Original Research Article

Antimicrobial Sensitivity and Resistance Associated with *Porphyromonas gingivalis* Present in Periodontitis Frameworks

ABSTRACT

Among the various bacterial species associated with the biofilm present in the periodontal bags, the Gram-negative anaerobic bacteria *Porphyromonas gingivalis* is pointed out as one of the most important causes of the chronic form of periodontitis. This work was aimed at analyzing the sensitivity of *P. gingivalis* to antibiotics and antimicrobial agents, as well as to elucidate whether there are reports of antimicrobial resistance associated with this pathogen. To this end, a bibliographic survey was carried out in the PubMed database of clinical trials published over the last 5 years using the descriptors "Antimicrobial resistance", "Periodontal antibiotic therapy" and "*Porphyromonas gingivalis*", resulting in 66 articles. For a better utilization and selection of the articles studied, exclusion criteria have been applied, thus this integrative review presents the results of 19 studies. Amoxicillin, Metronidazole, and Azithromycin are the most commonly used antibiotics. The use of systemic MET+AMX after RAR does not cause significant differences. AZI 500 mg/day for 3 days as an adjuvant therapy to RAR caused a reduction in the total count of *P. gingivalis*, being described as a beneficial short-term antimicrobial agent when used in periodontal treatment. Photodynamic therapy has shown benefits in reducing inflammation and in counting *P. gingivalis*. Another alternative is probiotic therapy that has proven effective. On the basis of these findings, it is concluded that there are several antimicrobial agents capable of promoting the reduction of this key pathogen. In none of these studies it was possible to conclude whether these activities are bacteriostatic or bactericidal or whether there are genes that guarantee antimicrobial resistance in the genome of *P. gingivalis*.

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, as well as to elucidate whether there are reports of antibiotic resistance associated with this pathogen when present in periodontitis.

2. METHODOLOGY

After establishing the focus of the research, the integrative literature review was conducted by searching for articles in the PubMed database published from July 2023 to July 2018. Three keywords have been established and verified on the DeCs-Descriptors in Health Sciences website.

2.1- Criteria to consider studies for this analysis.

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.

2.2- Data collection, extraction and management.

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.

3. RESULTS

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

Tabela 2.0 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
[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.	In conclusion, the propolis treatment significantly improved both PPD and CAL, along with a tendency to reduce *P. gingivalis* load on the GCF. Propolis therapy is likely to become an alternative treatment option for chronic periodontitis during periodontal support therapy.
[10]	This study was a prospective, randomized,	One hundred and two individuals	Placebo group n = 26	The detection of *P. gingivalis* was performed using	The present data indicate that

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	placebo-controlled, double-blind clinical trial. The following hypothesis 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”.	(average age 43.37 ± 9.85, 65 females, 35 smokers, n = 34/group) were included in the study 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.	AMX + MET Group of 3 days n = 24 AMX + MET Group of 7 days n = 25.	the real-time PCR method.	the systematic use of short and long antibiotic protocols (AMX + MET) adjuvant to non-surgical periodontal therapy leads to greater microbiological improvements in comparison only to subgingival debridement. Significant reductions in the concentration of the key pathogen of *P. gingivalis* were achieved The two antibiotic protocols investigated led to comparable microbiological and inflammatory results.
[11]	This parallel drawing study was a blind clinical trial, controlled and randomized. The study was approved	The following inclusion criteria were used: be ≥30 years old,	Sixty patients with type 2 diabetes mellitus (DM) with chronic periodontitis	A commercial extraction kit (DNeasy Blood & Tissue Kit, Qiagen, Hilden, Germany) was	Within its limits, the results of this study suggest that the use

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	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.	have at least 17 teeth and have≥8 periodontal bags with PD≥5 mm and CAL≥4mm	(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).	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.	of a 940 nm DL as an adjuvant of RAR did not promote additional effects in terms of bacterial reduction of three periodontal pathogens compared to RAR alone. Better clinical healing and increased HbA1c reduction in the RAR+DL group may be related to better wound healing, and suppression of other bacteria except the red complex bacteria in the above-mentioned DL treatment.
[12]	This study was designed as a randomized, controlled, single-blind, multicenter, with split mouth design to compare the antimicrobial effect	The inclusion criteria were the following: at least 16 natural teeth present in the cavity oral distributed in 4 squares, probe depth	Group 1 (control group): scraping and root smoothing (SRP) n=38; and the following experimental groups: Group	The microbiological tests were carried out by means of polymerase chain reaction (PCR) in real time by MIP	The red virulence complex represented by *P. gingivalis, T. dentistry,* and *T. forsythia*

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	of non-periodontal therapy 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).	periodontal (PPD) minimum of 5 mm per square with reabsorption clinically and radiologically proven bone and bleeding to probe (BoP) in all 4 squares.	2: laser diode SRP +940 nm n=38 ; Group 3: SRP+H2O2 photoactivation with 940 nm diode laser n = 38.	Pharma Laboratory, for determination qualitative and quantitative of nine periodontal pathogens, including *P. gingivalis* .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.	recorded high results significant (p =0,000) in the three investigated groups. In relation to the fundamental periodontal bacteria of the complex red (*P. gingivalis, T.dentistry*, e*T. forsythia*), all three groups high statistical results (p =0,000) with 1 month of postoperative
[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	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	At the beginning of the study, subgingival UFC/mL for periodontopathogenic bacteria (*P. gingivalis*, *T. forsythia*, *T. dentistry,* A. actinomycetemcomitans and P. intermediary) were comparable between the

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			after 1 month n=15; Group 3 – patients were subjected to RAR and PDT at the beginning of the study, followed by 2 additional aPDT sessions, which were performed after 1 and 3 months n=15.	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 intermediate P.	patients of all groups. In Group 1, there was no significant reduction in UFC/mL of periodontopathogenic bacteria at 6 months follow-up. In groups 2 and 3, there was a statistically significant reduction in UFC/mL periodontopathogenic bacteria at 6 months follow-up compared to their basal UFC/mL. There was no significant difference in UFC/ mL at 6 months between patients in groups 2 and 3
[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	This prospective study included participants with moderate, severe and advanced periodontitis (stage II: established periodontitis with	The selected subjects were divided into two groups, according to their body mass index (BMI) and waist circumference. Non-obese	Following the specifications of the manufacturer, the DNA genomic (gDNA) was extracted and purified using a Mini Commercial Genomic DNA	The total bacterial load was not significantly difference between follow-up periods and groups ($p<0,05$).

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	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 used twice a day. Every three months, patients were subjected to oral hygiene instructions, dental prophylaxis and supragingival toothbrushing.	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).	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.	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.	Within 9 months, *P. gingivalis* and decreased significantly in both groups (p<0,05) without significant difference between the groups. At 6 months, *T. fortress* significantly decreased in the non-obese group, while for the obese group small counts were observed only at 3 months. These reductions, however, were noted in both groups at 9 months. Although not observed difference between groups in no period, the periodontal treatment reducedT. dentist count within the obese

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					group (p<0,05).
[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 average microbial concentration (copies/µl) of Pg, Aa, Tf, Fn and Td from beginnings up to 3 and 6 months (P ≤0,05). Considering that the control sites showed significant reduction only in Pg from the beginning up to 6 months. Os test sites had a greater reduction in pathogens studied in all follow-up visits and intergroup analysis showed that at 6 months plaque samples

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					from test sites had average microbial concentrations significantly lower Pg, Aa, Tf, Fn, Td
[16]	The present study was conducted as a clinical-microbiological trial and prospective, blind, randomized and evaluator-controlled biochemistry in 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 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) 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	A total of 33 test sites in 11 patients with Grade A Stage II periodontitis were divided randomly in three 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.	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* number of copies and RANKL level scores were observed in all groups at 3 months of follow-up. In comparison between the groups, the reduction was greater in the group II (aPDT group) compared to group I (RAR group) and group III (group SMV), although the difference in scores was not statistically significant.

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		non-surgical treatment. (vi) Patients in whom loss was not expected post-treatment dentistry, indicating that the case has a good prognosis in maintenance.			
[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), and is also registered in the Brazilian Register of Clinical Trials (Registration Number: RBR-9sq542).	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 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	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].	*P. gingivalis* levels were higher in both patients groups than intermediate P. levels. However, it was not observed statistically significant difference in intra or intergroup analysis, for each bacteria evaluated at any post-treatment period (p>0,05).

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
			(157 J/cm2, 4.7 J, 100 mW).		
[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	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	aPDT mediated by green indocyanine significantly improved clinical and antimicrobial parameters in DM2 well controlled and poorly controlled with stage III and degree C periodontitis. The glycemic state is not has had a negative impact on the reduction of periodontal parameters in any of DM2 types. Periodontal bacteria, including *P. gingivalis* (Figure 2A) and *T. forsythia* (Figura 2B) indicated that RSD and ICG-PDT showed a significant reduction in both species bacterial in

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		hemoglobin (HbA1c) levels ranging from 6% to 10% for controlled DM2 and≥10% for uncontrolled DM2, in treatment of Diabetes with oral hypoglycaemic and/or diet[18].			all three groups from the beginning to 6 months. However, it was a significant reduction was observed for the ICG-aPDT group compared to the RSD group for both bacteria in all three groups at 6 o'clock.
[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	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, two species (*T. forsítiae Porphyromonas gingivalis*) were reduced after treatment. No statistically significant differences were observed among the individual levels of the species evaluated 5 years after therapy

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
	Declaration of 1975, revised in 2013.				
[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. 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).	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-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.	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%) (groupe B n19=); and placebo gel (group C n=18).	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.	The treatment of waste bags by means of subgingival USI and a single application of sodium hypochlorite gel can lead to substantial clinical benefits evidenced by scholarship.
[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)	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	Forty patients with stage III or IV periodontitis were carefully selected as participants in the study. RAR control group + placebo	Subgingival biofilm samples from all individuals were collected at the start of the study and in the six-month reassessment. As	Systemic use of azithromycin as an adjuvant to RAR provided additional benefits in terms of

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	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.	untreated periodontitis (stage III or IV of agreement with the American Academy of Periodontology (AAP) and European Federation of Periodontistry (EFP).	(n = 20) Azithromycin group RAR + AZI (n = 20)	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	parameters clinics or number of residual sick sites 12 months after treatment, compared to scratching and root smoothing + placebo. It can thus be speculated that AZI can provide benefits in patients with moderate chronic periodontitis, where the bacterial load and composition of the biofilm are less aggressive, while its benefits in cases of advanced periodontitis can remain limited due to the more resilient subgingival microbiota.
[22]	This was a 3-month double-blind, single-center clinical trial, randomized,	The inclusion criteria: systematically healthy, aged	Test group; probiotic gel and pills n=20 (Lactobacillus	Before treatment, grouped microbiological	Compared to the baseline, the only

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	placebo-controlled, parallel drawing. A authorization was obtained from the National Committee on Medical Ethics (no 0120-365/2018/5) of the Republic of Slovenia.	between 25 and 80 years, not treated with advanced periodontitis with 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).	brevis e Lactobacillus plantarum-ProlcSan) Control group (placebo) n=20	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 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).	difference statistically significant intra-group after 3 months was observed for reduced prevalence of *P. gingivalis* (p = 0,042) e*T. forsythia* (p =0,034) and reduction in proportions of *P. gingivalis* (p = 0,037) eT. forsythia (p= 0,047) in the placebo group. In terms of microbiologi cal changes, individuals in the probiotic group experience d a more frequent reduction below the limit level of F. nucleatum, while reductions in proportion and in total count of *P. gingivalis* and T. *forsythia*

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
					were observed only in the control group.
[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. Gingivalis were Significantly smaller in the test group.
[24]	The hypothesis to be tested in this prospective,	The following criteria for inclusion in the	Group A (SI +AMX+ MET 500mg 3 days)	Quantitative and qualitative microbiological	All periodontal pathogens

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
	randomized, triple-masked and placebo 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”.	study were considered: • age: 18–38 years (≤35 years 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	n=25 Group B (SI +AMX+ MET 500mg 7 days) n=25	analyses of periodontopathogens. actinomycetemcomitans, *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).	investigated presented in group AB of 3 days (Group A) statistically significant reductions in both follow-up. In the 7-day AB group, except A. actinomycetemcomitans, all other bacteria have also been reduced statistically significantly
[25]	The subjects of this study participated in the University	Patients with Periodontal and Peri-Implant	***	For DNA isolation, a commercial kit,	Intergroup comparison showed that

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
	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, 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).	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 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		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 spectroscopicall y using Qbit (Qiagen) spectroscopicall y 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 performed as six individual monoplex reactions with primers replaceable and probe targets	the quantities preoperativ e of *P. gingivalis* differed in both therapy sites (p >0.05). The quantities of *P. Gingivalis* were statistically smaller on site test (application of laser diode) than at the control site in 3 months (p <0,05). < 0.05).*P. gingivalis* a quantity decreased in times of monitoring at the test site, but no difference was found between 3 months and 6 months.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
		study. A total of 30 participants, who were diagnosed with S3GCP after clinical examination, were included in this study.			
[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	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	The microbiological results concerning the reduction of *P. gingivalis* had no statistical significance between the three groups at the beginning and after 6 months (p=0.190–0.859, respectively). Detection scores in intergroup analysis decreased; however, differences between the groups were not statistically significant.

Reference	Design of the studio	Criteria for inclusion	Test Groups and Controls	Method for detection of P. gingivalis.	Results
		periodontal therapy in Medicine 2023,59, 303 4 out of 17 of the last 12 months, patients who local and/or systemic antibiotic 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.			

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].

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] .

Within the limitations of this work, it is possible to conclude that there is insufficient evidence to clarify the occurrence of antimicrobial resistance in *P. gingivalis*, since all clinical trials included for analysis in this research report a microbial sensitivity to the different protocols described, however, this sensibility may or may not be associated with the relevant microbiological benefit, since chronic 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.*

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