J Clin Periodontol 2005; 32: 1055–1061 doi: 10.1111/j.1600-051X.2005.00828.x

Journal of Clinical Periodontology

Infection patterns in chronic and aggressive periodontitis

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Picolos DK, Lerche-Sehm J, Abron A, Fine JB, Papapanou PN. Infection patterns in chronic and aggressive periodontitis. J Clin Periodontol 2005; 32: 1055–1061.
doi: 10.1111/j.1600-051X.2005.00828.x. © Blackwell Munksgaard, 2005.

Abstract

Background: We revisited the postulate that localized aggressive periodontitis (LAP) patients have robust serum antibody (ab) responses to periodontal pathogens while patients with generalized aggressive periodontitis (GAP) show weak responses. We also studied ab responses in localized chronic (LCP) and generalized chronic periodontitis (GCP).

Methods: Fifty-seven patients (14–74 years, 25% male, 70% Hispanic, 26% African American) were studied (15 LAP, 19 GAP, 11 LCP, 12 GCP patients). Three plaque samples/subject were analysed with respect to 15 species, and serum immunoglobulin G (IgG) responses to the same bacteria were determined. Ab responses were expressed as log-transformed titres, and ''infection ratios'', i.e., log-transformed ratios of ab titre over the subject-based mean bacterial load for the homologous species.

Results: The results failed to corroborate the postulate that LAG patients have robust responses to infecting agents while GAP subjects exhibit weak responses. This held true for ab to ''red complex'', ''orange complex'', and health-associated species, and for both titres and infection ratios. Similarly, no differences were found between ab titres or infection ratios in chronic and aggressive periodontitis, or their extent-based subdivisions.

Conclusions: A distinction between the two principal categories of the current periodontitis classification cannot be established by the study of infection patterns.

Key words: antibody; bacteria; classification; infection; periodontitis

Accepted for publication 20 June 2005

Currently, two main forms of destructive periodontal disease are recognized, chronic and aggressive periodontitis (Armitage 1999). Although the Consensus Reports of the 1999 International Workshop for the Classification of Periodontal Diseases and Conditions (1999a, b) do list a number of characteristics that may help distinguish between the two major forms of periodontitis, the applicability of these criteria in everyday clinical practice is problematic. For example, one of the primary conditions that need to be fulfilled for diagnosis of aggressive periodontitis is ''rapid'' attachment and bone loss. However, any such assessment of disease progression requires either knowledge of the progression rate of the disease – an unlikely event at first examination – or some inference based on the severity of the condition with respect to the patient's age. However, according to the principles of the current classification, age should no longer constitute a primary determinant of diagnosis, and aggressive periodontitis may occur in elderly subjects as well. Similarly, diagnostic use of the postulated poor correlation between the presence of local microbial aetiology and disease severity in aggressive periodontitis is equally problematic, as the amount of plaque accumulations at initial presentation may poorly reflect the true, long-term status of the patient. Finally, ascertaining whether the disease aggregates in families, which is another primary feature of aggressive periodontitis, is not feasible in most instances.

In addition to the above shortcomings that create difficulties in the clinical application of the current classification system, an important limitation is the absence of a clear, biologic foundation for the distinction between the main disease categories. It is widely accepted that the bacteria of the dental plaque are the aetiological factors for both chronic and aggressive periodontitis (Socransky & Haffajee 1997). While several studies have shown important qualitative and quantitative differences in the periodontal microbiota between states of periodontal health and destructive periodontitis, a recent systematic review of the literature concluded that there is no evidence that the subgingival microbiota of periodontal lesions in chronic periodontitis are substantially different from those of corresponding lesions in aggressive periodontitis (Mombelli et al. 2002). Instead, it is generally accepted that the determinants of the varying level of susceptibility to periodontitis across subjects and types of disease are

largely ascribed to host factors (Page et al. 1997). According to the Classification Workshop, patients with localized aggressive periodontitis (LAP) display robust serum antibody (ab) responses to infecting periodontal bacteria, while patients with generalized aggressive periodontitis (GAP) show weak ab responses (1999b). We considered this topic worth revisiting for the following reasons: (i) the publications that have dealt with the issue have mainly examined subjects with early-onset periodontitis, i.e., subjects with localized (LJP) or generalized (GJP) juvenile periodontitis; (ii) the literature has mainly focused on ab responses to *Actinobacillus actinomycetemcomitans* and, to a lesser extent, to *Porphyromonas gingivalis*, with little reference to other periodontal microbiota; and (iii) importantly, the issue of weak *versus* robust responses has been solely addressed as a function of the level of serum antibodies to the above bacteria, without concomitant quantification of levels of bacterial colonization in the periodontal biofilm.

The present study was initiated in order to explore the level of serum immunoglobulin G (IgG) responses to several bacterial species in chronic and aggressive periodontitis, as well as in their extent-based subdivisions. We particularly focused on the postulate that localized and generalized forms of aggressive periodontitis are different with respect to the level of their ab responses to infecting periodontal bacteria.

Material and Methods

Subject sample

The subject sample included patients with periodontitis who were referred for periodontal therapy to the Clinic for Post-doctoral Periodontics, Columbia University School of Dental and Oral Surgery, over the time period January 2000–June 2002, from whom data were available on subgingival microbial profiles and serum IgG responses to periodontal bacteria. Subgingival bacterial plaque samples and blood samples are routinely collected from patients with moderate-to-severe periodontitis referred to the above clinic, and are processed at the Laboratory of the Division of Periodontics, Columbia University School of Dental and Oral Surgery. Over the above time period, such data were available from a total of 120 patients. After obtaining permission for data analysis from the Columbia University Medical Center Institutional Review Board, patient records comprising medical and oral health history, periodontal charts including full-mouth assessments of pocket depth and bleeding on probing at six sites per tooth, and a full-mouth set of intra-oral radiographs were screened by a post-doctoral clinical fellow in periodontics (author D. K. P.) and two periodontists (authors P. N. P. and J. B. F.).

Radiographic assessment of alveolar bone level (ABL)

Radiographic ABL, i.e., the distance between the cemento-enamel junction (CEJ) to the most coronal location along the root surface at which the periodontal ligament space appeared to have a normal width, was measured by a single calibrated examiner (author J. L. S.) using a viewer allowing $\times$ 5 magnification, at all mesial and distal tooth surfaces, to the nearest 0.5 mm. In cases where the CEJ could not be properly visualized (e.g., when obscured by dental restorations or in cases of apparent projection distortion), ABL was considered unreadable.

Periodontal diagnosis

Initial screening of patient records was performed jointly by authors D. K. P. and P. N. P. Subjects falling into the category ''periodontitis as a manifestation of systemic diseases'' (1999c) were excluded from all further analyses, as were all subjects with incomplete clinical and/or radiographic records that rendered assignment of periodontal diagnosis impossible. A total of 57 subjects, 14 men and 43 women, qualified for further analyses (Table 1). The mean age of the subjects was 32.5 years (standard deviation 12.7, range 14–74 years).

A diagnosis of either chronic or aggressive periodontitis was assigned to each of these patients jointly by authors D. K. P. and P. N. P., according to the criteria established by the 1999 International Workshop for the Classification of Periodontal Diseases and Conditions (Armitage 1999), as follows: In order to receive a diagnosis of *aggressive periodontitis*, patients were required to (i) be systemically healthy; (ii) display a severity of disease disproportionate to the amount of local aetiologic factors; and (iii) show evidence of rapid attachment loss and bone loss either with respect to their age, or based on comparisons of available sets of clinical or radiographic records obtained at different time points. In all other cases, a diagnosis of *chronic periodontitis* was assigned. Patients were further subdivided according to the extent of bone loss into a *localized* or a *generalized* periodontitis subgroup. Thus, in cases of aggressive periodontitis, subjects displaying bone loss in more than two teeth other than incisors and first molars were regarded as having GAP (1999b). Likewise, in cases of chronic periodontitis, subjects displaying bone loss at more than 30% of their tooth sites were assigned a diagnosis of generalized chronic periodontitis (GCP) (1999a).

Following the exact same criteria as above, author J. B. F. proceeded independently with assignment of diagnosis. A comparison between the earlier assigned primary diagnosis (chronic or aggressive) by the two examiners and that by author J. B. F. revealed a discrepancy in 25% of all cases (14 patients). Therefore, the charts of these particular patients were re-examined jointly by all three authors and a final consensus diagnosis was reached. As shown in Table 1, according to the latter final diagnosis, there were 23 patients with chronic periodontitis [11 with localized chronic periodontitis (LCP), 12 with GCP], and 34 patients with aggressive periodontitis (15 with LAP, 19 with GAP). Forty subjects (70%) were Hispanic, 15 (26%) African American and two were Caucasian.

Assessments of periodontal microbiota and serum ab responses

From the above subjects, three individual subgingival plaque samples, each

Table 1. Age and gender distribution in the four diagnostic categories

Diagnosis	*N*	Mean age (SD)	Range	Men	Women
Localized chronic	11	28.7 (8.0)	14–40	0	11
Generalized chronic	12	41.9 (10.1)	25–60	3	9
Localized aggressive	15	24.3 (7.4)	15–40	3	12
Generalized aggressive	19	34.5 (12.4)	20–74	8	11
All	57	32.5 (12.7)	14–74	14	43

obtained from a deep periodontal pocket, i.e., a site with probing depth of ⩾6 mm, were collected at the time of initial presentation, prior to any periodontal intervention. Samples were analysed by the checkerboard DNA–DNA hybridization technique (Socransky et al. 1994), as described earlier (Papapanou et al. 2000), with respect to the following 15 periodontal species: *A. actinomycetemcomitans* (ATCC 43718), *P. gingivalis* (ATCC 33277), *Tannerella forsythia* (ATCC 43037), *Treponema denticola* (ATCC 35404), *Fusobacterium nucleatum* (ATCC 10953), *Prevotella intermedia* (ATCC 25611), *Prevotella nigrescens* (ATCC 33563), *Campylobacter rectus* (ATCC 33238), *Eubacterium nodatum* (ATCC 33099), *Streptococcus intermedius* (ATCC 27335), *Micromonas micros* (ATCC 33270), *Eikenella corrodens* (ATCC 23834), *Capnocytophaga ochracea* (ATCC 33624), *Veillonella parvula* (ATCC 10790) and *Actinomyces naeslundii* (ATCC 49340).

A 5 ml venous blood sample was also collected at the same visit, and the level of serum antibodies to the same periodontal microbiota as above was determined by checkerboard immunoblotting (Sakellari et al. 1997), as described previously (Papapanou et al. 2000).

Statistical analysis

Descriptive statistics were initially employed to examine the clinical, radiographic, microbiological and serological profiles in the four diagnostic groups.

A cut-off point for ABL of ⩾4 mm was used to calculate extent and severity of bone loss according to the principles described earlier by Carlos et al. (1986) and Papapanou et al. (1991). Thus, extent describes the percentage of inter-proximal sites/subject with bone loss of ⩾4 mm, while severity represents the average bone loss/subject based exclusively on qualifying sites.

As both the microbiological and the ab data were found to be skewed, they were log transformed. All log transformations were performed as log (raw value +1), in order to circumvent the problem of raw values equal to zero. At a first step, differences were examined between the four diagnostic categories in mean log-transformed bacterial load for each species. A subsequent analysis of ab titres with respect to periodontal diagnosis examined (i) the mean log-transformed levels of specific serum IgG antibodies to periodontal microbiota, expressed in nanograms per millilitre, and (ii) ''infection ratios''. The latter were calculated as follows: first, within each subject, a mean log-transformed bacterial load across the three microbiologically sampled sites was calculated for each investigated species. Next, each subject's log-transformed specific ab titre was divided by the individual subject's mean bacterial load for the homologous species described above, generating a species-specific ''infection ratio''. Subject-based infection ratios were subsequently averaged within each diagnostic category. In other words, the obtained infection ratios (ab concentration/bacterial load) described a measure of ab responsiveness for each infecting bacterial species.

Analysis of variance and a post-hoc multiple comparison test (Student–Newman–Keuls test) were used to compare log-transformed bacterial levels, ab responses and infection ratios in the four diagnostic categories (LCP, GCP, LAP andGAP). All analyses were performed by using a commercially available statistical software (Statistical Analysis System version 9.0, SAS Institute, Carry, NC, USA).

Results

Table 2 describes a number of clinical variables in the study sample as a whole, as well as with respect to diagnostic category. The mean number of present teeth was fairly similar in the four groups and ranged between 28.2 and 29.1, indicating no substantial tooth loss. The average pocket depth ranged from 3.7 mm, in patients with LCP, to 5.4 mm, in patients with GAP. In the entire patient sample, the average number of sites/subject with pocket depth of 5 mm deep or deeper was 56.7. Subjects with LAP had on the average 37.1 deep (⩾5 mm) pockets, while patients with GCP, 78.8 such pockets. These mean values corresponded to an extent of deep sites ranging from 21.9% (LAP) to 44.5% (GCP).

Table 3 presents the loss of periodontal tissue support in the cohort, as reflected by radiographic measurements of ABL. The average ABL in the entire subject sample was 3.4 mm, and ranged from 2.4 mm in the LCP group to 4.3 mm in the GAP group. The extent of radiographic bone loss, describing the percentage of inter-proximal sites/subject with ABL of ⩾4 mm, ranged from 7.9% (LCP) to 51.8% (GAP). Similarly, the severity of bone loss, i.e., the average ABL based exclusively on qualifying sites, ranged from 4.4 mm in LCP patients to 5.7 mm in GAP patients.

Analysis of the bacterial data revealed that the prevalence of each of the 15 investigated species was 100% on the individual subject level. Analysis of variance supplemented by the Student–Newman–Keuls test revealed no differ-

Table 2. Clinical variables in the four diagnostic categories

Diagnosis	# of teeth	PD	# of sites with PD⩾5 mm	% of sites with PD⩾5 mm
Localized chronic	28.2 (2.2)	3.7 (0.8)	39.5 (24.2)	23. 0 (14.2)
Generalized chronic	29.1 (2.1)	4.1 (0.9)	78.8 (39.0)	44.5 (20.9)
Localized aggressive	28.5 (2.2)	4.9 (3.8)	37.1 (19.0)	21.9 (11.0)
Generalized aggressive	28.6 (2.9)	5.4 (2.4)	68.8 (26.2)	40.4 (15.3)
All	28.6 (2.3)	4.7 (2.5)	56.7 (31.9)	32.9 (18.0)

Mean values (standard deviations).
PD, probing depth.

Table 3. Radiographic loss of periodontal tissue support in the four diagnostic categories

Diagnosis	ABL (mm)	Extent (%)	Severity (mm)
Localized chronic	2.4 (0.4)	7.9 (7.0)	4.4 (0.5)
Generalized chronic	3.8 (0.8)	47.1 (22.6)	5.1 (0.7)
Localized aggressive	2.6 (0.7)	16.1 (10.8)	5.5 (1.4)
Generalized aggressive	4.3 (0.9)	51.8 (20.7)	5.7 (1.0)
All	3.4 (1.1)	32.6 (25.2)	5.3 (1.1)

Mean values (standard deviations).
Extent: % of sites/subject with ABL of ⩾4 mm.
Severity: mean ABL/subject based exclusively on sites with ABL⩾4 mm.
ABL, alveolar bone level.

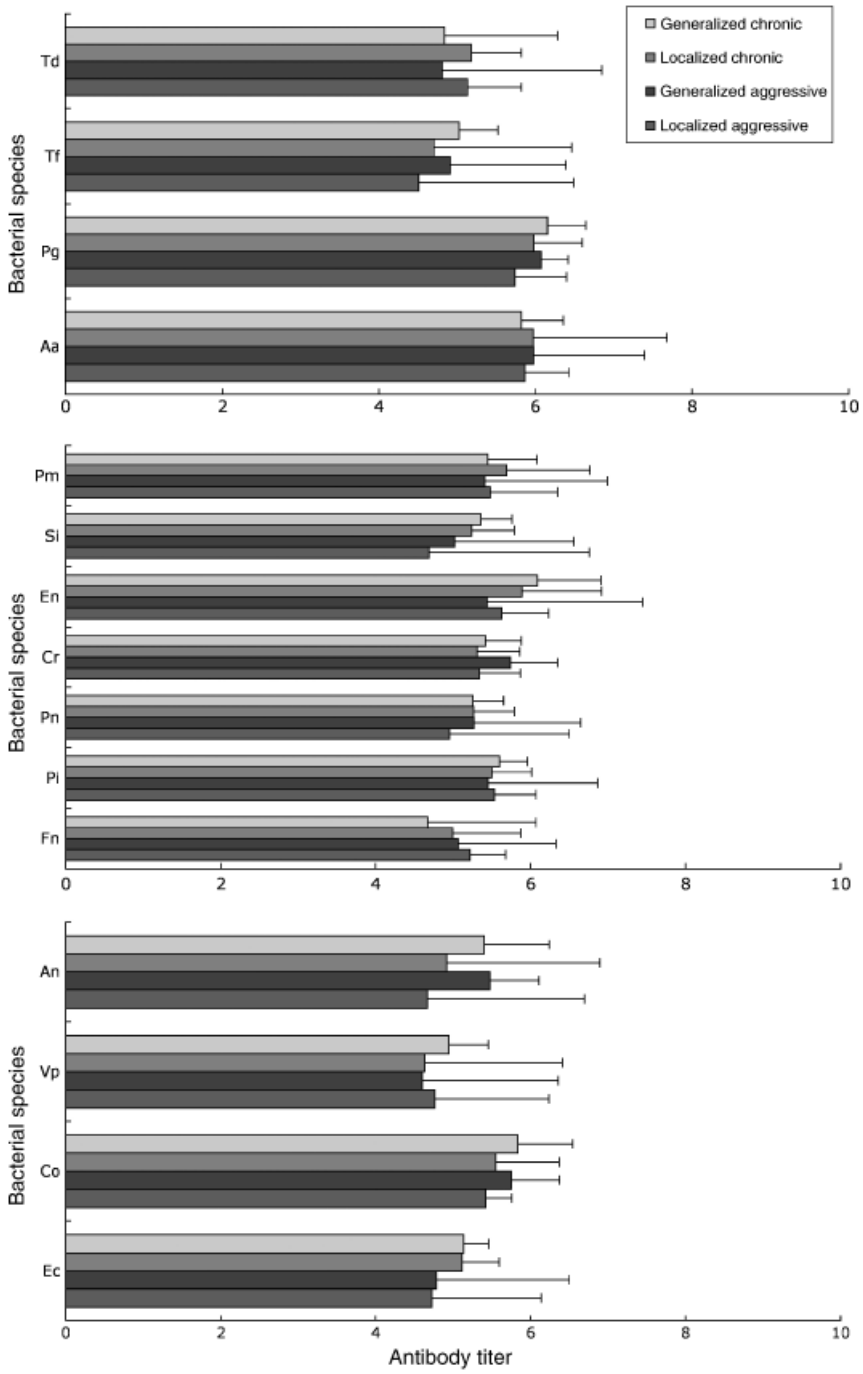

Fig. 1. Log-transformed serum antibody titres (ng/ml) in generalized chronic periodontitis (yellow bars), localized chronic periodontitis (green bars), generalized aggressive periodontitis (blue bars) and localized aggressive periodontitis (red bars). Error bars describe standard deviations. Top graph illustrates responses to ''red complex'' bacteria and *Actinobacillus actinomycetemcomitans*, middle graph responses to selected ''orange complex'' bacteria and lower graph describes responses to selected bacteria associated with gingivitis and periodontal health. Aa, *A. actinomycetemcomitans*; Pg, *Porphyromonas gingivalis*; Tf, *Tannerella forsythia*; Td, *Treponema denticola*; Fn, *Fusobacterium nucleatum*; Pi, *Prevotella intermedia*; Pn, *Prevotella nigrescens*; Cr, *Campylobacter rectus*; En, *Eubacterium nodatum*; Si, *Streptococcus intermedius*; Mm, *Micromonas micros*; Ec, *Eikenella corrodens*; Co, *Capnocytophaga ochracea*; Vp, *Veillonella parvula*; An, *Actinomyces naeslundii*.

ences in bacterial levels for any of the 15 investigated species across the four diagnostic categories (data not shown).

The serological responses to the investigated periodontal bacteria in the four diagnostic categories are presented in Figs 1 and 2. Figure 1 describes IgG titres and Fig. 2 ''infection ratios''. In both figures, the periodontal microbiota are grouped in three clusters, as follows: The top pair of graphs describes responses to the three established causative periodontal pathogens *A. actinomycetemcomitans*, *P. gingivalis* and *T. forsythia* (1996), as well as to *T. denticola*, a species which together with the latter two forms Socransky's pathogenic ''red complex'' (Socransky et al. 1998). The middle pair of graphs illustrates ab responses to selected ''orange complex'' bacteria, i.e., bacteria that are present in both periodontitis and gingivitis (Socransky et al. 1998). Finally, the lower pair describes responses to selected bacteria that are primarily prevalent in gingivitis and periodontal health (Socransky et al. 1998).

As becomes apparent from Figs 1 and 2, no consistent pattern of ab responses seems to emerge among the different diagnostic categories, irrespective of whether the data are expressed solely as ab levels or as infection ratios adjusted for bacterial load. Indeed, comparison of serum ab levels and infection ratios for each species between the LCP, GCP, LAP and GAP groups by means of the Student–Newman–Keuls test, adjusting for multiple comparisons, revealed no statistically significant differences between any diagnostic categories with respect to any tested species.

In a subsequent analysis, potential differences were examined between two aggregate diagnostic groups, i.e., chronic ($N = 23$) and aggressive ($N = 34$) periodontitis, regardless of the extent of the disease. Similarly, no statistically significant differences emerged between the two primary groups with respect to any of the investigated titres, and this was the case for both ab levels and infection ratios.

Discussion

In this study, two examiner teams using the currently established diagnostic criteria for classifying periodontitis (Armitage 1999) arrived in a non-concordant diagnosis in one-fourth of the patients evaluated. This finding underscores the difficulties encountered in the everyday clinical implementation of the current classification system. Our serological data failed to corroborate the Consensus Report's postulate that LAP patients display robust ab responses to infecting

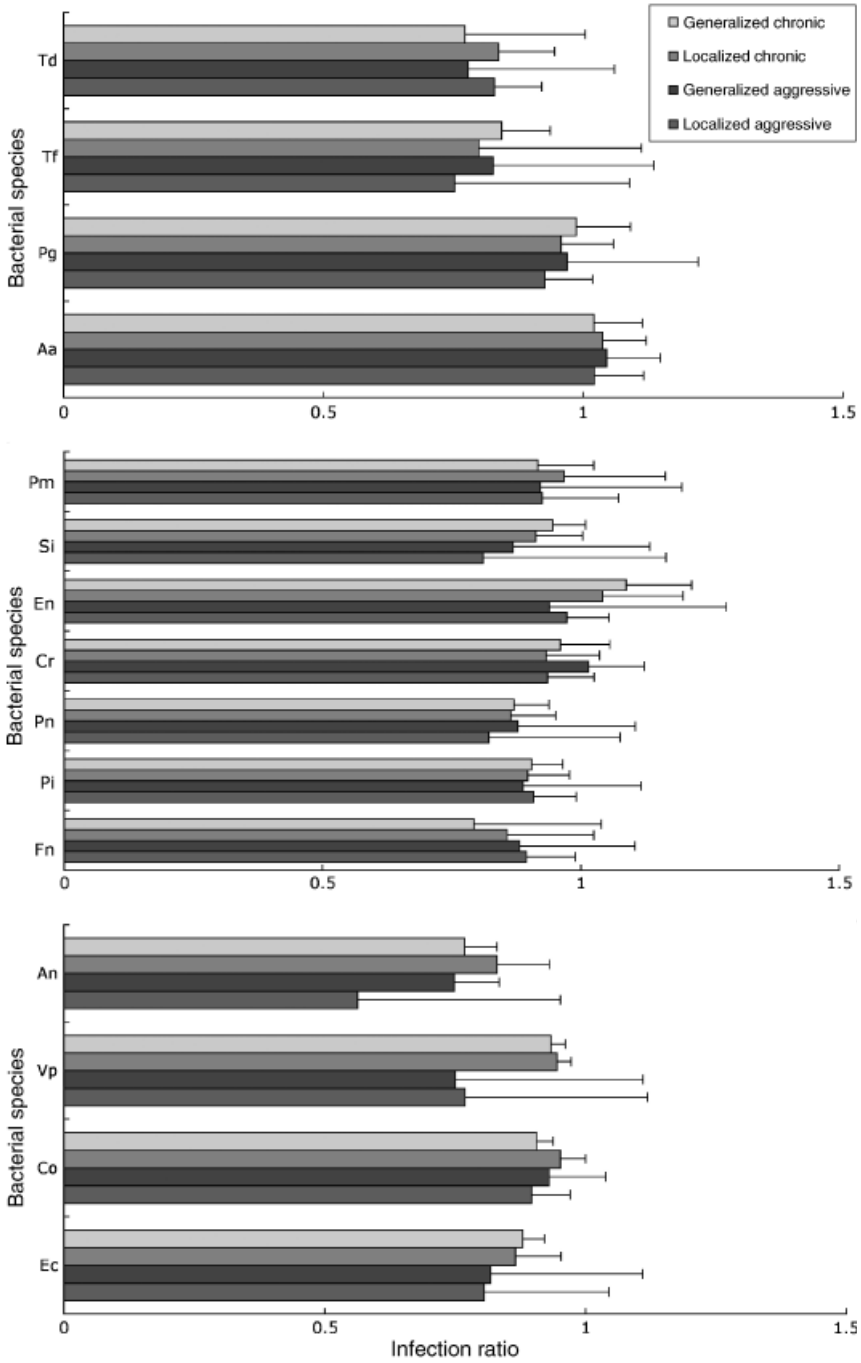

Fig. 2. Log-transformed infection ratios (ng/ml 10^{-6} bacterial cells) in the four diagnostic categories. Diagnostic categories, error bars, bacterial complexes and species abbreviations as in Fig. 1.

agents while GAP patients show weak responses. In fact, LAP patients tended to exhibit somewhat lower ab responses than their generalized periodontitis counterparts for the majority of the investigated species (nine out of 15 studied), including the three established causative pathogens *A. actinomycetemcomitans*, *P. gingivalis* and *T. forsythia*. These findings held true both when titres were expressed as unadjusted IgG levels and when expressed as adjusted infection ratios, and no statistically significant differences were detected between the subgroups. In addition, our data failed to reveal any statistically significant differences in ab responses/infection ratios between LCP and GCP patients, or between the entire aggregate groups (aggressive and chronic periodontitis). Thus, our data indicate that a distinction between the two main forms of periodontitis, or their extent-based subcategories, is not further facilitated by the study of infection patterns described above.

The postulate challenged in the present study, namely the different responsiveness to infecting agents between subjects with localized and GAP, has been in line with the concept that the level of serum ab responses reflect, by and large, a protective type of reaction to the bacterial challenge. According to this notion, high levels of systemic antibodies are thought to ''contain'' the extent of periodontal tissue support loss, while poor ab responses are expected to contribute to a more widespread periodontal destruction. This perception has been primarily founded on data from several studies in the early 80s that investigated serum ab responses to *A. actinomycetemcomitans* (Listgarten et al. 1981, Ebersole et al. 1982, Ranney et al. 1982, Genco et al. 1985). Using the accepted nomenclature of the time, these studies primarily compared subjects with LJP or GJP and, to a lesser extent, subjects with adult periodontitis, and demonstrated an inverse relationship between titre levels and extent of disease. Studies that have analysed antibodies to specific antigenic structures of *A. actinomycetemcomitans*, (e.g. Ebersole et al. 1983), also demonstrated higher titres in LJP patients. Similarly, a protective nature of ab responses was inferred based on studies that investigated titres to additional periodontal species (Gunsolley et al. 1987, Califano et al. 1997).

However, literature evidence also indicates that high ab levels do not necessarily confer protection from widespread disease. In a study examining titres to 18 common periodontal species, Gunsolley et al. (1990) failed to document an overall discernible pattern between ab levels and disease extent. Other studies have reported a positive correlation between serum ab reactivity to periodontal pathogens and the extent and severity of early-onset periodontitis or adult periodontitis (Mouton et al. 1981, Zafiropoulos et al. 1992). In a more recent study that examined titres to six periodontal species (Albandar et al. 2001), significantly elevated titres to *A. actinomycetemcomitans* and *P. gingivalis* were recorded in subjects with

generalized early-onset periodontitis, when compared with control subjects without destructive disease, while subjects with localized early-onset periodontitis displayed titres similar to controls. It appears, therefore, that high levels of ab in patients with periodontitis may be either indicative of an effective host response, which can contain the infection, or a sign of a chronic failure to control the disease (Page 1998). Nevertheless, the literature is rather consistent when ab levels between patients with periodontitis, irrespective of disease category, are compared with those of periodontitis-free individuals. Indeed, titres to most periodontal bacteria examined have been reported to be significantly higher in subjects with periodontitis than in periodontally healthy controls (Naito et al. 1984, Kinane et al. 1999, Craig et al. 2002, Papapanou et al. 2004b).

As mentioned in the ''Introduction'', the current classification presents with persisting problems that render the distinction between the major categories (chronic and aggressive) difficult. This was clearly demonstrated by our data, as three periodontists who applied the workshop criteria to the best of their ability differed in their diagnosis at 25% of all examined cases. With respect to the biologic differences between the diagnostic categories, we note that the postulated differences in responsiveness to infection between LAP and GAP have been based on an extrapolation from data from LJP and GJP patients and, as such, could not be verified in a group of patients classified as chronic and aggressive according to the new criteria, i.e., without considering the age of the subject as a primary classification determinant. It should also be emphasized that in the present study, responsiveness to infecting bacteria was also analysed by means of infection ratios that reflect a combined measure of both colonization and ab response and are biologically more relevant than the mere study of ab titres. Obviously, we cannot rule out that part of the discrepancy between our findings and those of other studies in the literature can be ascribed to the limited size of the examined sample or be attributed to variance because of specific subject sample characteristics such as race/ethnicity or smoking habits, both of which have been shown to affect ab levels and the proportion of specific serum IgG subclasses (Quinn et al. 1996, 1998, Gunsolley et al. 1997, Albandar et al. 2002). However, in all likelihood, the discrepancy is mainly because of the fact that, according to the current guidelines, the diagnosis of either chronic or aggressive periodontitis can be assigned to individuals of any age, rendering inferences based on patients with early-onset periodontitis not applicable. Nevertheless, it is interesting to note that, in our study, both the generalized chronic and the generalized aggressive patients were on the average approximately 10 years older than their localized periodontitis counterparts. This observation may possibly suggest that, in the absence of periodontal therapy, a localized periodontitis phenotype may have evolved with age into a generalized one.

Our finding of no conspicuous differences in ab responses and infection ratios between patients with chronic or aggressive periodontitis is in agreement with earlier studies that reported comparable serum ab levels in patients belonging to different diagnostic groups (Ebersole et al. 1991, Kojima et al. 1997, Guo et al. 2000). However, it must be recognized that the analysis of infection patterns undertaken in the present study is still simplistic, as it is solely based on quantitative assessments of bacterial colonization and ab response patterns, with no regard to other potentially important variables such as within-species heterogeneity in antigenic epitopes, ab subclasses or ab avidity. Nevertheless, our data reinforce the view that a biologically relevant basis for the distinction between chronic and aggressive periodontitis cannot be readily established using rudimentary assessments of infection, and suggest a need to further expand the armamentarium of potential diagnostic tools in the study of the pathobiology of periodontitis (Papapanou et al. 2004a).

Acknowledgements

Financial support was obtained by the Academic Advancement Fund, Columbia University School of Dental and Oral Surgery, and by an unrestricted grant from Colgate-Palmolive Inc., Piscataway, NJ. The expert technical assistance of Romi Celenti, Miriam-Herrera Abreu and Jun Yang, Division of Periodontics, Section of Oral and Diagnostic Sciences, Columbia University School of Dental and Oral Surgery, is gratefully acknowledged.

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Clinical Relevance

A new classification system for periodontal diseases was introduced in 1999, but the implementation of the revised diagnostic guidelines in the everyday clinical practice is problematic. Exemplifying this point, we report that three periodontists using the established criteria to assign periodontal diagnosis arrived in discordant decisions in 25% of the cases evaluated. Contrary to earlier literature postulates, our data failed to demonstrate that serological responses to periodontal bacteria differed between chronic and aggressive periodontitis or between their extent-based subdivisions (localized/generalized), suggesting that the biologic basis of the current classification cannot be readily confirmed by the study of infection patterns.