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Applied Research

Cite this article as:
J Can Dent Assoc 2011;77:b97

Analysis of Clinical Results of Systemic Antimicrobials Combined with Nonsurgical Periodontal Treatment for Generalized Aggressive Periodontitis: A Pilot Study

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Abstract

Objective: To assess the clinical benefit of either metronidazole and amoxicillin or doxycycline administered immediately after completion of full-mouth scaling and root planing (FRP) for treatment of generalized aggressive periodontitis.

Methods: Patients, 18 to 40 years of age, referred to the Karadeniz Technical University department of periodontology between January 2009 and September 2009 were randomly chosen for inclusion in the study if radiographic examination showed they had ≥ 20 teeth, clinical attachment loss and a probing pocket depth (PPD) ≥ 6 mm at 2 sites in ≥ 12 teeth, ≥ 3 of which were not first molars or incisors. Patients were divided into 3 groups and received FRP alone, FRP combined with metronidazole and amoxicillin, or FRP combined with doxycycline. PPD, clinical attachment level, gingival index, gingival bleeding index and plaque index values were measured at baseline and 2 months after treatment.

Results: Thirty-eight patients with untreated generalized aggressive periodontitis participated in the study. In all 3 groups, the periodontal index values 2 months after treatment were significantly lower than baseline values ($p < 0.05$). Values for PPD and clinical attachment level were more improved in the antibiotic groups than in the FRP group, and more improved in the metronidazole and amoxicillin group than in the doxycycline group ($p < 0.05$). However, no statistically significant intergroup difference was observed in the other clinical parameters ($p > 0.05$). Systemic use of metronidazole and amoxicillin or doxycycline was clinically superior to FRP for reducing PPDs ≥ 7 mm ($p < 0.05$).

Conclusion: Treatment of generalized aggressive periodontitis with FRP alone or FRP combined with systemic antibiotics provided significant clinical benefits that reduced the need for periodontal surgery. Both antibiotic treatments had additional clinical benefits over those of FRP alone.

Generalized aggressive periodontitis (GAP), a special form of periodontal disease, results in early tooth loss since it is characterized by episodic and rapid destruction of periodontal tissues.[1] Patients with GAP display an inadequate host response to periodontopathogenic bacteria because of the increased expression of a wide variety of immunologic and genetic risk factors.[2,3] This complex interaction between host risk factors and periodontal microflora causes extreme

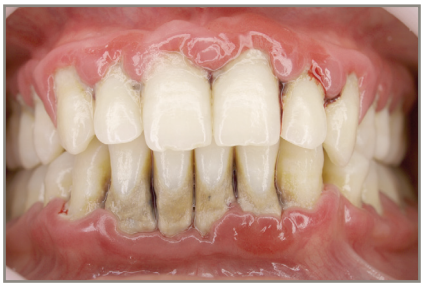

Figure 1a: Baseline clinical appearance of a 26-year-old patient.

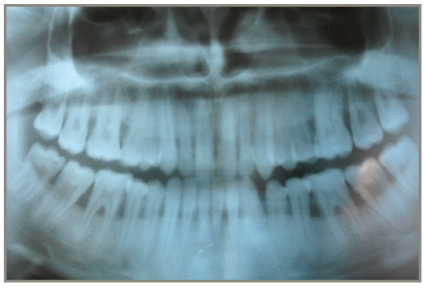

Figure 1b: Baseline panoramic radiograph.

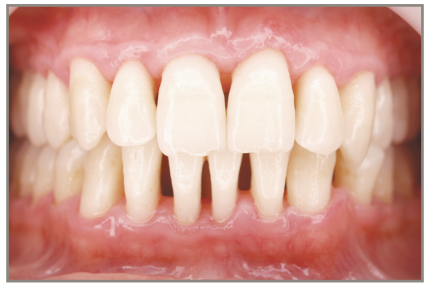

Figure 1c: Clinical condition at 2 months after the application of full-mouth scaling and root planing combined with metronidazole and amoxicillin.

sensitivity to periodontal disease. Additionally, certain environmental factors, such as psychosocial stress and smoking, may speed the formation and progress of aggressive periodontitis.[1-6]

As is typical of most forms of periodontitis, the reduction or elimination of pathogenic microflora is the first step in the treatment of GAP. The standard treatment protocol for attaining periodontal health and sustainability recommended for patients with GAP involves mechanical treatment (scaling and root planing [SRP] or periodontal surgery), antimicrobial treatment in combination with mechanical treatment, and supportive periodontal treatment applied at frequent intervals.[1,7]

Systemic antimicrobial treatment is widely used in the treatment of periodontal disorders to eliminate periodontal infections caused by *Aggregatibacter actinomycetemcomitans,* which invades subepithelial tissues and other important periodontopathogenic bacteria.[8] In various forms of periodontal disease, the use of systemic antimicrobials in combination with SRP has superior clinical and microbial results to those of SRP alone.[6,9-16] In particular, combinations of amoxicillin and metronidazole or doxycycline with mechanical treatment have effectively resolved the periodontal inflammation found in patients with GAP, eliminating various periodontopathogenic bacteria and maintaining a noticeable improvement in clinical parameters.[6,9,11,15-23]

A current alternative mechanical treatment option, full-mouth scaling and root planing (FRP),[24] also known as full-mouth disinfection, that does not involve antiseptics, is applied in combination with systemic antimicrobial treatment. FRP has been used alone or in combination with systemic antimicrobial treatment in some studies.[21,24-32] Although clinical results for FRP and full-mouth disinfection are not superior to those for SRP, these methods have advantages such as better control of infection and reduced treatment period, sessions and cost.[14,24] Recent studies have shown that the use of systemic antimicrobials immediately after or within 1 week of mechanical treatment increases its clinical and microbiological effectiveness.[14] Considering these findings, a systemic antimicrobial approach combined with FRP could be an effective treatment option for the prevention of bacterial contamination and control of infection for patients with GAP who have highly virulent periodontopathogens.

In this study, we assessed the short-term clinical results for the use of metronidazole and amoxicillin or doxycycline application immediately after FRP to treat patients with GAP.

Methods

Patient Selection

Participants were randomly chosen from patients referred to the Karadeniz Technical University, faculty of dentistry, department of periodontology, for periodontal problems or for routine periodontal visits between January 2009 and September 2009.

The patients were clinically and radiographically evaluated for GAP according to the criteria accepted by the American Academy of

Table 1 Demographic characteristics of the study subjects

Group	Mean age ± SD (y)	Age range (y)	No. of men	No. of women	No. of smokers
Met + Amo (n = 14)	29.6 ± 6.7	19–41	7	7	5
Dox (n = 12)	27.8 ± 6.3	18–40	5	7	5
FRP (n = 12)	30.8 ± 8.4	22–40	6	6	5

Dox = doxycycline; FRP = full-mouth scaling and root planing; Met + Amo = metronidazole and amoxicillin; SD = standard deviation.

Periodontology in 1999.[33] Patients were included if they were between 18 and 40 years of age, had ≥ 20 teeth, and showed clinical attachment loss and a probing pocket depth (PPD) of ≥ 6 mm at ≥ 2 sites in ≥ 12 teeth during the screening examination. At least 3 teeth other than the first molars and incisors had to be involved. Exclusion criteria were pregnancy, lactation, allergy to medications used in the study, use of antibiotics or anti-inflammatory drugs in the previous 6 months, a history of systematic periodontal therapy, and any condition requiring premedication before dental treatment. Information about participants' smoking status, age and sex were also recorded.

As required by the Declaration of Helsinki, participants were informed about the study and their written informed consent was obtained.

Experimental Design

After recruitment, participants were assigned to 1 of 3 groups: the metronidazole and amoxicillin (Met + Amo) group, the doxycycline (Dox) group, or the FRP group. All participants underwent a hygiene phase that involved supragingival scaling and polishing, and were instructed in proper oral hygiene. These sessions were repeated until sufficient plaque control (a plaque index[34] of < 30%) had been established, at which point the patient qualified for baseline examination. After satisfactory mouth hygiene was achieved, participants in all groups underwent FRP, which was completed in 1 session.

Immediately after completion of FRP, the Met + Amo group was prescribed 250 mg each of metronidazole and amoxicillin 3 times a day for 10 days; the Dox group was prescribed 200 mg doxycycline on the first day and 100 mg each day for the remainder of the 14 days; no antimicrobial treatment was prescribed for the FRP group. All participants were monitored for side effects of the prescribed antimicrobial agents.

Clinical Measurements

Clinical parameters for all teeth present were measured at baseline and 2 months after treatment (**Figs. 1a–c**). PPD, clinical attachment level (CAL), gingival index,[35] gingival bleeding index[36] and plaque index[34] were measured to identify the periodontal status of each participant. PPD values were classified as shallow (PPD ≤ 3 mm), moderate (PPD 4–6 mm) or deep (PPD ≥ 7 mm). Full-mouth periapical radiographs were taken to determine the level of periodontal bone loss for each participant (**Fig. 1b**). PPD and CAL were measured at 6 sites of each tooth (mesial, median and distal points at buccal and palatal aspects) with a Williams periodontal probe (Hu-Friedy, Chicago, IL).

Statistical Analyses

To evaluate any differences between the Met + Amo, Dox and FRP groups at baseline and 2 months after treatment, the Kruskal-Wallis test was used. In the variables that differed, paired group comparisons were made with the Mann-Whitney U test with Bonferroni adjustments. The Wilcoxon signed rank test was used to determine any within-group differences between the values for baseline and second month after treatment. P values < 0.05 were considered statistically significant.

Results

Study Population

Of the 38 patients with GAP enrolled in the study, 14 (7 men, 7 women) between 19 and 40 years of age (mean ± standard deviation 29.6 ± 6.7 years) were assigned to the Met + Amo group; 12 (6 men, 6 women) between 18 and 40 years of age (mean 27.8 ± 6.3 years) were assigned to the Dox group; and 12 (6 men, 6 women) between 22 and 40 years of age (mean 30.8 ± 8.4 years) were assigned to the FRP group. No difference in mean age, sex or smoking status was observed between the antibiotic and FRP groups (**Table 1**; $p > 0.05$).

Analysis of Clinical Parameters

Although baseline periodontal index values were not significantly different among the 3 groups, the PPD and CAL values at 2 months after treatment were more improved for the antibiotic groups than for the FRP group, and more improved for the Met + Amo group than for the Dox group ($p < 0.05$; **Table 2**). However, no significant difference was found among the groups for other clinical parameters (gingival index, gingival bleeding index, plaque index; $p > 0.05$; **Table 2**). Within-group assessments showed that the periodontal index values at 2 months after treatment for all 3 groups were significantly reduced compared with baseline values ($p < 0.05$; **Table 2**).

Analysis of Shallow, Moderate and Deep Periodontal Pocket Rates

Evaluation of intergroup PPD values at baseline and 2 months after treatment showed that shallow PPD regions (≤ 3 mm) had increased significantly for the antibiotic groups compared with those for the FRP group; no intergroup difference was detected in moderate (4–6 mm) PPD regions ($p > 0.05$; **Table 3**). More reduction in the deep (≥ 7 mm) PPD regions was observed for the antibiotic groups than for the FRP group, and for the Met + Amo group than for the Dox group ($p < 0.05$; **Table 3**). Within-group assessments for the antibiotic groups showed an increased number of shallow PPD regions and a decreased number of deep PPD regions ($p < 0.05$); the number of moderate PPD regions decreased only for the Met + Amo group ($p < 0.05$) and did not change for the Dox group. No significant difference in shallow, moderate and deep PPD values was found between baseline and 2 months after treatment for the FRP group ($p > 0.05$; **Table 3**).

Side Effects

Participants reported no side effects related to the use of antimicrobial agents.

Discussion

In the current study, FRP in combination with antibiotics (either metronidazole and amoxicillin or doxycycline) improved the PPD and CAL of participants with GAP and reduced their need for periodontal surgery. Although no specific treatment protocol involves the use of systemic antimicrobials for the treatment of periodontal disease, research[10,14] supports the use of mechanical treatment in combination with systemic antibiotics for GAP. Although a few studies[6,9,11,15-23] have investigated the use of systemic antimicrobials in nonsurgical periodontal treatment of GAP, only 1 previous study[21] involved antimicrobials in combination with FRP.

Although no significant difference among groups was observed in baseline values in the current study, the values for all clinical periodontal parameters for all 3 groups decreased 2 months after treatment. These results demonstrated that all 3 groups experienced clinical benefit from their treatment. However, the antibiotic groups had superior PPD and CAL values to those of the FRP group, and these values for the Met + Amo group were clinically superior to those for the Dox group.

For patients with GAP, metronidazole and amoxicillin, and doxycycline alone are thought to be the most appropriate antimicrobials to be combined with mechanical treatment.[6,11,15,16,19-23] Researchers[22,23] report that for treatment of aggressive periodontitis, both antibiotic regimens are clinically successful, and *A. actinomycetemcomitans* is eliminated by the 30th day; however, they argue that potential side effects and allergic conditions need to be considered in treatment selection. Additionally, researchers[6,37] have demonstrated that the metronidazole and amoxicillin combination should be the first option for antimicrobial treatment of GAP. Various studies[6,11,15-17,19-21] have pointed out that this combination is clinically and microbially superior to mechanical treatment and

Table 2 Within-group and intergroup comparison of clinical parameters

Clinical parameters	Groups	Mean ± SD		Z	*p*
		Baseline	2 months		
PPD (mm)	Met + Amo (*n* = 14)	4.86 ± 0.74	3.37 ± 0.39[a,b]	-3.29	0.001[c]
	Dox (*n* = 12)	4.96 ± 0.62	3.96 ± 0.34[b]	-3.05	0.002[c]
	FRP (*n* = 12)	4.93 ± 0.31	4.21 ± 0.19	-2.80	0.005[c]
		$\chi^2 = 1.452$ $p = 0.484$	$\chi^2 = 17.944$ $p = 0.001$		
CAL (mm)	Met + Amo (*n* = 14)	5.28 ± 0.81	3.91 ± 0.51[a,b]	-3.29	0.001[c]
	Dox (*n* = 12)	5.68 ± 0.81	4.63 ± 0.43[b]	-2.98	0.003[c]
	FRP (*n* = 12)	5.49 ± 0.45	4.70 ± 0.61	-2.80	0.005[c]
		$\chi^2 = 2.145$ $p = 0.342$	$\chi^2 = 12.413$ $p = 0.002$		
GI	Met + Amo (*n* = 14)	2.24 ± 0.68	0.77 ± 0.38	-3.29	0.001[c]
	Dox (*n* = 12)	2.22 ± 0.61	0.89 ± 0.28	-3.06	0.002[c]
	FRP (*n* = 12)	2.27 ± 0.49	1.13 ± 0.23	-2.80	0.005[a]
		$\chi^2 = 0.027$ $p = 0.987$	$\chi^2 = 5.850$ $p = 0.054$		
GBI (%)	Met + Amo (*n* = 14)	93.57 ± 0.11	25.21 ± 0.13	-3.30	0.001[c]
	Dox (*n* = 12)	95.17 ± 0.11	36.58 ± 0.17	-2.98	0.003[c]
	FRP (*n* = 12)	95.00 ± 0.10	37.70 ± 0.12	-2.80	0.005[c]
		$\chi^2 = 0.936$ $p = 0.626$	$\chi^2 = 5.392$ $p = 0.067$		
PI	Met + Amo (*n* = 14)	1.81 ± 0.75	0.20 ± 0.29	-3.29	0.001[c]
	Dox (*n* = 12)	1.96 ± 0.72	0.25 ± 0.35	-3.06	0.002[a]
	FRP (*n* = 12)	1.85 ± 0.68	0.35 ± 0.34	-2.70	0.007[a]
		$\chi^2 = 0.376$ $p = 0.829$	$\chi^2 = 4.165$ $p = 0.125$		

CAL = clinical attachment level; Dox = doxycycline; FRP = full-mouth scaling and root planing; GBI = gingival bleeding index; GI = gingival index; Met + Amo = metronidazole and amoxicillin; PI = plaque index; PPD = probing pocket depth; SD = standard deviation.

[a] *Significant difference compared with Dox group* ($p < 0.005$).

[b] *Significant difference compared with FRP group* ($p < 0.005$).

[c] *Significant difference between baseline and 2 months* ($p < 0.05$).

Table 3 Within-group and intergroup comparison of pocket-depth rates at baseline and 2 months after treatment

Clinical parameters	Groups (n = 38)	Mean ± SD (%)		Z	p
		Baseline	2 months		
Shallow (PPD ≤ 3 mm)	Met + Amo (n = 14)	30.35 ± 14.85	62.64 ± 14.17[a]	-3.29	0.001[b]
	Dox (n = 12)	27.66 ± 13.35	55.66 ± 11.47[a]	-3.06	0.002[b]
	FRP (n = 12)	32.40 ± 5.72	46.80 ± 9.35	-2.70	0.007
		χ^2 = 0.499 p = 0.779	χ^2 = 11.554 p = 0.003		
Moderate (PPD 4–6mm)	Met + Amo (n = 14)	37.78 ± 7.38	28.71 ± 12.31	-1.97	0.048[b]
	Dox (n = 12)	39.58 ± 8.75	30.66 ± 12.00	-1.77	0.075
	FRP (n = 12)	38.90 ± 8.41	31.00 ± 10.34	-1.78	0.074
		χ^2 = 0.389 p = 0.823	χ^2 = 0.261 p = 0.878		
Deep (PPD ≥ 7 mm)	Met + Amo (n = 14)	31.85 ± 16.43	8.64 ± 4.04[a,c]	-3.29	0.001[b]
	Dox (n = 12)	32.75 ± 16.25	13.66 ± 6.80[a]	-2.93	0.003[b]
	FRP (n = 12)	28.70 ± 9.21	22.20 ± 6.56	-1.83	0.066
		χ^2 = 0.113 p = 0.9945	χ^2 = 19.592 p = 0.001		

Dox = doxycycline; FRP = full-mouth scaling and root planing; Met + Amo = metronidazole and amoxicillin; PPD = probing pocket depth; SD = standard deviation.
[a] *Significant difference compared with FRP group* ($p < 0.005$).
[b] *Significant difference between baseline and 2 months* ($p < 0.05$).
[c] *Significant difference compared with Dox group* ($p < 0.005$).

other antimicrobials. Guerrero and colleagues[19,20] showed that a combination of mechanical treatment with metronidazole and amoxicillin effectively resolves inflammation in patients with GAP, and 7-day systemic use resulted in significant improvement in the second-month clinical parameters. Xajigeorgiou and colleagues [11] demonstrated that the use of metronidazole and amoxicillin resulted in a noticeable decrease in the levels of *A. actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola* in patients with GAP, whereas the effect of doxycycline on these microorganisms remains controversial. For this reason, it is not an appropriate treatment option for this patient group. The finding of the current study that the metronidazole and amoxicillin combination was more effective than doxycycline or FRP alone was consistent with the short-term results of these studies.

In all 3 groups in this study, shallow PPD values (≤ 3 mm) increased in the second month after treatment, whereas deep PPD values (≥ 7 mm) decreased in the antibiotic groups; this decrease was more noticeable in the Met + Amo group. The clinical superiority of metronidazole and amoxicillin for reducing deep-pocket regions was also observed in previous studies.[6,11,13,19-21] The decrease in deep PPD values is thought to be due to the

effect of this medicine combination on periodontopathogens.[6,11,19] The decrease in PPD prevents the progress of this disorder and effectively protects and maintains periodontal health.[6,11,19] The findings of the current study are consistent with those of these studies and showed that the metronidazole and amoxicillin combination decreased the need for surgical intervention. In addition, in this study, a significant decrease in deep PPD values in the Dox group was also observed, which also reduced the need for surgery in this group.

In recent years, the use of FRP in combination with antimicrobials has become a contemporary treatment approach. This method, in which FRP is done within 24 hours in either 1 or 2 separate sessions, is used to prevent periodontopathogens contaminating healthy areas.[24] Although FRP is not particularly better than conventional SRP (i.e., quadrant root planing) clinically or microbiologically, FRP has some advantages, such as enabling the use of antimicrobials immediately after its application and decreasing the number of treatment sessions.[14] The results of this study, which was planned after consideration of the superiority of FRP to other methods, show that this treatment approach may be used for patients with GAP, whose treatments can be long and difficult. Nevertheless, our results were obtained after a short period of time (2 months). Because of intense periodontal destruction and ethical concerns, such as the FRP-group (control-group) participants' need for antimicrobial treatment, the study period was limited to 2 months. Results of recent studies[11,20,23] support this short study period: they found that the clinical and microbiological activity of additional antimicrobial treatments become apparent from the 30th day.

In conclusion, the combination of FRP with either metronidazole and amoxicillin or doxycycline resulted in a pronounced improvement in clinical parameters. Two months after treatment, the number of shallow periodontal pockets increased, the number of deep periodontal pockets decreased, and the need for surgical periodontal treatment decreased. According to these early results, FRP in combination with either metronidazole and amoxicillin or doxycycline may be an appropriate treatment option for patients with GAP when intense periodontal destruction is observed. However, more comprehensive and long-term studies that observe clinical and microbiological activity together are also necessary.

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Acknowledgements: *We thank Dr. Bora Bagis for his assistance with preparation of the manuscript.*

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The authors have no declared financial interests in any company manufacturing the types of products mentioned in this article.

This article has been peer reviewed.

References

1. Parameter on aggressive periodontitis. American Academy of Periodontology. *J Periodontol.* 2000;71(5 Suppl):867-9.
2. Kinane DF, Hart TC. Genes and gene polymorphisms associated with periodontal disease. *Crit Rev Oral Biol Med.* 2003;14(6):430-9.
3. Meng H, Xu L, Li Q, Han J, Zhao Y. Determinants of host susceptibility in aggressive periodontitis. *Periodontol 2000.* 2007;43:133-59.
4. Tonetti MS, Mombelli A. Early-onset periodontitis. *Ann Periodontol.* 1999;4(1):39-53.
5. Kamma JJ, Slots J. Herpesviral-bacterial interactions in aggressive periodontitis. *J Clin Periodontol.* 2003;30(5):420-6.

6. Kaner D, Bernimoulin JP, Hopfenmuller W, Kleber BM, Friedmann A. Controlled-delivery chlorhexidine chip versus amoxicillin/metronidazole as adjunctive antimicrobial therapy for generalized aggressive periodontitis: a randomized controlled clinical trial. *J Clin Periodontol.* 2007;34(10):880-91.

7. Klokkevold PR, Nagy RJ. Clinical periodontology: treatment of aggressive and atypical forms of periodontitis. In: Newmann MG, Takei HH, Klokkevold PR, Carranza FA, editors. *Carranza's clinical periodontology.* Philadelphia: WB Saunders; 2006. p. 693-705.

8. Slots J. The search for effective, safe and affordable periodontal therapy. *Periodontol 2000.* 2002;28:9-11.

9. Sigusch B, Beier M, Klinger G, Pfister W, Glockmann E. A 2-step non-surgical procedure and systemic antibiotics in the treatment of rapidly progressive periodontitis. *J Periodontol.* 2001;72(3):275-83.

10. Haffajee AD, Socransky SS, Gunsolley JC. Systemic antiinfective periodontal therapy. A systematic review. *Ann Periodontol.* 2003;8(1):115-81.

11. Xajigeorgiou C, Sakellari D, Slini T, Baka A, Konstantinidis A. Clinical and microbiological effects of different antimicrobials on generalized aggressive periodontitis. *J Clin Periodontol.* 2006;33(4):254-64.

12. Haffajee AD, Torresyap G, Socransky SS. Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results. *J Clin Periodontol.* 2007;34(3):243-53.

13. Matarazzo F, Figueiredo LC, Cruz SEB, Faveri M, Feres M. Clinical and microbiological benefits of systemic metronidazole and amoxicillin in the treatment of smokers with chronic periodontitis: a randomized placebo-controlled study. *J Clin Periodontol.* 2008;35(10):885-96. Epub 2008 Aug 24.

14. Herrera D, Alonso B, Leon R, Roldán S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. *J Clin Periodontol.* 2008;35(8 Suppl):45-66.

15. Mestnik MJ, Feres M, Figueiredo LC, Duarte PM, Lira EA, Faveri M. Short-term benefits of the adjunctive use of metronidazole plus amoxicillin in the microbial profile and in the clinical parameters of subjects with generalized aggressive periodontitis. *J Clin Periodontol.* 2010;37(4):353-65.

16. Yek EC, Cintan S, Topcuoglu N, Kulekci G, Issever H, Kantarci A. Efficacy of amoxicillin and metronidazole combination for the management of generalized aggressive periodontitis. *J Periodontol.* 2010;81(7)964-74.

17. Buchmann R, Nunn ME, Van Dyke TE, Lange DE. Aggressive periodontitis: 5-year follow-up of treatment. *J Periodontol.* 2002;73(6):675-83.

18. Kone D, Kamagate A. Comparative study of 2 antibiotic combinations in the treatment of rapidly progressing periodontitis [Article in French]. *Odontostomatol Trop.* 2005;28(110):41-4.

19. Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, et al. Adjunctive benefits of systemic amoxicillin and metronidazole in nonsurgical treatment of generalized aggressive periodontitis: a randomized placebo-controlled clinical trial. *J Clin Periodontol.* 2005;32(10):1096-1107.

20. Guerrero A, Echeverría JJ, Tonetti MS. Incomplete adherence to an adjunctive systemic antibiotic regimen decreases clinical outcomes in generalized aggressive periodontitis patients: a pilot retrospective study. *J Clin Periodontol.* 2007;34(10):897–902. Epub 2007 Aug 17.

21. Moreira RM, Feres-Filho EJ. Comparison between full-mouth scaling and root planing and quadrant-wise basic therapy of aggressive periodontitis: 6-month clinical results. *J Periodontol.* 2007;78(9):1683-8.

22. Akincibay H, Orsal SO, Sengün D, Tözüm TF. Systemic administration of doxycycline versus metronidazole plus amoxicillin in the treatment of localized aggressive periodontitis: a clinical and microbiologic study. *Quintessence Int.* 2008;39(2):e33-3.

23. Machtei EE, Younis MN. The use of 2 antibiotic regimens in aggressive periodontitis: comparison of changes in clinical parameters and gingival crevicular fluid biomarkers. *Quintessence Int.* 2008;39(10):811-9.

24. Lang NP, Tan WC, Krähenmann MA, Zwahlen M. A systematic review of the effects of full-mouth debridement with and without antiseptics in patients with chronic periodontitis. *J Clin Periodontol.* 2008;35(8 Suppl):8-21.

25. Apatzidou DA, Kinane DF. Quadrant root planing versus same-day full-mouth root planing. *J Clin Periodontol.* 2004;31(3):152-9.

26. Wennstrom JL, Tomasi C, Bertelle A, Dellasega E. Full-mouth ultrasonic debridement versus quadrant scaling and root planing as an initial approach in the treatment of chronic periodontitis. *J Clin Periodontol.* 2005;32(8):851-9.

27. Quirynen M, Teughels W, van Steenberghe D. Impact of antiseptics on one-stage, full-mouth disinfection. *J Clin Periodontol.* 2006;33(1):49-52.

28. Knöfler GU, Purschwitz RE, Jentsch HF. Clinical evaluation of partial- and full-mouth scaling in the treatment of chronic periodontitis. *J Periodontol.* 2007;78(11):2135-42.

29. Kinane DF, Papageorgakopoulos G. Full mouth disinfection versus quadrant debridement: the clinician's choice. *J Int Acad Periodontol.* 2008;10:6-9.

30. Cionca N, Giannopoulou C, Ugolotti G, Mombelli A. Amoxicillin and metronidazole as an adjunct to full-mouth scaling and root planing of chronic periodontitis. *J Periodontol.* 2009;80(3):364-71.

31. Yashima A, Gomi K, Maeda N, Arai T. One-stage full-mouth versus partial-mouth scaling and root planing during the effective half-life of systemically administered azithromycin. *J Periodontol.* 2009;80(9):1406-13.

32. Cionca N, Giannopoulou C, Ugolotti G, Mombelli A. Microbiologic testing and outcomes of full-mouth scaling and root planing with or without amoxicillin/metronidazole in chronic periodontitis. *J Periodontol.* 2010;81(1):15-23.

33. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol.* 1999;4(1):1-6.

34. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand.* 1964;22:121-35.

35. Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand.* 1963;21:533-51.

36. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. *Int Dent J.* 1975;25(4):29-35.

37. Slots J, Ting M. Systemic antibiotics in the treatment of periodontal disease. *Periodontol 2000.* 2002;28:106-76.