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Impact of systemic antimicrobials combined with anti-infective mechanical debridement on the microbiota of generalized aggressive periodontitis: a 6-month RCT

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Abstract

Aim: To compare the effects of systemic amoxicillin (AMX) plus metronidazole (MET) or placebos combined with anti-infective mechanical debridement on the sub-gingival microbiota of generalized aggressive periodontitis (GAP).

Material and Methods: The study was a 6-month randomized, double-blinded, placebo-controlled clinical trial. Thirty-one subjects received full-mouth ultrasonic debridement followed by scaling and root planing with chlorhexidine rinsing, brushing and irrigation. During mechanical therapy, subjects received systemic AMX (500 mg)+MET (250 mg) or placebo, t.i.d. for 10 days. Sub-gingival samples were obtained from each patient and analysed for their composition by checkerboard at baseline, 3 and 6 months post-therapy. Significant differences between groups over time were examined by General Linear Model of Repeated Measures.

Results: High levels of periodontal pathogens, as well as some ''non-periodontal'' species were observed. Most of the periodontal pathogens decreased significantly over time ($p<0.05$), whereas ''non-periodontal'' bacteria tended to increase in both groups. Sites that showed attachment loss and probing depth increase harboured higher levels of *Dialister pneumosintes*, *Campylobacter rectus*, *Fusobacterium necrophorum*, *Prevotella tannerea* and *Peptostreptococcus anaerobius* than sites that improved after both therapies ($p<0.05$).

Conclusions: Systemic AMX+MET or placebos adjunctive to anti-infective mechanical debridement were comparable in lowering periodontal pathogens up to 6 months after treatment. Species not commonly associated with GAP were less affected by both therapies.

Key words: aggressive periodontitis; antimicrobials; checkerboard; DNA probes; periodontal therapy; RCT; sub-gingival microbiota

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Conflict of interest and source of funding

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The major goals of periodontal therapy are to suppress bacterial infection, modulate the host response and heal/regenerate periodontal tissues in order to provide a healthy periodontium favourable to the re-establishment of a long-lasting host-compatible periodontal microbiota

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(Haffajee et al. 2006, Teles et al. 2006). Mechanical periodontal therapy is the most common and probably the most effective treatment for achieving periodontal health for the vast majority of diseases (Cobb 1996, Serino et al. 2001). However, the adjunctive use of systemic and/or local antimicrobials has been indicated for the treatment of aggressive forms of periodontitis (Herrera et al. 2002, Haffajee et al. 2003, 2006). In particular, the combined administration of amoxicillin (AMX) and metronidazole (MET) seems to provide a significant clinical benefit in terms of periodontal attachment ''gain'' post-therapy (Guerrero et al. 2005, Xajigeorgiou et al. 2006). These agents have also been shown to present a synergic effect on the reduction of *Aggregatibacter actinomycetemcomitans*, a major pathogen associated with aggressive periodontitis (Pavicic et al. 1994). Although the additional use of antimicrobials may be justifiable for treating aggressive forms of the disease, there are issues that should be considered regarding their indication. First of all, the success of any periodontal therapy relies on the establishment of optimal mechanical and/or chemical plaque control (Feres et al. 2009, Escribano et al. 2010). Second, when one thinks of systemic antimicrobials, one should take into account the pharmacological characteristics of the drug, the host general health, the target microorganisms, the adverse effects and the costs (Seymour & Hogg 2008). Most of the antimicrobial regimens used in the treatment of periodontal diseases are based on guidelines for medical applications. Thus, are the dosages of antimicrobial agents commonly used for treating periodontitis adequate? Considering that periodontal infections are biofilm related, would the bactericidal concentration of these drugs reach the microorganisms within the biofilm? To make it more complicated, periodontal infections are polymicrobial and multi-factorial in nature (Socransky et al. 1998, Socransky & Haffajee 2002, 2005). The sub-gingival microbiota and the host response to infection may vary widely among subjects presenting the same periodontal diagnosis (Haffajee et al. 2004a). Consequently, knowledge of the microbial profiles that predominate in different types of periodontal diseases should lead to better therapeutic choices. However, data from studies on the effects of antimicrobial therapy on the microbiota may be quite confusing due to differences in study design, periodontal diagnosis and subject populations (Teles et al. 2006). There is a consensus that the microbial benefit of a periodontal therapy is related to the suppression and/or ''elimination'' of classical periodontal pathogens (van Winkelhoff et al. 1992, Pavicic et al. 1994, Muller et al. 1998). Although this is a reasonable therapeutic aim, it is important to remember that the sub-gingival microbiota is highly diverse, comprising even unknown or uncultivable species that may or may not play a role in disease (Paster et al. 2001, Colombo et al. 2009). Antimicrobials may have distinct effects on different segments of this microbiota (Haffajee et al. 1996). Furthermore, complete eradication of oral species from the mouth may not always occur (or be necessary) after therapy (van Assche et al. 2009). Thus, a successful periodontal therapy should lead to a shift in proportions or levels from a pathogenic to a host-compatible periodontal microbiota that should be sustained for prolonged periods of time (Teles et al. 2006). For individuals with aggressive or refractory periodontitis, investigators have demonstrated that therapeutic approaches including anti-infective repeated mechanical instrumentation associated with antimicrobials are successful in controlling disease progression accompanied by major reductions in periodontal pathogens (Collins et al. 1993, Haffajee et al. 2004b, Sigusch et al. 2005, Moreira & Feres-Filho 2007, Deas & Mealey 2010, Guarnelli et al. 2010). Therefore, the present investigation aimed to compare the effects of anti-infective mechanical debridement associated with systemic AMX plus MET or placebos on the sub-gingival microbiota of subjects with generalized aggressive periodontitis (GAP). We tested the hypothesis that the adjunctive use of systemic AMX plus MET combined with anti-infective mechanical debridement provides greater reductions in the counts of major periodontal pathogens than the anti-infective mechanical debridement alone (placebos) for over a 6-month period after therapy.

Material and Methods

This study was a randomized, double-blinded, placebo-controlled, single-centre, 6-month clinical trial. The study population, experimental design, treatment protocol and CONSORT checklist are described in detail in another paper presenting the clinical data (Varela et al. 2011). Briefly, research was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subject. The study protocol was approved by the Ethics in Human Research Committee of the Institute for Community Health Studies at the Federal University of Rio de Janeiro (CEP/IESC – UFRJ, protocol #45/2007). All patients were individually informed about the nature of the proposed treatment, its risks and benefits, and signed informed consent forms.

Subject population and sample size

Based on a large microbiological database of over 400 individuals in our population evaluated over 8 years, sample size calculation for microbial data was performed considering a difference of $1 \times 10^4 \pm 0.9 \times 10^4$ cells in the reduction of mean counts of the main outcome variable, ''red complex'' (*Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*) (Socransky et al. 1998), between groups after 3–6 months post-therapy (Colombo et al. 2005). A number of 14 individuals was estimated for each group with an α error of 5% and a power of 80%. A total of 40 subjects were to be selected to compensate for a possible 15% drop out rate during the course of the study.

GAP subjects aged 18–39 years were selected from March 2008 to June 2009 from a pool of first-time patients referred to the Division of Graduate Periodontics of the School of Dentistry at the Federal University of Rio de Janeiro (UFRJ), Brazil. Each patient had at least 16 teeth and four sites on different teeth (three of them other than central incisors or first molars) with a probing depth (PD) $\geqslant$ 6 mm, clinical attachment level (CAL) $\geqslant$ 5 mm, moderate to severe bone loss and bleeding on probing (BOP). Exclusion criteria included reported allergy to penicillin, MET or chlorhexidine (CHX); systemic conditions that could modify the progression or treatment of periodontal diseases, including diabetes and immunodeficiency; need for antibiotic coverage for periodontal procedures; long-term use of anti-inflammatory medication; periodontal treatment and/or use of

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systemic antimicrobials in the last 6 months; and pregnancy and nursing.

Experimental Design

Clinical exams were performed at baseline, 3 and 6 months after treatment by only one trained and calibrated examiner (D. H.). Intra-examiner calibration was carried out in four patients not included in the main study but presenting similar periodontal conditions of the study population. Pairs of examinations (PD and CAL) were conducted in each individual with 1 h interval between them. Intra-class correlation coefficients of >0.90 were obtained for both clinical parameters. Measurements were taken at six sites per tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual and disto-lingual) in all teeth, except third molars, and included PD and CAL, measured to the nearest millimetre with a periodontal probe (UNC-15, Hu-Friedy, Chicago, IL, USA), and the presence or absence of BOP, supragingival visible plaque (PL), gingival marginal bleeding (GI) and suppuration (SUP).

Medication and placebo were prepared and encased in identical opaque coded bottles by the School of Pharmacy of the Centre of Health Sciences/UFRJ. Patients were randomized into two experimental groups according to a computer-generated list. Allocation was implemented by a senior investigator (M. C. B. T.), not directly involved with the examination or treatment process, who also kept the identification code concealed from all other individuals until the statistical analyses were carried out.

Periodontal treatment was performed by a single experienced periodontist (V. M. V.). Before active treatment, all patients received oral hygiene instruction in two weekly sessions in order to lower their plaque accumulation to $<20\%$ of dental surfaces. Treatment was divided in two phases. Phase I consisted of full-mouth debridement with ultrasonics performed in two 1 h sessions under local anaesthesia, complemented by irrigation of all pockets with a commercial gel containing 0.2% CHX (Perioxidin gel, Gross S.A., Rio de Janeiro, Brazil), within a 24 h period. Additionally, patients were instructed to rinse and gargle twice a day with a 0.12% CHX solution (Perioxidin rinse, Gross S.A.), and brush their tongue twice a day with the same irrigation gel for the next 45 days. Immediately after the last session of Phase I, patients were assigned to one of the following therapeutic groups: Test group (systemic administration of AMX 500 mg plus MET 250 mg) or Control group (two different placebo tablets, each identical to the medication tablet). Antimicrobials or placebos were prescribed to be taken three times a day for 10 days, starting at the moment of randomization. Patients were instructed to return the empty bottles and their accompanying form filled with information for evaluating patients' adherence to the local and systemic antimicrobial scheme and side effects. Within a week after Phase I, patients started Phase II, which involved staged quadrant 1 h sessions of manual scaling and root planing (SRP) and irrigation of pockets with 0.2% CHX gel, completed within 4–6 weeks. Throughout this phase, a senior investigator (E. J. F.-F.) checked the smoothness of instrumented roots. At the 3-month follow-up visit, patients received reinforcement in oral hygiene, full-mouth supragingival plaque and calculus removal. Furthermore, sites with PD >4 mm and BOP were re-instrumented under local anaesthesia.

Microbiological assessment

Microbial analyses were performed at baseline, 3 and 6 months post-therapy by the checkerboard DNA–DNA hybridization technique (Socransky et al. 1994), with modifications. Individual sub-gingival plaque samples were taken from 14 non-adjacent sites per subject. Sites with different PD categories were sampled, including four sites with PD $\leqslant 3$ mm, five sites with PD = 4–6 mm and five sites with PD $\geqslant 7$ mm. The supragingival plaque was removed and sub-gingival samples were taken with individual sterile Gracey curettes (Hu-Friedy). The samples were placed in individual Eppendorf tubes containing 150 μl of TE buffer (10 mM Tris-HCl, 0.1 mM EDTA, pH 7.6). Samples were lysed by adding 150 μl of 0.5 M NaOH and boiling for 10 min. Denatured DNA was neutralized with 800 μl of 5 M $C_2H_3O_2NH_4$ and fixed in individual lanes on a nylon membrane (Hybond-N+, GE Healthcare Life Sciences, Piscataway, NJ, USA) using the Minislot 30 (Immunetics, Cambridge, MA, USA). The Miniblotter 45 apparatus (Immunetics) was used to hybridize 42 oral (Supporting Information, Table S1) and 27 ''non-periodontal'' (Supporting Information, Table S2) whole genomic DNA probes for 79 species. The probes were labelled with digoxigenin (''Random Primer Digoxigenin Labeling Kit'', Roche Molecular Systems, Alameda, CA, USA). DNA from serotypes a, b and c of *A. actinomycetemcomitans* was pooled in one probe, as well as *Propionibacterium acnes* types I and II. For the ''non-periodontal'' species, DNA from *Enterobacter agglomerans*, *Enterobacter cloacae*, *Enterobacter gergoviae*, *Enterobacter sakazakii*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella oxytoca* and *Klebsiella pneumonia* was combined in an enteric probe, whereas DNA from *Neisseria subflava*, *Neisseria polysaccharea*, *Neisseria meningitidis* and *Neisseria lactamica* was pooled in a *Neisseria* spp. probe.

Bound probes were detected using anti-digoxigenin phosphatase-conjugated antibody (Roche Molecular Systems) and fluorescence (ECF, GE Healthcare Life Sciences) by an imaging capture system (Storm TM 860, Molecular Dynamics, GE Healthcare Life Sciences). Membranes were first hybridized against the ''non-oral'' probes. After image detection and capture (ImageQuant version 5.2, Molecular Dynamics), probes were removed by washing the membranes twice for 15 min at 65°C with a stripping solution (0.2 M NaOH, 3.5 mM SDS) and for 5 min with 2 × SSC (0.3 M sodium chloride, 30 mM trisodium citrate, pH 7.0). Membranes were then hybridized with the oral probes as described previously. Signals captured on the computer were evaluated visually by comparison with the standards at 10^5 and 10^6 cells for the test species on the same membrane. They were recorded as: 0 = not detected; 1 = $<10^5$ cells; 2 = $\sim 10^5$; 3 = 10^5–10^6 cells; 4 = $\sim 10^6$; 5 = $>10^6$ cells. The sensitivity of this assay was adjusted to permit detection of 10^4 cells of a given species by adjusting the concentration of each DNA probe. This procedure was carried out in order to provide the same sensitivity of detection for each species. Failure to detect a signal was recorded as zero, although conceivably, counts in the 1–1000 range could have been present.

Statistical analysis

Data entry in a database was carried out by a junior investigator (M.X.S.-S.) and

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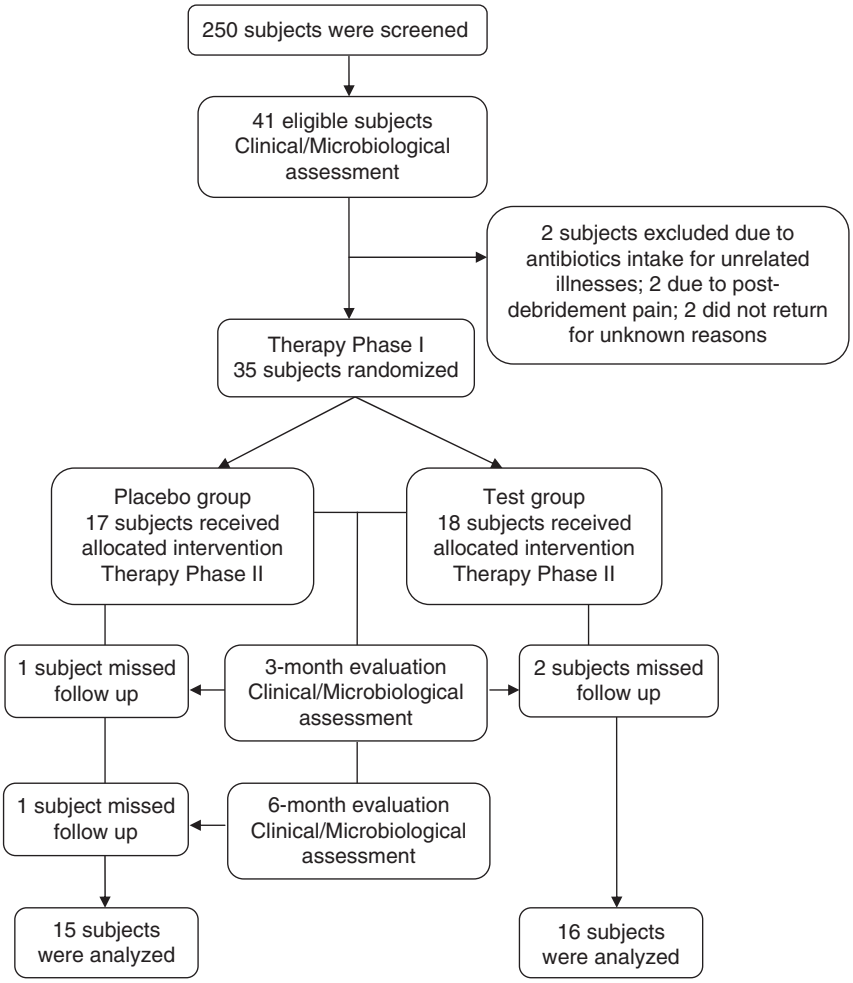

Fig. 1. Flow chart of the study design.

checked by a second one (D. H.). Furthermore, data entry was error-proofed throughout the entry process by a senior investigator (A. P. V. C.). A statistical program (SPSS, Statistical Package for the Social Sciences, version 17.0, Chicago, IL, USA) was used for all analyses. Clinical parameters for the 14 sampled sites were computed in each patient and averaged within groups. Microbial data were presented as mean levels ($\times 10^5$ bacterial cells) of the tested species. The levels of each species were calculated by transforming the scores 0–5 in counts. Mean counts were computed for each patient and within groups. Regarding demographic data, mean age, frequency of gender and frequency of never-smokers or smokers were computed for each group. Significant differences in demographic, clinical and microbiological parameters between therapeutic groups at baseline were determined by the Mann–Whitney and χ^2-tests. Differences in clinical and microbiological changes between groups over time were evaluated by General Linear Model (GLM) for Repeated Measures. The primary microbiological outcome variable of the study included differences between therapies for changes in mean counts of the red complex species. Secondary outcome variables included changes in counts of ''unusual'' species, as well as in counts of bacteria at sites that lost or gained attachment after treatment. The mean levels of each species at baseline and 6 months in those sites were computed for the groups and differences tested by the Mann–Whitney test. Adjustments for multiple comparisons were made as described by Socransky et al. (1991). In brief, an overall p of $0.05 = 1-(1-k)^{42}$ for oral species and $0.05 = 1-(1-k)^{25}$ was computed where k was the desired individual p-value. Thus, from this computation, a p-value <0.0012 and <0.002 was considered to be statistically significant at $p<0.05$ for the analyses of oral and non-periodontal species, respectively.

Results

Clinical and demographic features

The flow chart of the experimental design is presented in Fig. 1. Forty-one individuals were eligible for the study and were examined for full-mouth periodontal clinical parameters and microbiological sampling. Six patients did not return for the first treatment visit, when patients were randomly allocated into the two groups. Of the 35 patients treated, two subjects in the test group missed the 3-month evaluation but returned for the 6-month visit. In the placebo group, one patient missed the 3-month visit and returned at 6 months, whereas the other patient missed the 6-month recall. Per-protocol analysis was performed for microbiological data. The 31 subjects who finished the study reported full adherence to the prescribed course of the systemic antimicrobials/placebos and the CHX rinses.

Adverse effects reported by individuals in both groups included mainly oral ulcerations (test, 2/16 *versus* control, 3/15), metallic taste (test, 1/16 *versus* control, 3/15), dizziness (test, 0/16 *versus* control, 3/15), nausea (test, 2/16 *versus* control, 3/15), diarrhoea (test, 2/16 *versus* control, 1/15), tongue staining (test, 2/16 *versus* control, 1/15), tooth staining (test, 5/16 *versus* control, 5/15), taste alterations (test, 5/16 *versus* control, 10/15) and mouth burning (test, 7/16 *versus* control, 3/15). No differences between groups were observed for these side effects.

The mean age of subjects in the control and test groups were 32.4 ± 1.0 and 33.5 ± 1.1 years, respectively. Only two current smokers were present in each group. Higher proportion of males was found in the test (43%) than in the control (13.3%) group; however, no significant differences were observed between groups for these demographic parameters. Because microbiological assessment was performed in 14 periodontal sites per patient, the clinical parameters of these sites were evaluated (Table 1). Significant reductions in mean PD, CAL, PL and BOP, as well as the frequency of sites with deep PD and high CAL were observed in both groups over time ($p<0.01$). Major

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Table 1. Periodontal clinical parameters (mean ± SEM) of the sites sampled for microbiological analysis of subjects in the clinical groups at baseline, 3 and 6 months after therapy

Clinical parameters*	Control ($n = 15$)			Test ($n = 16$)		
	baseline	3 months	6 months	baseline	3 months	6 months
Clinical attachment level †	5.2 ± 0.2	4.4 ± 0.2	4.4 ± 0.2	5.6 ± 0.3	4.1 ± 0.2	4.1 ± 0.3
Probing pocket depth†	4.9 ± 0.2	3.5 ± 0.2	3.5 ± 0.2	5.2 ± 0.2	3.3 ± 0.1	3.2 ± 0.1
% of sites with						
Supragingival biofilm†	69.6 ± 6.2	26 ± 6	26 ± 4	64.2 ± 6.4	24 ± 4.5	26 ± 2.6
Bleeding on probing†	83.6 ± 4.4	54 ± 6.4	69 ± 5.3	85 ± 3.1	45 ± 3.7	60 ± 4.7
Gingival bleeding	19.5 ± 3.1	21 ± 4.4	20.3 ± 6	17 ± 3	9.7 ± 2	14 ± 4
Suppuration	0.9 ± 0.6	0	0	1.7 ± 1.2	0.4 ± 0.4	0
Clinical attachment level <4 mm†	45.2 ± 5.2	49.3 ± 4.2	47.4 ± 3.7	39.7 ± 5.4	54.3 ± 5.7	54.1 ± 5.9
Clinical attachment level 4–6 mm†	18.8 ± 4.3	34.3 ± 3.4	37.7 ± 3.1	23.2 ± 3.1	30 ± 4.0	30.2 ± 3.9
Clinical attachment level >6 mm†	36.1 ± 3.0	16.4 ± 2.5	15.3 ± 2.2	37.1 ± 4.0	15.7 ± 2.3	15.8 ± 2.6
Probing pocket depth < 4 mm†	45.2 ± 4.7	63.3 ± 2.3	63.6 ± 2.8	43.3 ± 4.7	67.7 ± 2.9	72.1 ± 3.1
Probing pocket depth 4–6 mm†	23.1 ± 4.4	31.4 ± 2.3	31.6 ± 2.7	24.6 ± 3.3	27.8 ± 2.8	25.2 ± 3.1
Probing pocket depth >6 mm†	31.7 ± 2.1	5.3 ± 0.9	4.8 ± 0.9	32.1 ± 2.3	4.5 ± 0.6	2.7 ± 0.4

*No significant differences between groups over time were observed for these variables (GLM; $p > 0.05$).
†Refers to significant differences over time within the groups (GLM; $p < 0.01$).
GLM, General Linear Model.

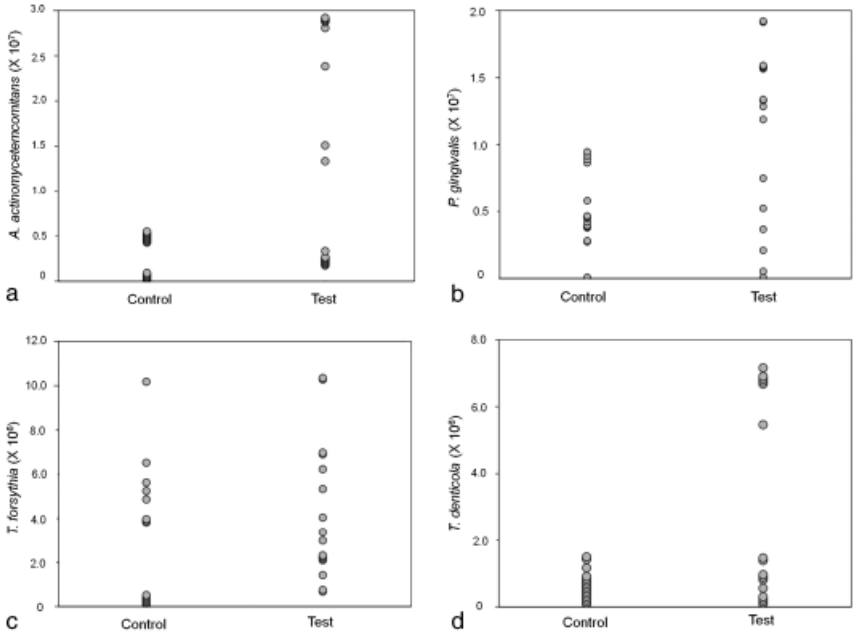

Fig. 2. Inter-individual variability in the levels of (a) *Aggregatibacter actinomycetemcomitans*, (b) *Porphyromonas gingivalis*, (c) *Tannerella forsythia* and (d) *Treponema denticola* in the control ($n = 15$) and test ($n = 16$) clinical groups at baseline. Each circle represents the mean counts of a bacterial species in the 14 sites sampled from each individual for microbial analysis.

changes were seen from baseline to the 3-month visit. However, no significant differences between groups were detected for any of these clinical outcomes (GLM, $p > 0.05$).

Microbiological features

For microbiological analysis, sites with shallow, moderate and deep PD were selected from each GAP individual. Although no differences in the clinical characteristics of these sites were found between groups at baseline (Table 1), a great heterogeneity in the sub-gingival microbiota was observed for several species. Figure 2a–d shows the baseline inter-variability in the mean counts of (a) *A. actinomycetemcomitans*, (b) *P. gingivalis*, (c) *T. forsythia* and (d) *T. denticola* in the 14 sampled sites from subjects of the two groups. Despite this variability, the microbial profiles of both groups were very similar at baseline (Fig. 3, red line). These GAP patients harboured high counts of classical periodontal pathogens such as *A. actinomycetemcomitans* and species of the red and orange complexes (Fig. 3). Likewise, species not considered members of the periodontal microbiota were frequently detected, although in lower levels than the oral species (Fig. 4). The only species that differed significantly in counts between groups at baseline were *Filifactor alocis*, enterics ($p < 0.05$), *Streptococcus gordonii* and *Neisseria mucosa* ($p < 0.01$, Mann–Whitney test). However, after adjustments for multiple comparisons, none of the comparisons were statistically different between groups.

Several pathogenic species of the periodontal microbiota decreased similarly in both groups over time (Fig. 3). After adjusting for multiple comparisons, significant reductions were observed for *A. actinomycetemcomitans*, *P. gingivalis, T. forsythia*, *Campylobacter rectus* and *Parvimonas micra*, whereas the host-compatible species *Actinomyces oris* increased (adjusted $p < 0.0012$, GLM). Most of the ''non-periodontal'' species tested showed a tendency to increase after both treatment approaches (Fig. 4). Significant changes were observed for *Dialister pneumosintes* and *Lactobacillus acidophilus* (adjusted $p < 0.0012$, GLM). In contrast, the counts of *Eubacterium saphenum* diminished significantly after therapy in both groups (adjusted

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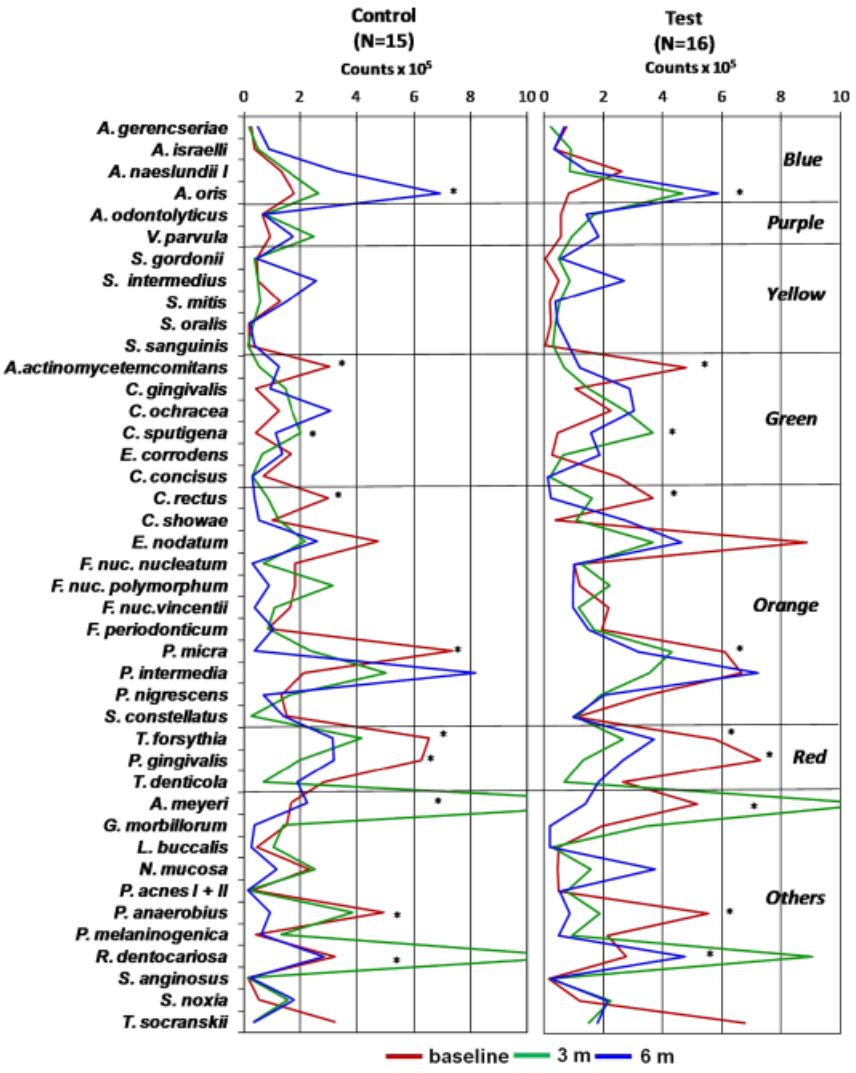

Fig. 3. Changes in mean levels ($\times 10^5$ cells) of oral species in the clinical groups at baseline, 3 and 6 months post-therapy. The mean counts of each species were determined for each subject and then average across subjects in each group for each time point separately. The species were ordered according to the complexes described by Socransky et al. (1998). *Adjusted $p < 0.0012$ refers to significant differences within the groups over time (GLM test).

$p < 0.0012$, GLM). Other organisms including *Actinomyces meyeri*, *Rothia dentocariosa, Capnocytophaga sputigena*, *Pseudomonas aeruginosa* and *Gardnerella vaginallis* increased significantly at 3 months but reduced at the 6-month visit (adjusted $p < 0.0012$, GLM). For all the species evaluated, no significant differences in mean level changes were found between groups, except for *N. mucosa* at a non-adjusted $p = 0.004$ (GLM).

In order to compare the microbial composition of sites that gained or lost attachment in both clinical groups after therapy, the counts of each species at baseline and at 6-month visits were computed. Marked bacterial differences between groups were seen in sites that did or did not respond to the therapeutic protocols, particularly with regard to systemic AMX and MET (Fig. 5). Of interest, high mean levels of *D. pneumosintes*, *Peptostreptococcus anaerobius, C. rectus, F. necrophorum* and *Prevotella tannerea* were related to sites that lost attachment after both therapies ($p < 0.05$, Mann–Whitney test). Pathogenic species such as *Treponema socranskii*, *T. denticola*, *Prevotella nigrescens* and *Prevotella melaninogenica* were significantly more elevated in sites that did not respond to treatment with systemic antimicrobials than sites that reduced PD and CAL ($p < 0.05$, Mann–Whitney test).

Discussion

The treatment of aggressive periodontitis has been a challenge for clinicians due to the lack of a well-established treatment protocol. Difficulties in determining the aetiology and diagnosis of these diseases (van der Velden 2005), the great variability in their microbial composition and clinical manifestations (Gajardo et al. 2005, Ximenez-Fyvie et al. 2006, Faveri et al. 2008, 2009), as well as the unavailability of guidelines for the use of systemically administered antibiotics (Shaddox & Walker 2009) have lead to conflicting decisions on the selection of different therapeutic approaches. In the current study, we evaluated the 6-month microbiological effects of systemic AMX plus MET or placebos associated with anti-infective mechanical debridement in the treatment of GAP. Our data indicated that both therapies were comparable in reducing major periodontal pathogenic species over time, including *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia* and species of the orange complex. These findings indicate that mechanical therapy consisting of repeated instrumentation and topical use of CHX was as effective as its association with systemic AMX plus MET in lowering putative periodontal pathogens. In accord with these results, investigators have indicated that in GAP, good long-term clinical and microbiological results can only be achieved if repeated mechanical instrumentation is adequately used, regardless of adjunctive antibiotic administration (van Winkelhoff et al. 1992, Loesche & Giordano 1994, Flemmig et al. 1998, Sigusch et al. 2005, Guarnelli et al. 2010). Few other studies have also evaluated the 6-month effect of adjunctive AMX+MET on the sub-gingival microbiota of GAP. Xajigeorgiou et al. (2006) showed that the association of these antimicrobials was the only protocol that reduced significantly the levels of *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia* and *T. denticola*. However, no significant changes in prevalence were observed within or among the four groups (SRP, AMX+MET, MET and doxycycline). Yek et al. (2010) reported a reduction in the frequency of the red complex at 6 months, but no differences were detected between groups. Although these studies indicate that systemic AMX+MET provide an additional benefit in terms of

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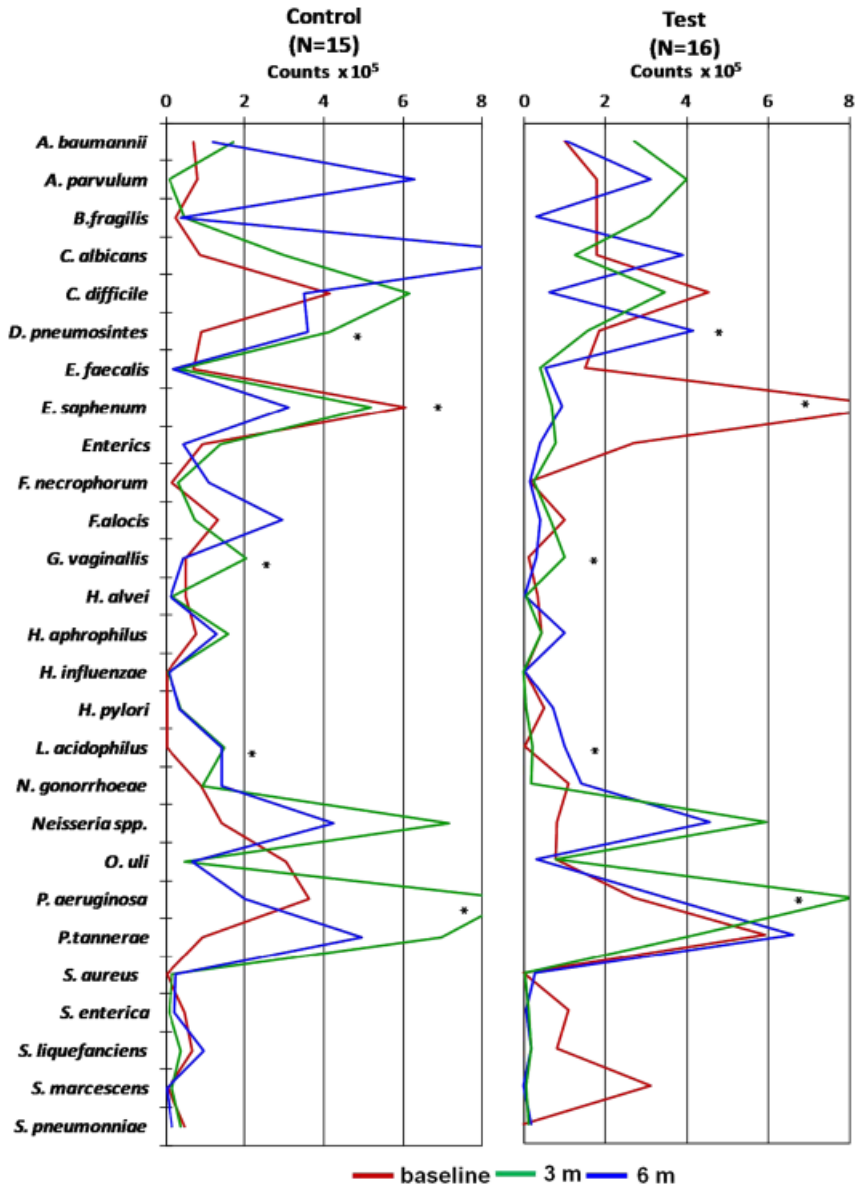

Fig. 4. Changes in mean levels ($\times 10^5$ cells) of ''non-periodontal'' species in the clinical groups at baseline, 3 and 6 months post-therapy. The mean counts of each species were computed for each individual, and then averaged across subjects in each group at each time point separately. *Adjusted $p < 0.002$ refers to significant differences within the groups over time (GLM test).

reducing periodontal pathogens, some issues concerning methodologies should be considered. Both investigations have examined only few bacterial species from a very complex microbiota. The number of samples per patient was small or pooled. In Xajigeorgiou et al. (2006), for example, it is noticeable that the control group harboured lower levels of pathogens than the AMX+MET group at baseline. Therefore, greater reductions were observed in the test group. At 6 months, though, the control group had fewer patients positive for *T. denticola*, *A. actinomycetemcomitans* and *T. forsythia* than the test group. In the study by Yek et al. (2010), some species such as *A. actinomycetemcomitans* and *P. nigrescens* were not detected in the control group at baseline, making comparisons between groups after treatment difficult. More recently, Mestnik et al. (2010) reported the short-term (3-month follow-up) microbiological changes after treatment with SRP+AMX +MET or SRP+placebo. The authors showed that the use of systemic antimicrobials led to greater reductions in mean counts and proportions of periodontal pathogens, particularly species of the orange complex. In sites with initially deep PD, the mean counts of *A. actinomycetemcomitans* were significantly lower in the test compared with the placebo group. As reported by other authors, major changes in prevalence and counts of sub-gingival species after periodontal treatment with or without antimicrobials are usually more pronounced in the first 3 months after therapy (Feres et al. 2001, Colombo et al. 2005, Haffajee et al. 2006, Teles et al. 2006). We did find that reductions in periodontal pathogens were significantly greater from baseline to 3 months, but no differences between groups were seen. When comparing our data with those studies, one could argue that the lack of an additional effect of AMX+MET on the reduction of periodontal pathogens may have been due to the lower dosage of MET (250 mg) administered in the present study. Although the ideal dosage of systemic antimicrobials for the treatment of periodontitis is empiric, some investigators have used 500 mg of MET (Xajigeorgiou et al. 2006, Mestnik et al. 2010, Yek et al. 2010). This may have been a limitation in our study, given that periodontal diseases are biofilm-related infections (Socransky & Haffajee 2002) and higher concentrations of systemic antimicrobials may be required for a more efficient inhibitory effect on periodontal pathogens (Eick et al. 2004).

The impact of both treatments on microorganisms not considered periodontopathogenic was variable. Of interest, relatively high counts of medically important pathogens associated with a variety of diseases in humans and antimicrobial multi-resistance (Costerton et al. 1999, Gootz 2010) were observed in the sub-gingival microbiota of GAP patients. Although the role of these pathogens in the aetiology of periodontitis has not been determined, several of these species have been isolated from periodontal lesions (Slots et al. 1990, Rams et al. 1992, Colombo et al. 2002, 2009, Botero et al. 2007, Fritschi et al. 2008, Persson et al. 2008, Souto & Colombo 2008a, b). Moreover, studies have shown that antagonistic and synergistic interactions do occur between members of the oral microbiota and ''non-oral'' species in the periodontal biofilm, reinforcing the very dynamic and complex relationships that occur in the periodontal microenvironment (Okuda et al. 2003, Kolenbrander et al.

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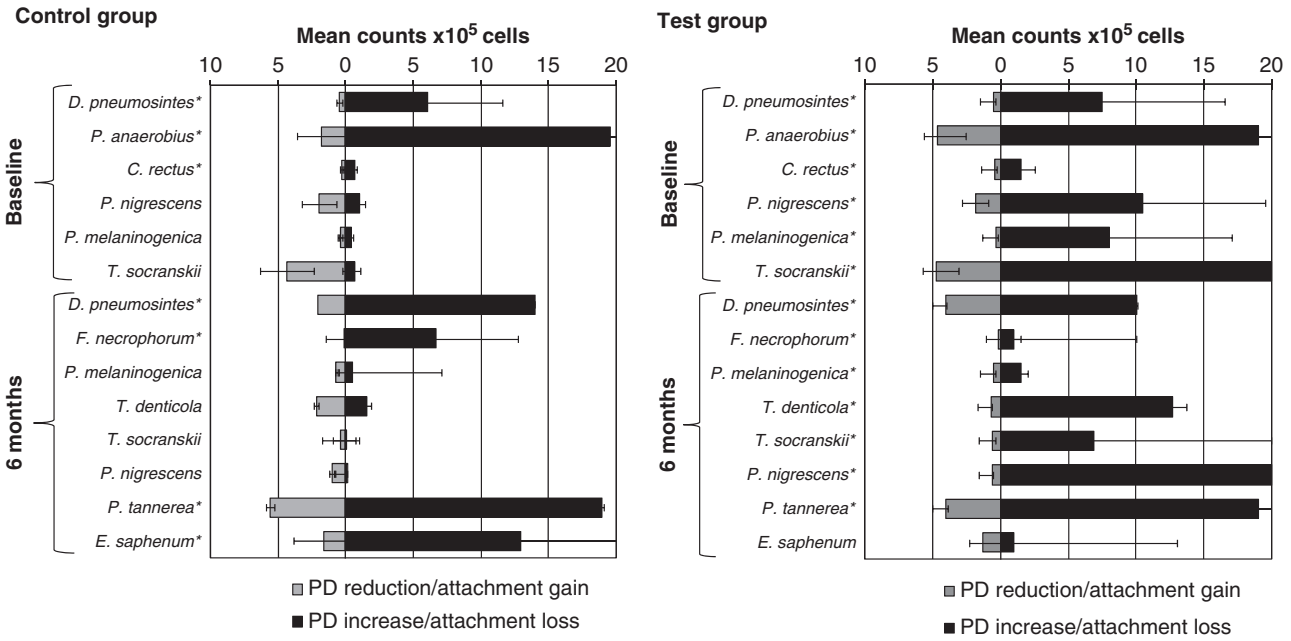

Fig. 5. Bacterial species that differed significantly in mean levels ($\times 10^5$ cells) at baseline (upper bars) and at 6 months (lower bars) between sites that gained or lost clinical attachment after therapy in the control (placebo) and test (systemic antibiotics) groups ($^*p < 0.05$; Mann–Whitney test).

2006, Watanabe et al. 2009). In general, the majority of these species had an increase in mean levels after therapy. Surprisingly, the strictly anaerobic rod *D. pneumosintes* increased significantly over time in both therapeutic groups. In addition, sites that did not respond after treatment harboured significantly higher levels of *D. pneumosintes* than sites that improved. This species has been associated with endodontic infections (Rôças & Siqueira 2006) and different forms of periodontitis (Contreras et al. 2000, Ferraro et al. 2007). Recently, Colombo et al. (2009) reported that subjects and/or sites refractory to mechanical periodontal therapy combined to periodontal surgery and systemic AMX+MET harboured a high prevalence of this microorganism in the sub-gingival microbiota. Thus, it is possible that for sites or individuals with GAP and high levels of *D. pneumosintes* other therapeutic approaches would provide better clinical and microbiological outcomes.

As mentioned previously, one of the difficulties in determining a therapeutic protocol for GAP is the great microbial variability observed among individuals. This may be a key factor in treatment failure, especially when additional antimicrobials are used. We found indeed a great inter-individual variability of bacterial species, particularly periodontal pathogens in the sub-gingival microbiota of GAP subjects. Data from other studies have also shown that periodontal sites may differ significantly in microbial composition among subjects and within subjects with the same clinical characteristics (Haffajee et al. 2004a, Kolenbrander et al. 2006, Teles et al. 2006). Even in a small number of GAP patients, it is clear that some subjects harbour very high levels of putative pathogens, whereas others present much lower counts of these species. If the main microbial goal of periodontal therapy is to suppress periodontal pathogens, then one could ask what the therapy for those in whom these pathogens are already lowered would be. For instance, Haffajee et al. (1996) showed that patients with high proportions of classical periodontal pathogens presented a better clinical response to systemic antimicrobials than subjects with low levels of these species. Thus, if different antimicrobial agents are better suited for treatment of distinct sub-gingival profiles, the need for microbial analysis of GAP patients previously and/or after treatment is justified (Shaddox & Walker 2009).

In conclusion, systemic AMX plus MET or placebos combined with an anti-infective mechanical therapy were comparable in lowering periodontal pathogens up to 6 months after treatment. Therefore, we rejected the hypothesis of greater microbiological benefits of systemic antimicrobials in relation to the mechanical therapy alone. Species not commonly associated with GAP were less affected by both therapies. Further prospective RCT evaluating the clinical and microbiological effects of different combined mechanical and antimicrobial therapeutic approaches are essential to establish guidelines for the treatment of GAP.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Oral bacterial taxa used for development of whole genomic DNA probes tested against subgingival biofilm samples.

Table S2. Non-periodontal bacterial taxa used for development of whole genomic DNA probes tested against subgingival biofilm samples.

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Clinical Relevance

Scientific rationale for the study: Studies have reported the clinical benefits of the full-mouth disinfection, as well as systemic antimicrobials combined to SRP in the treatment of GAP. However, little is known about their effects on the subgingival microbiota. Alternatively, a combination of repeated mechanical therapy with topical and systemic antimicrobials may provide an improved long-lasting microbiological outcome.

Principal findings: The anti-infective mechanical debridement with or without adjunctive systemic antimicrobials was able to decrease the levels of most periodontal pathogens, but species not usually considered as periodontal microorganisms tended to increase.

Practical implications: The high microbial diversity and the fact that species not usually associated with periodontitis may play a role in treatment failure indicate the need for determining the microbial profiles of GAP previously to treatment.

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