 additional aPDT sessions, which were performed after 1 and 3months n=15.	intermediate P.	
Peralta,et al. [14]	This parallel, unicentric group clinical trial with duration of 9 months, was registered at Clinicaltrials.gov (NCT03103204) and approved by the Ethics Committee (protocol 36828114.4.0000.5501). The protocol consisted of complete oral periodontal debridement in up to 24 hours, in two one-hour sessions each, brushing of the tongue with chlorhexidine gel 1% for 1 minute, subgingival irrigation with chlorhexidine gel 1% after scratch and cheeks with chlorhexidine 0.12% for 30 minutes. Followed at the beginning and end of each session, with I'm gonna make a gargle in the last 10 seconds. Furthermore, during Fourteen days, chlorhexidine 0.12% was	This prospective study included participants with moderate, severe and advanced periodontitis (stage II: established periodontitis with characteristic damage caused to the dental support, including interdental CAL of 3 to 4 mm, PPD maximum ≤ 5 mm and X-ray bone loss in the coronal tertiary between 15% and 33%; stage III and IV: – by less interdental CAL ≥ 5mm, PPD ≥ 6 mm and bone loss radiographic extending up to a light third of the root), as described by Tonneti, et al.28(2018).	The selected subjects were divided into two groups, according to their body mass index (BMI) and waist circumference. Non-obese group (n=39), BMI ≤ 29.9 kg/m2e waist circumference < 102 cm for men and < 88 cm for women. Obese group (n=55), BMI ≥ 30 kg/m2and waist circumference > 102 cm for men and > 88 cm for women.	Following the specifications of the manufacturer, the DNA genomic (gDNA) was extracted and purified using a Mini Commercial Genomic DNA Kit (Life Technologies, Carlsbad, CA, USA). The total microbial count of *Tannerella forsythia, Porphyromonas gingivalis, Treponema dentistry*, and Aggregatibacter actinomycetemcomitans was performed by quantitative polymerase chain reaction in real time (qPCR) using a set of TaqMan (Life Technology, Carlsbad, CA, USA) primers/sondes on PCR system in time real, following the manufacturer's instructions.	At 9 months, *P. gingivalis* decreased significantly in both groups ($p<0.05$) with no significant difference between the groups. Concluding that chlorhexidine, in concentrations of 2%, 1% and 0.12% in gel and mouthwash, is an effective antimicrobial agent for reducing p counts. gingivalis.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	used twice a day. Every three months, patients were subjected to oral hygiene instructions, dental prophylaxis and supragingival toothbrushing.				
Sukumar et. Al. [15]	This randomized and controlled clinical trial following mouth drawing divided was approved by the institutional ethics committee and the Scientific review of SRM University and was conducted in the department of Periodontics, SRM Dental College, Ramapuram, Chennai from May 2019 to November 2019. The study was registered under clinical trial records, India with CTRI number CTRi/2019/05/019057. The guidelines of Consolidated Standards of Reporting Trials (CONSORT) were being followed andFigure 1 shows the study design.	The inclusion criteria consisted of patients with bilateral periodontal destruction in posterior jaw segments involving a minimum number of 3 permanent teeth in each segment. Bags included moderate periodontics with probing depth of 4-6 mm and clinical insertion loss.	Control group (RAR as single treatment) n=30 Test group (RAR + Multiple applications of PDT (photodynamic therapy) n=30 *(RAR). PDT was employed with diode laser (810 nm) and green indocyanine dye (ICG) at the start of the study, 1st, 2nd and 4th week after RAR.	This was achieved in Real-time PCR, setting a standard curve using dilutions in PCR amplicon series obtained by amplification of regions hyper variables of the V5-V6 region of the gene 16 s rRNA representing 789 a 1068 pairs of bases of the E. coli genome.	Test Sites Showed Reduction Statistically significant in the average microbial concentration (copies/µl) of *P. gingivalis*, from the beginning to 3 and 6 months. We conclude that *P. gingivalis* is sensitive to laser therapy alone, as well as in synergism with an indocyanine green dye.
Rahman, et al. [16]	The present study was conducted as a clinical-microbiological trial and prospective, blind, randomized and evaluator-controlled biochemistry in	Patients included in this study were-(i) in the age group of 35 - 60 years of both sexes (ii) Patients with Grade A and Stage periodontitis II (moderate disease) (iii)	A total of 33 test sites in 11 patients with Grade A Stage II periodontitis were divided randomly in three	Quantification of *Porphyromonas gingivalis* was evaluated by RT –PCR technique and the estimation of RANKL levels was verified by ELISA. All evaluations were made at the beginning and 3 months	A significant reduction in *P. gingivalis* copy number was observed in all groups at 3 months of follow-up. When comparing groups, the

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	split mouth drawing. The design of the study was approved by Institutional Review Board (IRB) before the start of the study. (Ref No. BCD Exam/383/2017-1) and carried out under the legal agreement with the ethical standards established by the Helsinki Declaration of the World Medical Association. Each patient received a detailed verbal and written description of the study and a signed consent term was obtained from all patients.	Patients with <0.25% bone loss per year, high rates of biofilm deposition, but slow rate of progression,(iv) Non-smoking patients and patients without diagnosis of diabetes or other systemic diseases. (v) Patients with probe depth≤5 mm, RAL (Relative fixation level)≤4 mm, horizontal bone loss, requiring non-surgical treatment. (vi) Patients in whom loss was not expected post-treatment dentistry, indicating that the case has a good prognosis in maintenance.	groups:Group I: Treated only with RAR (Group RAR);Group II: treated by RAR followed by aPDT (aPDT group);GROUP III: Treated by RAR followed by single subgingival administration of 1.2% simvastatin gel (grupo SMV) Clinical parameters including API, PBI, PPD and RAL were evaluated.		reduction was greater in the group II (aPDT group) compared to group I (RAR group) and group III (SMV group), although the difference in scores was not statistically significant. significant. Concluding that laser therapy and simvastatin gel 1.2% have the capacity to reduce *P. gingivalis* counts.
Claudio,et al. [17]	A randomized, controlled parallel clinical trial was conducted, developed in one place with follow-up after 90 and 180 days. The present study was conducted between June 2016 and January 2020 according to the new CONSORT-2010 DECLARATION[39], and received the approval of the Research Ethics Committee with Human Beings of the Faculty of Dentistry of Araçatuba (CAAE n.◦ 55.845.416,0. 0000.5420),	In order to be included in this study, patients should the following inclusion criteria: age≥30 to≤70 years[27], diagnosis of DM2 decompensated (HbA1c≥7,0%) [1,40] and periodontitis stages III and IV, degree C with at least 6 locations with PD and CAL≥5 mm and BOP [6,41] in at least 15 teeth, excluding third molars.	Thirty-one patients with uncompensated DM2 and periodontitis were randomly divided into two groups: RAR group (n=15): dimensioning and root planing (PRS); and SRP+aPDT group (N=16): SRP followed by 3 applications consecutive aPDT, immediately, 48 and 96 h after in pockets with	Cones of sterile absorbent paper (#30, Tanari, Manacapuru, AM, Brazil) were introduced into the gingival sulcus, to the bottom of the bag periodontal, staying in place for 30 seconds.[30]. After the withdrawal, the absorbent paper cones were placed in eppendorf tubes containing 500μL buffered saline solution (PBS, pH 7,0) and frozen to -80◦C for subsequent microbiological analysis[30].	Within the limitations of the study, a reduction in *P. gingivalis* counts was found in all groups with statistically insignificant differences. It is concluded that *P. gingivalis* is sensitive to both laser therapy protocols.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	and is also registered in the Brazilian Register of Clinical Trials (Registration Number: RBR-9sq542).		probing depth (PD)≥5mm. In SRP+aPDT, after 1 min irrigation with methylene blue (10 mg/ml), the sites were irradiated with a 660 nm diode laser for 50 s (157 J/cm2, 4.7 J, 100 mW).		
Al-Khureif, et al. [18]	This clinical study was a 6-month clinical trial, divided mouth, parallel arm, double-blind, randomized and controlled, designed and conducted in accordance with the Helsinki Declaration (1975) following the guidelines of the Consolidated Standards of Reporting Trials (CONSORT). This ECR has been registered at clinictrials.gov under the identifier: NCT04857346.	Individuals with diagnosis of chronic periodontitis of according to the new classification and definition of case of periodontitis that had probing depth (PD) of ≥6 mm, loss of insertion clinical interdental (CAL) of ≥5 mm and X-ray evidence of bone loss extending to the middle third of the root and beyond (≥3mm)[6]. The individuals were grouped on the basis of the well-controlled and poorly controlled diabetic state, having have been diagnosed at least 1.5 years before the study. The individuals were included if they had glycated hemoglobin (HbA1c) levels ranging from 6% to 10% for controlled DM2 and≥10% for uncontrolled DM2, in treatment of Diabetes with	A split mouth drawing was used, in which a location was designated for control (isolated treatment of RSD), while the other contralateral location was chosen for treatment of test (ICG-aPDT/RSD) in all patients.	The identification of *Porphyromonas gingivalis* was through PCR was performed using Species-specific primers. Initiators for DNA Sequences ribosomal 16S were selected	Indocyanine green-mediated PDT significantly improved antimicrobial parameters. It is concluded that there is a proven sensitivity of *P. gingivalis* to lasetaria alone, as well as combined with indocyanine green.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
		oral hypoglycaemic and/or diet[18].			
Cruz, et al. [19]	Volunteers with type 2 DM and severe periodontitis 18 directed to the Periodontal Clinic of Guarulhos University and included in a previously published RCT13(NCT02135952) were called again and inserted this study. Patients were informed about the nature, potential risks and study benefits and signed the term of free and informed consent. This study was approved by Guarulhos Ethics Committee in Clinical Research of the University and was conducted according to Helsinki Declaration of 1975, revised in 2013.	Patients who participated in RCT (NCT02135952) were included in this study13.	Control group (RAR+placebo, n=29) or Test (SAR+MTZ+AMX test; n=29). MTZ (400 mg three times per day) day [TID]), AMX tablets (500 mg TID) and placebo were prescribed for 14 days and started on the first SRP Session.	The biofilm samples were evaluated for the content of 40 bacteria Species by DNA-DNA chess hybridization, as described earlier 19,20.	In the test group, *Porphyromonas gingivalis* counts were reduced after treatment. Therefore, it is concluded that this pathogen is sensitive to the antimicrobial action of Amoxicillin and Metronidazole.
Radulescu, et al. [20]	This study was conducted as a triple-blind clinical trial randomized placebo-controlled 12 months with a parallel drawing of three independent groups by one allocation ratio of 1:1:1.	Sixty-two patients who were treated for stage III-IV periodontitis and enrolled in SPT were included in the study based on the following criteria: (1) active periodontal therapy completed at least 6 months before enrolment in the study, (2) presence of at least 4 non-	Patients selected were randomly divided into three groups and further treated with a single subgingival administration of gel NaOCl (group A n=20); CHX gel (chlorhexidine 1%)	A molecular genetic analysis was performed to detect *P. gingivalis.* A semi-quantitative analysis of bacteria was evaluated using the commercial kit micro-IDent® plus (Hain Lifescience GmbH, Nehren, Germany), which is based on the STRIP DNA technology.	Treatment of Waste Bags Using Subgingival USI and a single application of sodium hypochlorite gel demonstrated the ability to reduce *P. gingivalis* counts, as well as similar results were obtained with the use of

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	The study was approved by the Committee of Research Ethics of the University of Medicine and Pharmacy Victor Babes Timisoara (approved on 1/21.01.2018).	adjacent locations with probe bag depths (PPDs) ≥ 4 mm with probe bleeding (BOP), or the presence of 5–8 mm PPDs with or without BOP.	(groupe B n19=); and placebo gel (group C n=18).		1% chlorhexidine gel. Proving the sensitivity of this pathogen to sodium hypochlorite gel and 1% chlorhexidine gel.
Povšič, et al. [21]	This was a 12-month, randomized, drawing clinical trial parallel, placebo-controlled, double-blind and unicentric. registered in the EU Register of Clinical Trials (EUDRA-CT: 2015-004306-42) and approved by the National Committee for Medical Ethics (46/08/15), as well as by the Agency for Medicines and Devices Doctors of the Republic of Slovenia.	The criteria for inclusion were between 25 and 70 years of age, presence of at least 20 teeth (excluding third molars) and moderate to advanced untreated periodontitis (stage III or IV of agreement with the American Academy of Periodontology (AAP) and European Federation of Periodontistry (EFP).	Forty patients with stage III or IV periodontitis were carefully selected as participants in the study. RAR control group + placebo (n = 20) Azithromycin group RAR + AZI (n = 20)	Subgingival biofilm samples from all individuals were collected at the start of the study and in the six-month reassessment. As samples were taken from the 4 deepest locations of the each quadrant of the jaw using two ends of paper absorbent (diameter: 0.30 mm; Maillefer, Ballaigues, Switzerland). The mass spectrometry of laser assisted matrix desorption/ionization flight time (MALDI TOF MS) (MBT COMPASS 4.1, Microflex, Bruker Daltonics, Bremen, Germany) was employed for the identification of colonies bacterial plates containing a total count of colonies of 30–300 colonies. A reference laboratory was used for protocol adjustment and calibrations before microbiological analysis	The systemic use of azithromycin as an adjuvant to RAR provided a reduction in *P. gingivalis* counts. Therefore, the sensitivity of this pathogen to azithromycin can be confirmed.
Pudgar, et al. [22]	This was a 3-month double-blind, single-center clinical trial, randomized, placebo-controlled, parallel drawing. A	The inclusion criteria: systematically healthy, aged between 25 and 80 years, not treated with advanced periodontitis with	Test group; probiotic gel and pills n=20 (Lactobacillus brevis e	Before treatment, grouped microbiological samples were taken from 4 sub glyph locations of each participant – one sample per jaw square at the deepest spot of the DP with two	In terms of microbiological changes, reductions in the proportion and total count of *P. gingivalis*

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	authorization was obtained from the National Committee on Medical Ethics (no 0120-365/2018/5) of the Republic of Slovenia.	depth of probe (PD) of ≥5 mm in at least four teeth in four different quadrants (stage III or IV according to classification AAP/EFP of 2018), has stable occlusion and with the presence of at least 16 teeth of which at least 12 have been scored (excluding molar third).	Lactobacillus plantarum-ProlcSan) Control group (placebo) n=20	absorbent paper tips (diameter 0.30 mm; Maillefer, Ballaigues, Switzerland) – and placed in test tubes containing 1.5ml of reduced transport fluid. the number of colonies of *Porphyromonas gingivalis* Tannerella forsítifoi counted after 14 days. Bacterial colonies were identified using mass spectrometry of desorption flight time/matrix-assisted laser ionization (MALDI TOF MS) (MBT COMPASS 4.1, Microflex, Bruker Daltonics, Bremen, Alemanha).	were observed only in the control group. Concluding that *P. gingivalis* is not sensitive to Lactobacillus brevis and Lactobacillus plantarum-ProlcSan probiotic gel and tablets.
Collins, et al. [23]	This clinical trial was designed as a double-blind ECR parallel. From March 2015 to February 2018, the potential candidates were selected in the Department of Periodontics of the Pontifical Faculty of Dentistry Catholic University Madre y Maestra (PUCMM), Santo Sunday, Dominican Republic (campus Santo Domingo). The protocol was also registered (ISRCTN12151923, BMC Springer Nature).	Consecutive subjects were selected with clinical examination and radiographic and medical history, using the following criteria of inclusion: (1) severe chronic generalized periodontitis [18], corresponding to general periodontitis in stage III or IV, with grades B–C [1]; (2) at least 10 functioning teeth, excluding molar third; (3) places with DP ≥ 5 mm, in ≥ 2 teeth at ≥ 1 quadrante, at the initial visit; (4) X-ray evidence of bone loss ≥ 30% in at least 30% of dentition; and (5) at least 30 years.	Systemically healthy patients with periodontitis in stages III-IV, degrees B-C, were randomly assigned to receive metronidazole or placebo as a supplement to periodontal surgery, after subgingival instrumentation. Placebo group (Operation + placebo) n= 18 Test group (surgery + Metronidazole 500mg) n=20	Of each quarter, the place with deepest PD and BOP was selected for subgingival sampling for analysis microbiological. Next, bacterial DNA was extracted and processed with quantitative PCR multiplex (qPCR) for detection and quantification of Aggregatibacter actinomycetemcomitans,*Porphyromonas gingivalis,* and *Tannerella forsythia.*	At the end of the study, P counts. Gums were significantly lower in the test group. Concluding that this pathogen is sensitive to metronidazole 500mg.
Cosgarea, et al. 24]	The hypothesis to be tested in this prospective, randomized, triple-masked and placebo	The following criteria for inclusion in the study were considered: • age: 18–38 years (≤35 years	Group A (SI +AMX+ MET 500mg 3 days) n=25	Quantitative and qualitative microbiological analyses of periodontopathogens. actinomycetemcomitans,	*P. gingivalis* presented in the group of 3 and 5 days statistically significant reductions in

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	controlled was that "systemic use of AMX and MET administered for 3 days in addition to the Subgengival Instrumentation leads to non-clinical results lower compared to the 7-day protocol".	at the time of diagnosis) • ≥12 teeth distributed in all four squares • AgP (Armitage, 1999): primary characteristics (family aggregation, rapid loss of insertion and bone destruction, except for periodontitis, otherwise clinically healthy) and/or secondary characteristics (depots microbials inconsistent with the severity of tissue destruction periodontal, widespread loss of interproximal insertion affecting the minus three permanent teeth, except first molars and incisors) • plaque scores in whole mouth	Group B (SI +AMX+ MET 500mg 7 days) n=25	*Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola*, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus, andFilifator alocisforam performed using real-time polymerase chain reaction (rtPCR), as recently described (Cosgarea et al.,2020).	both follow-ups. Concluding that both amoxicillin and medronidazole have the ability to reduce *P. gingivalis* counts.
Doğan, et al. [25]	The subjects of this study participated in the University Zonguldak Bülent Ecevit, Faculty of Dentistry, Department of Periodontology, Zonguldak, Turkey, between January 2013 and February 2016. The protocol of this study randomized split mouth and control was approved by Ethics Committee in Clinical Research,	Patients with Periodontal and Peri-Implant Diseases and Conditions (S3GCP) with at least six teeth with Interdental probe depth (PD)‡6 mm and clinical fixation level (CAL)‡5, and at least three of these six teeth without first molars and incisors were included in the study. Severe damage to periodontal support tissue was observed in these patients, which was not compatible with age and plaque levels. X-ray bone loss/age was used to determine the degree of	A total of 18 patients were randomly assigned to the test group (Modified Widman Flap + 810nm -5 laser therapy) and 18 to the control group (Modified Widman Flap only).	For DNA isolation, a commercial kit, QIAGEN, the QIAamp DNA Mini Kit (Qiagen Sciences, MD) was used according to the manufacturer's guidelines. The amount of DNA obtained after isolation was measured spectroscopically using Qbit (Qiagen) spectroscopically and recorded for to confirm the existence of DNA in the samples. The molecular detection and qualification of the bacteria were determined using primers (TaqMan) and probes marked with 3¢-FAM and 5¢-TAMRA dyes. Real-time polymerase chain reaction (PCR) was	The amounts of *P. Gingivalis* were statistically lower at the site test (application of diode laser) than in the control site in 3 months. It is concluded that *P. Gingivalis* is sensitive to 810nm -5 laser therapy

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
	Zonguldak University Bülent Ecevit, School of Medicine, Zonguldak, Turkey, in in line with the Helsinki Declaration of 1975, as revised in 2000 (protocol ID: 2012-125-30/10).	periodontitis of patients.21If bone loss/age % was >1,0, it was Recognized as Grade C. The tooth with the most severe bone loss as a percentage The length of the root was determined for X-ray bone loss. Systemically healthy patients with at least 20 teeth were included in this study. A total of 30 participants, who were diagnosed with S3GCP after clinical examination, were included in this study.		performed as six individual monoplex reactions with primers replaceable and probe targets	
*Il*yes, et al. [26]	This study was conducted as a double-blind, randomized, placebo-controlled clinical trial of 6 months with a parallel drawing of three independent groups by an allocation ratio of 1:1:1.	Criteria for inclusion: individuals over 25 years of age, at least 8 places with DP≥5 mm and showing bleeding at probe, clinical loss of insertion≥5mm, patients who have not undergone periodontal therapy in the last 12 months. Patients with the following conditions were excluded: psychiatric disorders clinically relevant, alcohol consumption, autoimmune diseases, HIV infection, diabetes untreated mellitus, pregnancy or lactation, patients receiving periodontal therapy in Medicine 2023,59, 303 4 out of 17 of the last 12 months, patients who local and/or systemic antibiotic	Group A n=21 (additionally treated with a single subgingival administration of piperacillin plus Tazobactam gel) Group B n=22 (gel de doxiciclina) Group C n=21 (gel placebo)	It was carried out by molecular genetic analysis of the samples collected. The presence of *P. gingivalis* was evaluated using a commercial kit micro-IDent® (Hain Lifescience, Nehren, Germany). The same sites were used to collect microbiological samples during the reassessment period of 6 months	Microbiological results regarding the reduction of *P. gingivalis* were not statistically significant between the three groups at baseline and after 6 months. Thus, *P. gingivalis* showed little or no sensitivity to the administration of piperacillin plus Tazobactam gel and to doxycycline gel.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of *P. gingivalis*	Results
		therapy within 3 months before the initial examination of this study, candidiasis, allergy to piperacillin, tazobactam, doxycycline, or any tetracycline or penicillin or any excipient of the products used, systemic medication that can influence the clinical characteristics of periodontitis, patients who have rinse or irrigated with antiseptics less than a month before the initial examination, conditions that require antibiotic protection.			

"However, in recent years photodynamic therapy with lasers has gained a lot of space in the research scene. The literature addresses its application with or without RAR, i.e. being applied both with non-surgical therapy and with subgingival instrumentation. Among the lasers, diode lasers (LD) have been frequently used in periodontal therapy because they show better absorption properties of hemoglobin, melanin and pigmented bacteria causing periodontal disease. The antibacterial effect of lasers can be enhanced by the inclusion of a photosensitizing dye, known as photodynamic therapy (PDT). The principle of operation is that the photosensitizer goes through a transition from a basic state of low energy to a triple state of higher energy, producing a highly reactive state of oxygen" [18]. "This triple-state photosensitizer can react with biomolecules in two different ways – Type I and Type II reactions. Type I pathway involves electron transfer reaction as a result of the interaction between the excited state of the photosensitizer with an organic cell substrate molecule, which produces free radicals or radical ions. The Type II pathway mainly involves the interaction of the triplet state photosensitizer with oxygen, leading to the formation of singlet oxygen, which induces oxidative damage by interacting with a large number of biological substrates, resulting in toxic effects on the bacterial cell" [15].

Research points out that the benefits of the use of lasers are mostly clinical and related to the reduction of inflammation [11]. Results of the Kokak study [11] show that "the use of a 940 nm DL as an adjuvant of RAR did not promote additional effects in terms of bacterial reduction of three periodontal pathogens, including *P. gingivalis* compared to RAR alone". "These findings differ from the result of the studies in which the red virulence complex represented by *P. gingivalis, T. dentistry* and *T. forsythia* recorded highly significant results when used DL 940 nm adjuvant to RAR" [12]. This type of therapy has also been associated with promising results when mediated by the Indocyanine dye [18].

An alternative that is also being researched is the use of probiotic therapy as a reducing agent of periodontopathogens. Most of the work related to this modality of periodontal treatment reports the application of probiotic tablets containing 10 colony-forming units (UFCs) of B.lactis HN019 adjuvant to RAR, the results show that in fact there is a reduction in the count of *P. gingivalis* and in vitro trials demonstrate a decrease in the adhesion of this bacteria to the oral epitheliums [22]. Finally, it is also worth mentioning the application of propolis that has been related to the trend of reduction of *P. gingivalis* in the crevice gingival fluid. Propolis therapy is likely to become an alternative treatment option for chronic periodontitis during periodontal support therapy [9].

As for the methods of detection of *P. gingivalis* the vast majority of the articles address the use of the PCR method, due to the specificity of results and time of execution, such that of each quadrante, the place with the deepest depth of probe was selected for the collection of subgingival samples for microbiological analysis. "The bacterial DNA was then extracted and processed with quantitative PCR to detect and quantify the pathogen of interest" [23].

"On the other hand, there are reports that the oral cavity is a reservoir of tetracycline-resistant genes mainly carried by transposon Tn916, and suggested the potential risk of widespread use of minocycline, a topical agent that has been shown to be effective in reducing periodontopathogens, which is discouraged due to concerns about emerging oral pathogens carrying genetic determinants responsible for antimicrobial action" [28].

It has been demonstrated that *P. gingivalis* is not sensitive to Lactobacillus brevis and Lactobacillus plantarum-ProlcSan probiotic gel and tablets, as no reductions in their proportion and total counts were observed [22]. Similar results were also observed in the study that investigated the effect of administering piperacillin plus Tazobactam gel and doxycycline gel [26]. Although most of the articles presented reported the sensitivity of *P. gingivalis* to their protocols, microbiological reduction is not always accompanied by a clinical benefit, since periodontal disease is multifactorial.

5. CONCLUSION

Chronic periodontitis is a complex, multifactorial, biofilm-dependent disease, and has as its gold-standard method for its treatment Radical Scratching and Alignment (RAR), widely described in the literature. The use of antimicrobial agents has been as an adjuvant method to RAR and no adverse effects have been found. *Porphyromonas gingivalis* is a key pathogen for the installation of periodontitis and it

is relevant to study its sensitivity, as well as the occurrence of antimicrobial resistance (RA). In this bias, analysis of 19 articles made in this review of integrative literature allows us to conclude that there are various agents of antimicrobials capable of promoting the reduction of this key pathogen in the periodontal bag. However, this reduction is not always accompanied by clinical benefits, which justifies the non-adoption of antibiotic administration in most periodontitis treatments. In none of these studies it was possible to conclude whether these activities were bacteriostatic or bactericidal or whether there were genes that guaranteed RA in the genome of *P. gingivalis.*

ACKNOWLEDGEMENTS

Thanks to the educational institutions involved, Federal University of Ceará and State University Ceará.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal disease on the health, nutrition and well-being of humanity: A call for global action. Journal of Clinical Periodontology. 2017;44(5):456-462.
2. Kassebaum NJ, Smith AG, Bernabé E, Fleming TD, Reynolds AE, Vos T, GBD oral health contributors. (2017) Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions in 195 countries, 1990–2015: a systematic analysis of the global burden of disease, injury, and risk factors. Journal of Dental Research. 2015;96(4): 380-387.
3. Kinane DF, Preshaw PM, Loos BG, Working Group 2 of the seventh european workshop on periodontology (in alphabetical order). Host-response: Understanding the cellular and molecular mechanisms of host-microbial interactions–consensus of the Seventh European Workshop on Periodontology. Journal of clinical periodontology. 2011;38: 44-48.
4. Sanz M, Marco del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Wimmer G. Periodontitis and cardiovascular diseases: Consensus report. Journal of clinical periodontology. 2020;47(3):268-288.
5. Steffens JP, Marcantonio RAC. Classification of periodontal and peri-implant diseases and conditions 2018: practical guide and key points. UNESP Dentistry Journal. 2018;47:189-197.
6. Socransky SS, Haffajee AD, Cugini MA, Smith CKJR, Kent Jr RL. Microbial complexes in subgingival plaque. Journal of Clinical Periodontology. 1998;25(2):134-144.
7. Hung HC, Douglass CW. Meta-analysis of the effect of scaling and root planing, surgical treatment, and antibiotic therapies on periodontal probing depth and attachment loss. J Clin Periodontol. 2002; 29(11):975–86.
8. Haffajee AD, Teles RP, Socransky SS. The effect of periodontal therapy on the composition of the subgingival microbiota. Periodontol. 2000;2006(42):219–58. Available:https://doi.org/10.1111/j.1600-0757.2006.00191.x
9. Nakao R, Senpuku H, Ohnishi M, Takai H, Ogata Y. Effect of topical administration of propolis in chronic periodontitis. Odontology. 2020;108:704-714.
10. Cosgarea R, Eick S, Jepsen S, Arweiler NB, Juncar R, Tristiu R, Sculean A. Microbiological and host-derived biomarker evaluation following non-surgical periodontal therapy with short-term administration of systemic antimicrobials: Secondary outcomes of an RCT. Scientific reports, 2020;10(1):16322.
11. Kocak E, Sağlam M, Arslan U, Kayis SA, Kebapcilar L, Loos BG, Hakki SS. Effect of applying diode laser as an adjuvant to non-surgical periodontal therapy on the reduction of red complex microorganisms in type 2 diabetics with chronic periodontitis. Lasers in Medical Science, 2020;35:1403-1410.
12. Odor AA, Bechir ES, Forna DA. Effect of hydrogen peroxide photoactivated decontamination using 940 nm Diode Laser in Periodontal Treatment: A Pilot Study. Photobiomodulation, Photomedicine, and Laser Surgery, 2020; 38(10):614-624.
13. Acharya S, Hakami, AR, Allemailem KS, Alqahtani K, Al Saffan A, Aldakheel FM, Divakar DD. Efficacy of single versus multiple sessions of photodynamic therapy

as a complement to scaling and root planing on periodontopathogenic bacteria in patients with periodontitis. Photodiagnosis and Photodynamic Therapy. 2020;32:102035.

14. Peralta FDS, Cortelli SC, Rovai ES, Aquino DR, Miranda TB, Costa FO, Cortelli JR. Clinical and microbiological evaluation of non-surgical periodontal therapy in obese and non-obese individuals with periodontitis: a 9-month prospective longitudinal study. Journal of Applied Oral Science. 2020;28.
15. Sukumar K, Tadepalli A, Parthasarathy H, Ponnaiyan D. Evaluation of the combined efficacy of photodynamic therapy using indocyanine green photosensitizer and non-surgical periodontal therapy on clinical and microbial parameters in the treatment of subjects with chronic periodontitis: a randomized split-mouth design. Photodiagnosis and Photodynamic Therapy. 2020;31:101949.
16. Rahman S, Gayathri GV, Mehta DS. A Clinical-Microbiological and biochemical study evaluating the adjunctive use of antimicrobial photodynamic therapy and local drug administration of 1.2% Simvastatin Gel Compared to Scaling and Root Planing Alone. Photodiagnosis and Photodynamic Therapy, 2020;32:102017.
17. Claudio MM, Nuernberg MAA, Rodrigues JVS, Belizário LCG, Batista JA, Duque C, Theodoro LH. Effects of multiple sessions of antimicrobial photodynamic therapy (aPDT) in the treatment of periodontitis in patients with uncompensated type 2 diabetes: A randomized controlled clinical trial. Photodiagnosis and Photodynamic Therapy. 2021;35:102451.
18. Al-Khureif AA, Mohamed BA, Siddiqui AZ, Khan AA, Divakar DD. Repeated application of photodynamic and antibiotic therapy as a complement to root surface debridement in patients with grade C and stage III or IV aggressive periodontitis. Photodiagnosis and Photodynamic Therapy. 2020;29:101610.
19. Cruz DFD, Duarte PM, Figueiredo LC, da Silva HDP, Retamal-Valdes B, Feres M, Miranda TS. Metronidazole and amoxicillin for patients with periodontitis and diabetes mellitus: 5-year secondary analysis of a randomized clinical trial. Journal of Periodontics. 2021;92(4):479-487.
20. Radulescu V, Boariu MI, Rusu D, Roman A, Surlin P, Voicu A, Stratul SI. Clinical and microbiological effects of a single application of sodium hypochlorite gel during subgingival re-instrumentation: A triple-blind randomized placebo-controlled clinical trial. Clinical oral investigations. 2022;26(11):6639-6652.
21. Povšič K, Čuk K, Milavec S, Erčulj V, Seme K, Gašperšič R. Systemic azithromycin as an adjunct to scaling and root planning in patients with stage III/IV periodontitis: 12-month results of a randomized controlled clinical trial. Clinical Oral Investigations. 2021;25:5997-6006.
22. Pudgar P, Povšič K, Čuk K, Seme K, Petelin M, Gašperšič R. Probiotic strains of Lactobacillus brevis and Lactobacillus plantarum as adjunct to non-surgical periodontal therapy: 3-month results of a randomized controlled clinical trial. Clinical oral investigations. 2021;25:1411-1422.
23. Collins JR, Ogando G, González R, Figuero E, Marín MJ, Sanz , Herrera D. Adjunctive efficacy of systemic metronidazole in the surgical treatment of periodontitis: a double-blind parallel randomized clinical trial. Clinical Oral Investigations. 2022;26(5):4195-4207.
24. Cosgarea R, Jepsen S, Heumann C, Batori-Andronescu I, Rosu A, Bora R, Sculean A. Clinical, microbiological and immunological effects of 3- or 7-day systemic antibiotics adjuvant to subgingival instrumentation in patients with aggressive periodontitis (stage III/IV grade C): A randomized placebo-controlled clinical trial. Journal of Clinical Periodontology. 2022;49(11):1106-1120.
25. Doğan ŞB, Akça G. Clinical evaluation of diode laser-assisted surgical periodontal therapy: A split-mouth randomized clinical trial and bacteriological study. Photobiomodulation, photomedicine and laser surgery. 2022;40(9):646-655.
26. Ilyes I, Rusu D, Rădulescu V, Vela O, Boariu MI Roman A, Stratul SI. A Placebo-Controlled Trial to Evaluate Two Locally Administered Antibiotic Gels (Piperacillin Plus Tazobactam vs. Doxycycline) in Patients With Stage III-IV Periodontitis. Medicine. 2023;59(2):303.
27. Rams TE, Degener JE, van Winkelhoff AJ. Antibiotic resistance in human chronic periodontitis microbiota. J Periodontol. 2014 Jan;85(1):160-9.
DOI: 10.1902/jop.2013.130142
Epub 2013 May 20. PMID: 23688097

28. Nakao R, Takigawa S, Sugano N, Koshi R, Ito K, Watanabe H, et al. Impact of minocycline ointment on periodontal treatment of oral bacteria. Jpn J Infect Dis. 2011;64(2):156–60. EPUB 04/27/2011.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/112867