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2017 WORLD WORKSHOP

Classification and diagnosis of aggressive periodontitis

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objective: Since the initial description of aggressive periodontitis (AgP) in the early 1900s, classification of this disease has been in flux. The goal of this manuscript is to review the existing literature and to revisit definitions and diagnostic criteria for AgP.

Study analysis: An extensive literature search was performed that included databases from PubMed, Medline, Cochrane, Scopus and Web of Science. Of 4930 articles reviewed, 4737 were eliminated. Criteria for elimination included; age > 30 years old, abstracts, review articles, absence of controls, fewer than; a) 200 subjects for genetic studies, and b) 20 subjects for other studies. Studies satisfying the entrance criteria were included in tables developed for AgP (localized and generalized), in areas related to epidemiology, microbial, host and genetic analyses. The highest rank was given to studies that were; a) case controlled or cohort, b) assessed at more than one time-point, c) assessed for more than one factor (microbial or host), and at multiple sites.

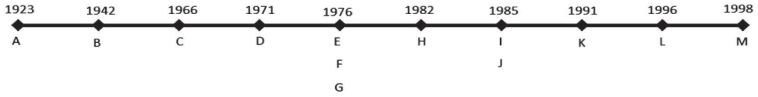
Results: Epidemiologic studies provided insight into ethnic and societal factors affecting AgP. DNA analysis of microbes showed some consistency but significant variability. Host factor analysis was less consistent. Many genetic studies were conducted but few had either sufficient power or looked at multiple genes in AgP.

Conclusions: Conflicting data resulted for several reasons; 1) the classification was too broad, 2) the disease (AgP) was not studied from its inception, at differing time points (temporal), and at different locations (topographic). New technologic advances coupled with a more delimiting definition of disease will allow for genetic, host and microbial factor analyses in an unbiased manner. As such we predict that progress can be made in identifying a robust group of genetic, host, and microbial risk-markers associated with periodontal disease that can improve diagnostic capability in disease associated with juveniles, adolescents, and post-adolescent individuals.

KEYWORDS

aggressive periodontitis, diagnosis, epidemiology, genetics, inflammation and innate immunity, microbiology

This report focuses on aggressive periodontitis (AgP). The most recent effort to classify AgP was presented as a report in 1999 by the American Academy of Periodontology (AAP) committee on the classification of periodontal diseases.[1] This newly proposed terminology was to the greatest extent based on clinical presentation. The committee concluded that all periodontal diseases were infectious in nature but could be categorized as either slowly-progressing (chronic), or,



AgP Timeline Highlights Prior to 1999

A: **1923**: **Gottlieb B.** Z Stomatol 1923;21:195-201.	**[Described AgP as "Diffuse Alveolar Atrophy"]**
B: **1942**: **Orban B, and Weinmann JP.** J Periodontol 1942;13:31-45.	**[Supported Gottlieb's term "Periodontosis" as non-inflammatory form of AgP]**
C: **1966**: American Academy of Periodontology. *World Workshop in Periodontics (Proceedings).* Chicago: American Academy of Periodontology, 1966: 167.	**[Dismissed "Periodontosis as a unique disease entity]**
D: 1971: **Baer PN.** J Periodontol 1971;42(8):516-20.	[**Revived interest in "Periodontosis", promoted term Juvenile Periodontitis]**
E: **1976**: **Newman MG, *et. al.*** J Periodontol 1976;47:373-379	[***Actinobacillus actinomycetemcomitans*** **associated with Juvenile Periodontitis (JP)]**
F: **1976**: **Slots J.** Scand J Dent Res 1976;84:1-10.	[***Actinobacillus actinomycetemcomitans*****(*Aa*) associated with JP]**
G:1976: **Listgarten MA.** J Periodontol 1976;47(3):139-47	**[Described thin biofilm on root surfaces of subjects with JP]**
H: 1982: Goodson JM, *et. al.* J Clin Periodontol 1982;9(6):472-81.	**[Illustrated episodic nature of periodontal diseases]**
I: **1985**: **Moore W, *et. al.*** Infect Immun 1985;48:507-19	[**Challenged microbial disease specificity as related to *Aa* and JP]**
J: **1985**:**Dewhirst FE, *et. al.*** J Immunol 1985;135(4):2562-8.	**[Highlighted the importance of cytokines as related to bone loss]**
K: 1991: **Loe H, and Brown LJ.** J Periodontol 1991;62:608-616	**[Epidemiological analysis of JP or early onset periodontitis]**
L: **1996**: **Brown LJ, *et. al.*** J Periodontol 1996;67(10):968-75	**[Identified the rate of progression in early onset periodontitis or JP]**
M: **1998**: **Socransky SS, *et. al.*** J Clin Periodontol 1998;25(2):134-44.	**[Codified combinations of bacteria related to stages of diseases]**

FIGURE 1A Timeline: research related to aggressive periodontitis prior to 1999. Major events are depicted prior to 1999 (A through M) that influenced our understanding of the disease from its inception in the early 1900s to the most recent 1999 classification system

rapidly-progressing (aggressive) diseases.[1,2] The AAP 1999 workshop group concluded that many similarities were seen when chronic periodontitis (CP) and aggressive periodontitis were compared (Figure 1A; highlights of early literature). However, AgP was designated as a separate disease because of its aggressive nature, the location of the lesions, the familial tendencies, and the thinness of its subgingival biofilm.[3] The data suggested that AgP could be provoked by specific bacteria in some well-defined cases. Immune responsiveness was thought to influence disease manifestation and progression. However, age was not considered as part of the distinguishing features of AgP. Both systemic and local factors such as smoking and trauma were proposed as risk modifiers that could complicate diagnostic accuracy.[2]

Overtime this new classification produced an explosion of information. Despite the information generated, roadblocks to a better understanding of "aggressive periodontitis" continue to exist. In many ways the work published since that time has highlighted deficiencies in the definitions proposed in 1999 and has blurred the distinction between the localized (LAgP) and generalized version of disease (GAgP). In this review we focus especially on LAgP and we suggest it needs redefinition; where possible we distinguish this type from GAgP.

Evidence that has undermined defining LAgP as a distinct entity includes challenges to the:

1. Specificity of the microbial infection[4]
2. Immune localization of LAgP[5]
3. Relationship between LAgP and GAgP[6]
4. Unique innate and acquired cellular responses projected for LAgP[7,8]

Evidence that support consideration of LAgP as a distinct entity that remain include:

1. Localization[9,10]
2. Rate of progression[2,10]
3. Age of onset[11]

METHODS FOR LITERATURE SEARCH

After our extensive review of the literature we have come to two conclusions: 1) there is tremendous interest in AgP, which has expanded exponentially probably because of the broader definition provided in 1999, and 2) it is time for a fresh look at the way in which we classify AgP, especially LAgP (see Figure 1B).

LITERATURE REVIEW

Epidemiology

Relevant findings

Table 1 provides epidemiologic data that re-enforces differences seen in the prevalence of LAgP in various ethnic and

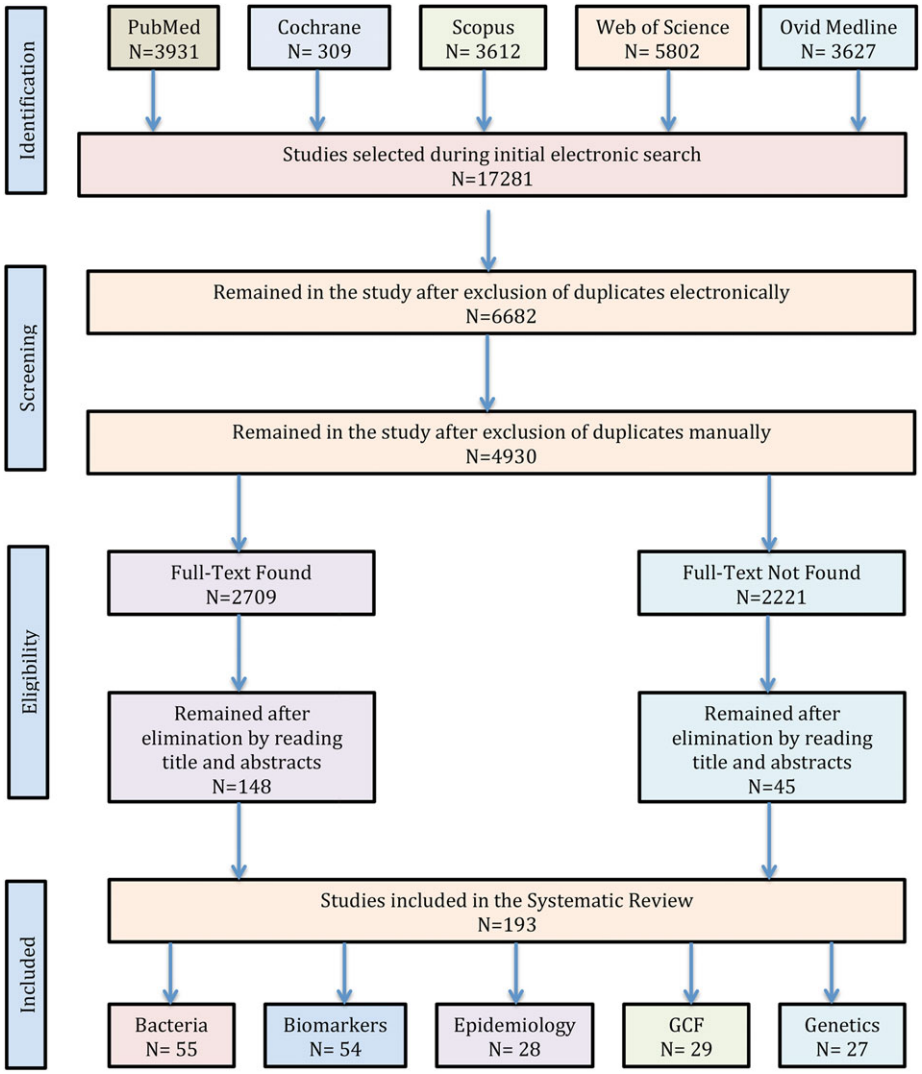


FIGURE 1B Flow-chart depicting the systematic review of the literature. A review of the literature was performed since the last official classification in 1999 was developed using the keywords; "Aggressive Periodontitis," "Severe Periodontitis," "Juvenile Periodontitis," "Localized Juvenile Periodontitis," "Periodontosis," "Early Onset Periodontitis," and "Rapidly Aggressive Periodontitis." Databases in Pub Med, Cochrane, Scopus, Web of Science, Ovid Medline were searched. Duplicates were excluded as were nonEnglish texts and papers without abstracts

racial populations.[12–22] A higher prevalence of LAgP was seen in individuals of African and Middle Eastern descent and a relatively low prevalence was found in individuals of Caucasian descent.[15,22]

Critical evaluation

A variety of methods and endpoints were used for the diagnosis and characterization of disease in these studies (Table 1).[12–22] However, in spite of these differences, the data support the belief that both genetic and perhaps socioeconomic factors are related to disease susceptibility.

Knowledge gaps and suggestions for resolution

Methodologic variations need to be narrowed. New definitions are needed that include; age of onset, lesion location, and rate of progression in the primary case definition. However, key risk modifiers that include familial tendencies, ethnicity, and socio-economic factors need to be considered. Microbiologic and host factors should be included in the assessment if possible to gain a better understanding of etiology and pathogenesis.

Microbiology

Relevant findings

Studies from 1998 forward examined a broad spectrum of bacteria using DNA technologies (Table 2).[23–36] In one-half the studies *Aggregatibacter actinomycetemcomitans* was implicated as a risk marker, and in another half *Porphyromonas gingivalis,*[23,25,27,32–35] *Tannerella forsythia,*[27,29,32,34,35] and *Selenomonads* emerged as markers of risk (Table 2). A recent study[37] showed that in younger individuals

TABLE 1 Epidemiologic studies of aggressive periodontitis

Author; year	Location	Age in years	Number	Clinical parameters	% aggressive periodontitis	Assessments
Lopez *et. al,*[12]; 2001	Chile	12 – 21	9,203	Full Probing CAL	4.5%	Poor oral hygiene related to disease
Albandar *et. al,*[13]; 2002	Uganda	12 – 25	690	Full Probing CAL	4.2%	High prevalence of LAgP, males higher than females
Collins *et. al,*[14]; 2005	Dominican Republic	12 – 21	1,973	CAL	15% had attachment loss of 2 mm or greater	Attachment loss common in adolescent Dominicans
Levin *et. al.*[15]; 2006	Israel	18 – 30	642	Probing CAL and Radiographs	6.7%	Smoking and ethnicity important
Costa *et. al.*[16]; 2007	Brazil	12- 15 at follow – up	360; 44 with CAL of > 4 mm followed for BL	Probing CAL and Radiographs	BL increased from 2.1 to 7.5% in subjects with disease	Disease progresses rapidly in those with disease; .67 mm rate
Eres *et. al.*[17]; 2009	Turkey	13 – 19	3,056	Probing and Radiographs	0.6%	Female: Male = 1.25: 1.0 Ethnic and social issues related to disease
Lopez *et. al.*[18]; 2009	Chile	16 – 17	160	Probing and Radiographs Progression	Shows elevated extent and severity in cases vs controls	No pattern. Typical plaque and gingivitis levels do not hold. Bleeding related to disease
Elamin *et. al.*[19]; 2010	Sudan	15 – 17	1,200	Probing CAL	African = 6.0% Afro/Arab = 2.3%	Males more at risk; Africans more at risk
Sadeghi[20]; 2010	Iran	15 – 18	5,590	Probing CAL	0.13%	Low prevalence in this population
Susin et. al.[21]; 2011	Brazil	14 -29	612	Probing and Attachment	5.5% AgP twice as frequent in non-whites	Socioeconomic, smoking and calculus significant risk
Kissa *et. al.*[22]; 2016	Morocco	16 – 21	830	Probing CAL	4.9%	High risk population

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic, clinical condition assessed by probing, clinical attachment levels, bone loss, tooth-based or average score? Recession considered or not. Incidence and severity considered or not?

A. actinomycetemcomitans was associated with disease whereas this was not the case in older subjects.

Notably, three longitudinal cohort studies assessed disease progression.[29,30,38] All studies were performed in ethnically distinct and socio-economically disadvantaged populations. Two of these examined a broad spectrum of bacteria at specific sites.[29,30] Both examined temporal (time-related) and topographic (site specific) levels of microbial deposits as they related to disease. Both studies indicated that *A. actinomycetemcomitans* was associated with a consortium of other microbes but was; 1) present in low abundance prior to any periodontal destruction, or 2) present in healthy as well as diseased sites in vulnerable individuals and thus not necessarily predictive of future disease, 3) decreased to very low if not undetectable levels after disease occurred. Further, the 3rd cohort study[38] indicated that high leukotoxin producing and "more" virulent strains of *A. actinomycetemcomitans* might act as exogenous agents.

Critical evaluation

In most studies, aside from the cohort studies, the older age of the subjects and the lack of microbial analysis prior to disease weakened conclusions regarding the relationship of microbial factors to disease initiation. Moreover, the lack of standardization in sample collection (point versus scaler) and sample processing (DNA extraction by different methods), made it unlikely that data would lead to identification of unique microbiologic risk-markers. Undoubtedly these methodologic differences could have had a profound influence on outcome measures.

Although it appears as if *A. actinomycetemcomitans* is important in some cases, different combinations of bacteria that occur in different ethnic populations may show similar clinical patterns of destruction.[4] Thus, although the make-up of a microbial consortium may vary from case to case and from population to population, metabolic end-products that can challenge the host, may be similar.[39]

TABLE 2 Studies of multiple bacterial species in localized aggressive periodontitis

Author; year	Country	Number of subjects	Healthy controls yes or no	Multiple bacteria	Culture/ DNA/other	Pooled/1 or multiple times	Assessments
Takeuchi *et. al.*[23]; 2003	Japan	50 AgP, 10 LAgP	Yes	7 bacterial species	Culture/DNA	Sites/1 Time	*T. forsythensis, C. rectus, P. gingivalis, T. denticola, Aa* there but lower
Cortelli *et. al.*[24]; 2005	Brazil	178 CP, 25 AgP	No	5 bacterial species	DNA	Pooled/1 Time	Aa leukotoxic strain higher
Gajardo *et. al.*[25]; 2005	Chile	LAgP 30, 6 GAgP, 17 CAP	No	8 bacterial species	Culture	Pooled/1 Time	*C. rectus, P. gingivalis, E. corrodens P. micros Capnos* high
Aberg *et. al.*[26]; 2009	Sweden	13 AgP	No	6 bacterial species	Culture and DNA	Not Pooled/1 Time	*Aa* not necessarily connected with CAL
Faveri *et. al.*[27]; 2009	Brazil	15 LAgP, 25 GAgP, 30 CAP, 50 C	Yes	40 species	DNA/DNA	Not pooled/1 Time	*Aa* associated with onset. *P.gingivalis, T. forsythia, E. nodatum, P. intermdedia, T. denticola* associated with progression
Lopez *et. al.*[28]; 2011	Chile	87 AgP, 73 C	Yes	40 species	DNA/DNA	Not Pooled/1 Time	Cluster of bacteria as in above seen in disease
*Shaddox *et. al.*[29]; 2012	USA	31 LAgP, 20 C	Yes	422 species	HOMIM	Not Pooled/1 Time	*Aa, Tannerella sp, Solobacterium, P. micra* and Capnos associated with disease
* Fine *et. al.*[30]; 2013	USA	16 LAgP, 16 C	Yes	422 species	HOMIM	Not Pooled/Several Times	Consortium of *Aa, F. alocis* and *S. parasanguinis* associated with disease
Oettinger-Barak *et. al.*[31]; 2014	Israel	21 LAgP, 12 CAP	No	13 species	Culture and PCR	Unknown/1 Time	*Aa, P. micra, F. nucleatum, T. forsythia* associated with disease
Feng *et. al.*[32]; 2014	China	25 LAgP, 56 GAgP, 34 C	Yes	8 species	PCR	Pooled/1 Time	*P. gingivalis, T. forsythia, C. rectus, P. intermedia, F. nucleatum* associated
Dahlen *et. al.*[33]; 2014	Ghana	98 AgP	Site Control	9 species	Culture/PCR	Pooled/1 Time	*P. intermedia, P. gingivalis* associated with disease
Chahboun *et. al.*[34]; 2015	Morocco	13 LAgP, 37 GAgP, 20 CAP	No	11 species	Culture	Pooled/1 Time	*Aa, P. gingivalis, T. forsythia, P. intermedia, F. nucleatum* associated with disease
Li et. al.[35]; 2015	China	10 AgP, 10 C	Yes	> 400	HOMIM	Pooled/1 Time	*P. gingivalis, T. denticola, T. forsythia* associated with disease
Minguez et. al.[36]; 2016	Morocco	32 AgP, 27 CAP	No	9 species	Culture	Pooled/1 Time	*Aa* found frequently in diseased subjects

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic? Disease assessed by probing, clinical attachment levels, bone loss? Sampling by curette or paper point? Pre-selection of microbes? Identification of microbial species by DNA or culture? Cracking buffer method to isolate and purify microbial DNA?

Abbreviations: *Aa = Aggregatibacter actinomycetemcomitans*; *C. rectus = Campylobacter rectus*; *T. denticola = Treponema denticola*; *P. gingivalis = Porphyromonas gingivalis*; *P. micros = Peptostreptococcus micros*; *Capnos = Capnocytophaga sp.*; *T. forsythia = Tannerella forsythia or forsythensis*; *E. corrodens = Eikenella corrodens*; *E. nodatum = Eubacterium nodatum*; *F. alocis = Fusobacterium alocis*; *S. parasanguinis = Streptococcus parasanguinis*; *P. intermdia = Prevetolla intermedia*; CAL = Clinical Attachment Level; AgP = Aggressive Periodontitis; LAgP = Localized Aggressive Periodontitis; GAgP = Generalized Aggressive Periodontitis; CP = Chronic Periodontitis; CAP = Chronic Adult Periodontitis; C = controls; HOMIM = Human Oral Microbe Identification MicroArray.

Data suggest that in a subset of African and Middle Eastern subjects *A. actinomycetemcomitans* may occur in the early stages of disease. It appears as if specific *A. actinomycetemcomitans* virulence factors can suppress the host response, which will allow for the overgrowth of a "toxic" combination of "other" bacteria in the local environment. This hypothesis implicates toxic LPS, leukotoxin, and cytolethal distending toxin in disease activity.

Knowledge gaps and suggestions for resolution

Design and methodologic differences confound interpretation. Resolution of these controversies will emerge only after we; 1) better define disease, 2) perform longitudinal studies documenting the early stages of disease, 3) examine suspected microbes in the context of the total flora relative to disease development, and 4) use standardized methods for plaque collection, DNA extraction, microbiologic identification, and statistical interpretation of data in an unbiased manner. Metabolomics may help to sort out these variables in the future.[6] However, this trajectory will only succeed if our definitions of disease and methodologies become more consistent so that they can be reproduced.

Host response elements

Relevant findings

The infectious disease model proposed in 1999 encouraged researchers to examine host/pathogen interactions by comparing antibody responsiveness to *A. actinomycetemcomitans, P. gingivalis,* and other putative pathogens.[40] It was proposed that the aggressive form of disease went from the localized to the generalized form if serum IgG or IgA levels to *A. actinomycetemcomitans* or other pathogens were ineffective over time thus allowing other suspected pathogens to overgrow in an unrestrained manner.[40] The International Workshop for the Classification of Periodontal Diseases highlighted the importance of the host antibody response to infectious agents concluding that patients with a robust antibody response would not progress from LAgP to GAgP.

Twelve current studies related to local host responses in AgP were examined (Table 3).[30,41–51] Of these, 9 studies[41,42,44–46,49–52] looked at multiple crevice sites within a patient population. Of these, 5 manuscripts[46,48–50,52] reported multiple mediators at the local site. Two of these[46,52] were cohort in nature and these found macrophage inflammatory proteins (MIP)1a, interleukin (IL)-1b, and tumor necrosis factor (TNF)a, to be elevated prior to disease. These cytokines could act as potential risk markers at the site level. Undoubtedly these cytokines could drive immune responsiveness at that site. Other more restrictive studies[44,45,51] examined individual pre-selected factors, i.e., lactic acid dehydrogenase and matrixmetalloproteinases (MMPs), and thus had a built-in bias (Table 3).

A number of carefully performed studies failed to support the relationship between serum antibody titers to purported pathogens and disease progression.[5] A study of note by Ebersole *et al.* showed that local gingival crevicular antibody responses to *A. actinomycetemcomitans* antigens were elevated at the local site indicating a local antibody response.[42] It is clear that polymorphonuclear leukocytes (PMNs) and macrophages respond to cytokines in the initial stages of infection. Cytokines and chemokines are key elements of the cellular response to inflammatory instigators. Granulocyte colony stimulating factors (GCSFs), (IL)-17/23, TNFa, MIP1a have all shown modest support as biomarkers of disease, but results need further confirmation.[46] More recently MIP1a, IL-6, and IL-1b have been suggested as potential biomarkers and have been promoted as potentially useful biomarkers singly or in concert.[46,52] The relevance of these cytokines to clinical classification and disease initiation and progression is still to be determined.

Knowledge gaps and suggestions for resolution

Cytokine networks are known to act as signaling molecules for cells to perform their host protective functions in both distant (i.e., homing of lymphocytes at the regional lymph nodes) and local sites (repopulation of sensitized lymphocytes to the local tissue). Over the years the importance of systemic as well as local expression of cytokines indicates that cytokines form an overall network that has relevance to the balance between host protection and destruction. Once again because the host response is time-related, these important interactions will not be resolved until time-to-infection-and-disease is considered. Similar principals of standardization described for microbiology need to be applied here.

Genetic factors

Relevant findings

Table 4 summarizes the results derived from 22 studies. In total, 30 loci and genes were identified in which one or several genetic variants were associated with AgP (Table 4).[53–74] Studies were based either on candidate-gene approach (CGA) or genome-wide association studies (GWAS) (Table 4).

In the last 10 years, it has become clear that many chronic diseases (i.e., AgP, chronic periodontitis) as well as LAgP and GAgP, are polygenic. Thus, a single genetic defect of major effect will not be responsible for the development of these forms of periodontitis. Many single nucleotide polymorphisms (SNPs) (perhaps some in linkage disequilibrium) together with environmental and lifestyle factors may be deterministic in phenotypic expression of disease.[39,73] In this

TABLE 3 Studies assessing biomarkers associated with localized aggressive periodontitis

Author; year	Country	Number of subjects	GCF-host marker	1 or multiple sites	1 or multiple times	Control yes/no	Conclusions
Kuru *et. al.*[41]; 1999	Turkey	LAgP 15	AST *Aa, Pg* and *PI*	4 Sites	1 Time	No	AST elevated as inflammation increases. *Aa, Pg* up and *Pi* down
Ebersole *et. al.*[42]; 2000	USA	LAgP 12	Antibody to Aa in serum and GCF	28 Sites	Multiple Times	No	Elevated Ab to *Aa* lower *Aa* at site; GCF parallels serum; specificity changes overtime
Kurtis *et. al.*[43]; 2005	Turkey	LAgP 20	MCP-1 and TNFa	1 Site	1 Time	Yes	Levels higher in LAgP but concentrations not higher
Alfant *et. al.*[44]; 2008	USA	LAgP 23	MMP's	3 Sites	1 Time	Yes	MMPs 1–3, 8,9,12,13 all higher in LAgP deep sites vs. control sites
Castro *et. al.*[45]; 2011	Argentina	LAgP 36	LDH, AST, NE and AP	6-8 Sites Pooled	1 Time	Yes	Only LDH showed best connection to LAgP
Shaddox *et. al.*[46]; 2011	USA	LAgP 34	9 Mediators	2 Sites	1 Time	Yes	TNFa, INFg, IL-1b, IL-2, IL-10, IL-12, GM-CSF, MIP1a all higher in diseased sites vs. normal sites and vs. controls; MCP1 and LL 4 decreased
Khongkhunthian *et. al.*[47]; 2013	Thailand	LAgP 15	ADAM8	1 Site	1 Time	Yes	ADAM8 elevated in all disease categories vs. healthy controls
*Fine *et. al.*[30]; 2013	USA	LAgP 15	7 Mediators	Multiple Sites	Several Times	Yes	MIP1a &b, IL-1 and IL-8 elevated in saliva of LAgP prior to BL, MIP 1a elevated in site prior to BL in LAgP subjects
Goncalves *et. al.*[48]; 2013	USA	LAgP 30	8 Mediators	1 Site	1 Time	No	IL-8 lower in non-*Aa* sites
Zhang *et. al.*[49]; 2016	China	LAgP 15	5 Mediators	4 Sites	1 Time	Yes	AP, TNFa, CRP elevated in diseased groups; IL-6 and IL-10 decreased
Shaddox *et. al.*[50]; 2016	USA	LAgP 13	14 Stimulated Mediators	2 Sites	1 Time	Yes	10 cytokines elevated by stimulation in LAgP blood; IL-6 in control
Gunpinar *et. al.*[51]; 2017	Turkey	AgP 80	MCP-1	4 Sites Pooled	1 Time	Yes	MCP-1 elevated in AgP vs. controls

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic, clinical condition assessed by probing, clinical attachment levels, bone loss? Sampling by pooling? Pre-selection of marker? Identification by split samples or by multiplex system?

Abbreviations: AST = Aspartate aminotransferase; MCP1 = Monocyte chemoattractant protein 1; TNFa = Tumor necrosis factor alpha; INFs = Interferon gamma; ILs = Interleukins; GM-CSF = Granulocyte-Macrophage Colony Stimulatig Factor; MMP = Matrixmettaloproteinases; MIP1a = Macrophage Inflammatory Protein 1 alpha; LDH = Lactic acid dehydrogenase; CRP = C reactive protein; NE = norepinephrine; AP = alkaline phosphatase; ADAMS = A disintegrin and metalloproteinase; *Aa = Aggregatibacter actinomycetemcomitans*; *Pg = Porphyromonas gingivalis*; *Pi = Prevetolla intermedia*; AgP = Aggressive Periodontitis; LAgP = Localized Aggressive Periodontitis.

respect, the study by Scapoli *et al*., who studied gene-gene interactions, is noteworthy.[62] The strong familial tendency of LAgP and GAgP may be because of the fact that polygenicity is perhaps in the order of 20–50 risk alleles, rather than > 100 risk alleles such as have been found in, for instance, adult rheumatoid arthritis and Crohn's disease.

The most studied genes appeared to be *CDKN2B-AS1* (*ANRIL*), *IL6*, and *GLT6D1*. For *CDKN2B-AS1* (*ANRIL*), where there were three papers reviewed. For *IL6* and *GLT6D1* there were two independent studies reporting an association with AgP. The remaining loci and genes ($n = 27$) proposed to be associated with AgP, were found in just one study each. Three studies out of the total of 22, specifically mentioned genes associated with either LAgP or GAgP.[55,57,58] Thus, *CDKN2B-AS1* (*ANRIL*) appears to be associated with LAgP, whereas the IL6 relationship is unclear because the number of study participants specifically having LAgP was low (n = 24). One study,[62] identified ten gene-gene interactions associated with AgP (Table 4).

Overall, several genetic polymorphisms associated with AgP were located on chromosome 1, in 6 out of 22 studies. This chromosome may contain "hot spots" related to AgP.

TABLE 4 The various genes or loci harboring minor allele frequencies (polymorphisms) significantly associated with aggressive periodontitis

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Suzuki *et. al.*[53]; 2004	Japanese	*COL1A1*	Collagen Type I Alpha 1 Chain	17	CGA	48615234[e]
Suzuki *et. al.*[53]; 2004	Japanese	*COL4A1*	Collagen Type IV Alpha 1 Chain	13	CGA	109661461[e]
Suzuki *et. al.*[53]; 2004	Japanese	*IL6ST*	Interleukin-6 Signal Transducer	5	CGA	55215302[e]
Nibali *et. al.*[54]; 2006	British	*CYBA* (*NADPH oxidase*)	NADPH Oxidase 4	11	CGA	rs4673
Nibali *et. al.*[55]; 2009	Caucasian	*IL6*	Interleukin-6	7	CGA	rs2069825[c] rs4719714[c]
Gürkan *et. al.*[56]; 2009	Turkish	*AGT*	Angiotensinogen	1	CGA	rs699
Schaefer *et. al.*[57]; 2009	German	*CDKN2B-AS1 (ANRIL)*	Antisense noncoding RNA in the INK4 locus (the regulatory region influences the activity of CAMTA1)	9	CGA	rs1333048 rs1333042 rs2891168
Ernst *et al.*[58]; 2010	German and Northern Irish	*CDKN2B-AS1 (ANRIL)*	Antisense noncoding RNA in the INK4 locus (the regulatory region influences the activity of CAMTA1)	9	CGA	rs1333048 rs496892 rs2891168
Schaefer *et. al.*[59]; 2010	German and Dutch	*PTGS2* (*COX2*)	Prostaglandin-Endoperoxide Synthase 2 (Cyclooxygenase-2)	1	CGA	rs6681231[h]
Schaefer *et. al.*[60]; 2010	German and Dutch	*DEFB1*	Beta-Defensin-1	8	CGA	rs1047031
Schaefer *et. al.*[61]; 2010	German and Dutch	*GLT6D1*	Glycosyltransferase-6 domain 1	9	GWAS	rs1537415 rs11103111 rs1333239 rs7466817 (rs1537415, rs11103111, rs1333239, rs7466817) (rs11103111, rs1333239, rs7466817, rs1537415)
Scapoli *et. al.*[62]; 2011	Italian	*FCGR2A*	Fc gamma Receptor IIa	1	CGA	rs1801274
Scapoli *et. al.*[62]; 2011	Italian	*IL6*	Interleukin-6	7	CGA	rs4719714
Scapoli *et. al.*[62]; 2011	Italian	*SEPSECS* (*SEPS*)	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase	15	CGA	rs11327127
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *IL2*[f]	TNF Receptor Superfamily Member 1B * Interleukin-2	1 * 4	CGA	rs1061622 * rs2069762
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *IL6*[f]	TNF Receptor Superfamily Member 1B * Interleukin-6	1 * 7	CGA	rs1061622 * rs2069825
Scapoli *et. al.*[62]; 2011	Italian	*SEPSECS* (*SEPS*) * *IL2*[f]	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase * Interleukin-2	15 * 4	CGA	rs11327127 * rs2069762
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL18*[f]	Interleukin-6 * Interleukin-18	7 * 11	CGA	rs2069825 * rs1946518

(Continues)

TABLE 4 (Continued)

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL1*[f]	Interleukin-6 * Interleukin-18	7 * 11	CGA	rs4719714 * rs1946518
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *TNF* (*TNF-Alpha*)[f]	TNF Receptor Superfamily Member 1B * Tumor necrosis factor-Alpha	1 * 6	CGA	rs1061622 * rs1799964
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL-4* (*IL-4STR*) [f]	Interleukin-6 * Short tandem repeat polymorphism within interleukin-4	7 * 5	CGA	rs2069825 * rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*FCGR2A, IL6, IL-4* (*IL-4STR*)[f]	Fc gamma Receptor IIa, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4	1, 7, 5	CGA	rs1801274 rs36215817 rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*SEPS, IL2, IL6, IL-4* (*IL-4STR*)[f]	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase, Interleukin-2, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4	15, 4, 7, 5	CGA	rs11327127 rs2069762 rs36215817 rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*IL2, IL6, IL-4* (*IL-4STR*), *FCGR2A*[g]	Interleukin-2, Interleukin-4, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4, Fc gamma Receptor IIa	4, 7, 5, 1	CGA	rs2069762 rs36215817 rs8179190 rs1801274
Schaefer *et. al.*[63]; 2011	German, Dutch	*CDKN2B-AS1* (*ANRIL*)	Antisense noncoding RNA in the *INK4* locus (the regulatory region influences the activity of *CAMTA1)*	9	CGA	rs3217992 rs518394 rs1360590 rs11790231[d]
Martelli *et. al.*[64]; 2012	Italian	*IL18*	Interleukin-18	11	CGA	(-137)[e] (-607)[e]
Bochenek *et. al.*[65]; 2013	German, Austrian and Dutch	*CAMTA1*	Calmodulin Binding Transcription Activator 1	1	CGA	rs17030881 rs10864294
e Silva *et. al.*[66]; 2013	Brazilian	*CTLA-4*	Cytotoxic T-lymphocyte Associated Protein 4	2	CGA	rs231775
e Silva *et. al.*[66]; 2013	Brazilian	*CD28*	CD28 Molecule	2		rs3116496
Schaefer *et. al.*[67]; 2013	Dutch, German-Austrian	*IL10*	Interleukin-10	1	CGA	rs61815643[d] rs6667202
Yang *et. al.*[68]; 2013	Chinese	*TNF* (*TNF-Alpha*)	Tumor Necrosis Factor-Alpha	6	CGA	rs1800629
De Jong *et. al.*[69]; 2014	German	*SLC23A1*	Solute Carrier Family 23 Member 1 (Vitamin C transporter)	5	CGA	rs6596473
Schaefer *et. al.*[70]; 2014	German	*IL2RA*	Interleukin-2 Receptor Subunit Alpha	10	CGA	rs4625363
Schaefer *et. al.*[70]; 2014	German, Dutch	*PRDM1*	PR Domain 1	6	CGA	rs6923419 rs6924535[h]
Schaefer *et. al.*[70]; 2014	Dutch	*IRF5*	Interferon Regulatory Factor 1	5	CGA	rs56303857 imm_7_ 128356335[e]

(Continues)

TABLE 4 (Continued)

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Gao *et. al.*[71]; 2015	Chinese	*APOE*	Apolipoprotein E	19	CGA	rs429358
Gao *et. al.*[71]; 2015	Chinese	*LRP5*	Low Density Lipoprotein Receptor-Related Protein 5	11	CGA	rs312016 rs682429
Hashim *et. al.*[72]; 2015	Sudanese	*GLT6D1*	Glycosyltransferase-6 domain 1	9	CGA	rs1537415
Schaefer *et. al.*[73]; 2015	German, Dutch and Irish	*TGFBRAP1*	Transforming Growth Factor Beta Receptor Associated Protein 1	2	CGA	rs2679895
Schaefer *et. al.*[73]; 2015	German and Dutch	*PLG* (*PLASMINOGEN*)	Plasminogen	6	CGA	rs4252120
Song *et. al.*[74]; 2016	Chinese	*DBP*	Vitamin D-binding protein	19	CGA	rs17467825, rs17467825 + rs4588[i]

Abbreviations: GWAS = Genome wide association study; CGA = Candidate gene approach

* Current gene names (previous nomenclature, i.e., alias) based on GeneCards® www.genecards.org

[a]Significantly in both LAgP (n = 146) and GAgP cohort (n = 159)

[b]Significantly in a subgroup of GAgP (n = 130) vs. controls (n = 339)

[c]Only significantly in a subgroup of LAgP (n = 24 patients) vs. controls (n = 144)

[d]Significantly associated SNP only in the Dutch cohort

[e]rs number not identified. Therefore chromosome position, imm_number or polymorphism is given

[f]The combination of minor alleles for both genes also appears to be associated with AgP

[g]The nonparametric approach pointed to five markers; the potential role of *IL-4-STR*, *IL-2*, *SEPS* already highlighted by logistic regression, is confirmed by Multifactor Dimensionality Reduction algorithm analysis. Furthermore, a significant involvement of *FCGR2A* and *IL-6* variants was also identified

[h]Haplotype tagging SNP for rs20417

[i]Significantly associated haplotype

Critical evaluation

Over the years, several candidate loci and genes have been proposed for AgP, but because of the absence of; 1) sufficient power, and 2) correction for multiple testing, false positive and negative results (type I and II errors) cannot be excluded.[63,73] Thus, because of underpowering, findings of nonsignificant associations for one selected SNP cannot rule out a potential disease association of the gene in question.[63,73]

The loci and genes *CDKN2B-AS1* (*ANRIL*), *IL6*, and *GLT6D1*, seem sufficiently validated. However, we argue that individuals with the diagnosis AgP may form a heterogeneous group. Thus, there are not yet loci and genes validated sufficiently and specifically for LAgP or GAgP.

Knowledge gaps and suggestions for resolution

Gaps will continue to exist in this area because of the limited number of individuals diagnosed with the AgP, especially LAgP. Genetic analysis requires large and well-defined populations using unbiased methods (thus GWAS is preferable to selection of pre-determined markers). A more restrictive definition of disease will be useful here.

Generalized aggressive periodontitis

Eighteen papers were reviewed. Case definitions and methodologic approaches differed substantially.[27,75–91] Of note, Teles *et. al.*[82] examined IL-10/IL-1b ratios and a broad spectrum of bacteria [more information is provided in; a) Table 5, b) the supplementary table in the online *Journal of Peridontology*, and c) appendices, also in the online journal].

DISCUSSION

Three focused questions that follow were designed to define the uniqueness of LAgP in support of a new case definition:

1) What are the unique features of LAgP?

2) Is LAgP a distinct entity that differs from Chronic Periodontitis?

3) What are the roadblocks that exist?

Features unique to LAgP

Aside from the age on onset, the location of the lesions, and the rapidity of the breakdown, there are several added

TABLE 5 Bacteriology and biomarkers in generalized aggressive periodontitis subjects

Author; year	Country	Number of subjects	Marker	Method of assessment	Multiple sites	Multiple times	Control yes/no	Assessments
Miura *et. al.*[75]; 2005	Japan	GAgP 18	Bacteria	Multiple	Multiple	-	Yes	*Aa* and *Tannerella* co-exist with *Pg*
Emingil *et. al.*[76]; 2005	Turkey	GAgP 26	EMAP and MIP-1	GCF	1 Site	1 Time	Yes	EMAP-II higher volume
Ximenez *et. al.*[77]*;* 2006	Mexico	GAgP 19	Bacteria	DNA/DNA; Multiple	Multiple	1 Time	Yes	*Pg, Tannerella* and *P. nigrecens*
Gurkan *et. al.*[78]; 2006	Turkey	GAgP 30	TGF b	GCF	1 Site	1 Time	Yes	TGF b level higher in GAgP and CP
Bostanci *et. al.*[79]; 2007	Turkey	GAgP 26	RANKL and OPG	GCF	1 Site	1 Time	Yes	Ratio higher in GAgP and CP
Faveri *et. al.*[27]; 2009	Brazil	GAgP 10	Bacteria	16S rRNA/ Multiple	3 Sites	-	No	*Selenomonas sp.*
Turkoglu *et. al.*[80]; 2010	Turkey	GAgP 18	Adrenomedullin (ADM) & HNP 1–3	GCF	1 Site	1 Time	Yes	ADM elevated in GAgP and CP
Casarin *et. al.*[81]; 2010	Brazil	GAgP 40	IL-1b, INF g, IL-10 and PGE 2; *Aa* and *Pg*	GCF	2 Sites	1 Time	No	*Aa* and *Pg* higher in GAgP and IgG to *Aa* and *Pg* lower in GCF
Teles *et. al.*[82]; 2010	Brazil	GAgP 31	Eight cytokines; DNA/DNA	GCF and bacteria	14 Sites	1 Time	Yes	IL-1b to IL-10 ratio higher in GAgP subjects and also > in *Aa* and *Capno*
Goncalves *et. al.*[83]; 2012	Brazil	GAgP 15	Bacteria	HOMIM	Multiple	I Time	Yes	*Aa, C. hominis, Peptostrepto, P. alactolyticus*
Shaker and Ghallab.[84]; 2012	Egypt	GAgP 25	IL-17 and IL-11: Red complex by PCR	GCF and Bacteria	4 Sites	1 Time	Yes	IL-17 increased and IL-11 decreased; *Aa* elevated in GAgP
Heller *et. al.*[85]; 2012	Brazil	GAgP 75	Bacteria	DNA/DNA/ Multiple	Multiple	1 Time	No	*Eubacterium nodatum*
Ertugrul *et. al.*[86]; 2013	Turkey	GAgP 20	B2microglobula A2 macroglob	GCF	4 Sites	1 Time	Yes	Both higher in GAgP
Lourenco *et. al.*[87]; 2014	Brazil	GAgP 24	Bacteria	HOMIM	Multiple	1 Time	Yes	*Aa, C. hominis, Peptostrepto, P. alactolyticus*
Baltacioglu *et. al.*[88]; 2014	Turkey	GAgP 30	TOS, RANKL/OPG	GCF	10 Sites	1 Time	Yes	RANKL/OPG ratio higher in GAgP
Sánchez *et. al.*[89]; 2015	Argentina	GAgP 30	Bacteria	PCR	*Aa* and *Pg*	1 Time	Yes	*Aa* associated with GAgP
Elabdeen *et. al.*[90]; 2015	Sudan	GAgP 19	Bacteria	DNA/DNA	Multiple	1 Time	Yes	*Eubacterium yurii* and *E. nodatum*
Toyman *et. al.*[91]; 2015	Turkey	LAgP 23	IL-1b, MMP-3, t-PA, PAI 2	GCF	6 Sites	1 Time	Yes	All higher in CP and GAgP

Inconsistent Study Factors: Age, disease definition, randomization, enrollment at school or clinic? Site of collection? Single sites and single collections vs multiple sites and multiple collections? Method of collection? Method of identification and analysis?

Abbreviations: GCF = Gingival crevicular fluid; GAgP = Generalized aggressive periodontitis; CP = Chronic periodontitis; EMAP = Endothelial-monocyte-activating-protein; MIP-1 = macrophage inflammatory protein 1; TGF b = Transforming growth factor beta; RANKL = Receptor activator of nuclear factor kappa-B ligand; OPG = Osteoprotegerin; ADM = Adrenomedullin; HNP 1–3 = Human neutrophil peptide; IL-1b = Interleukin 1 beta; INF g = Interferon gamma; PGE 2 (Prostaglandin E 2); MMP-3 = Matrixmetalloproteinase-3; t-PA = Tissue plasminogen activator; PAI 2 = plasminogen activator inhibitor 2; B2 microglob = Beta 2 microglobulin; A2 macroglob = A2 macroglobulin; TOS = Total oxygen status; *Aa* = *Aggregatibacter actinomycetemcomitans*; *Pg* = *Porphyromonas gingivalis*; *Pi* = *Prevetolla intermedia*; LAgP = Localized aggressive periodontitis

features that appear to be unique to LAgP. For example it has been reported that; 1) PMNs and macrophages show a level of hyperactivity,[7] 2) antibody responsiveness can be elevated either at a peripheral or local level,[42] 3) specific subpopulations of bacteria are prevalent in specific populations[23,35] and 4) a particularly thin biofilm composed of Gram negative bacteria have been reported on root surfaces of LAgP subjects.[3,92]

Is LAgP a distinct entity?

Our current literature review suggests that there are phenotypic differences between CP and LAgP that include; age of onset, location of initial lesions, and rate of progression (based on limited exposure because of age). There are several hints as described above that suggest microbiologic, pathophysiologic and genetic differences between CP and LAgP. However, it is premature to point to pathophysiologic differences between these two entities until these data are ascertained in larger, more diverse, better-defined and controlled populations. This can only be resolved if better definitions of disease are provided.

Overall, periodontitis is defined as an inflammatory disease of the supporting tissues around teeth, which can cause irreversible loss of periodontal ligament, alveolar bone, tooth mobility and ultimately, if left untreated, tooth exfoliation. The disease is caused by an aberrant immune response (immunologic intolerance) to resident microbial communities on the teeth, which extend into the submarginal region. Normally, and for most people, the host lives in symbiosis with this biofilm. Often a nonprogressive gingivitis develops (perhaps needed to train the immune system to induce tolerance). However, an individual may convert from a symbiotic microbial and immune state to an aberrant and dysbiotic microbiome and host response. These exaggerated dysbiotic host inflammatory reactions are destined to result in the destruction of the periodontal tissues and can be episodic in nature and nonlinear and disproportionate to an assorted collection of risk factors.[93]

From a pathophysiologic point of view both LAgP and CP have a common end result, the loss of bone and disorientation of the attachment apparatus results from disruption in homeostatic balance between deposition and resorption of bone.[94] Initially identified as a noninflammatory condition (termed periodontosis) it is now clear that both LAgP and CP are entities resulting from inflammatory responses to a biofilm starting point, which results in bone loss. However, overall it is clear that LAgP demonstrates a unique phenotype but a more in depth understanding of the differences among events leading up to bone loss in LAgP as compared to CP need to wait for a more exacting definition of early events.

Roadblocks toward a better understanding

A major roadblock in the current LAgP definition is its failure to identify the early time-dependent issues related to disease. Because a gold standard case definition is still lacking it behooves us to develop the optimal way of describing the disease in each of its stages.

Classifications are used to assess clinical conditions in an individual and in groups of individuals. Diagnosis is used to guide treatment on an individual level. Case definitions are used to differentiate groups of individuals who share similar features with regard to causes, prognosis, and response to treatment.[95] Classification is difficult if a gold standard is lacking as in the case of LAgP.

Every disease has time dependent events that help define disease initiation and progression. A classification scheme that can effectively incorporate early events in disease progression can provide information that could reveal important pathophysiologic events. Early detection typically results in discovery of causal factors and cost effective preventive interventions. Use of a time dependent approach could unravel the initiating microbial causes and host response elements related to LAgP.

Several epidemiologists have focused their attention on the multifactorial approach to disease that specifies that; 1) a single component is rarely a sufficient cause of disease, 2) host susceptibility may play a vital role in disease initiation and development, and 3) a harmless agent could produce disease in an immune-compromised individual.[96] In this approach three overlapping issues are of paramount importance in disease development that include; time, place, and person.

"Time" relates to the extent of exposure to an agent. In the case of LAgP, the more disease seen in younger individuals indicates that either the initiating component or the host response to that component permits disease to occur at a more rapid rate. With respect to bacteria, time relates to the incubation period, or, the time required for the biofilm to reach a critical mass that challenges the host (this can include a broad spectrum of species and bacterial products, e.g., LPS, leukotoxin, other toxins, antigenic proteins). With respect to the host response, time relates to fluctuation in host resistance or susceptibility often determined by genetic and epigenetic risk factors as well as life style and life events that modulate both innate and acquired immunologic responses, effectively determining the immune fitness.[97]

"Place" typically relates to an area of increased risk. In our case, place relates to geographic location (Africa, Middle East, North America, etc.) as well as topographic location (i.e., tooth surface). Geography translates into areas with lower socio-economic status (diet or living conditions, greater exposure to toxins because of crowding), and homogeneity with respect to genetic status (i.e., immune resistance or susceptibility because of lack of population diversity). Although

we do have some evidence that the JP2 strain of *A. actinomycetemcomitans* evolved as an exogenous agent from North Africa most of the infections we see are related to members of the indigenous flora.[98] Also, relevant in our case, place refers to the distribution of the disease in the oral cavity, specifically on the interproximal surface of molars and incisors.

"Person" typically relates to the individual who possesses either inherited or acquired risk factors (i.e., lifestyle risk factors related to ethnic and socioeconomic factors) that make him or her more vulnerable to disease. Age, gender, and race are all considered. Of the components described, typically age has the highest significant person feature, but gender and race also apply. Age relates to the opportunity for exposure, latency of incubation period and physiologic responsiveness or lack thereof. This translates into individual susceptibility. Gender could be especially meaningful in pubescent periods when different hormonal products could influence immune responsiveness or the lack thereof. Race could imply genetic susceptibility.

CONSIDERATIONS WHEN REDEFINING AGGRESSIVE PERIODONTITIS

Any new definition should be based on the; a) age of the subject, b) location of lesions, c) extent of disease (stages). The first diagnosis could be in; 1) childhood (prepubertal), 2) adolescence (puberty), and 3) early adulthood (postadolescence).

The definition of disease in addition to age could include; a) the location of the lesion and the stage or extent of disease (one, two or three or more teeth). This staged approach would signify the severity of disease (i.e., one tooth is less severe than two teeth, etc.). This staged approach would also enable the practitioner and researcher to identify the "burned out" or contained disease (i.e., a disease confined to one tooth or two teeth etc.). In its simplest form the staged definition could be categorized as Stage 1, a disease limited to one tooth, Stage 2 limited to two teeth, Stage 3 limited to three teeth (molars and incisors), and Stage 4 the classic Löe and Brown definition of disease.[99]

To prevent confusion with trauma or other noninfectious disease initiators, a diseased tooth would be defined as having proximal attachment loss but would not be based on buccal or lingual recession.

This staged definition would be helpful to examine microbial initiators, host-response elements, and pathophysiologic changes. It would also be helpful in genetic distinctions between the classic Löe and Brown disease and early stage disease that is contained. It should be especially helpful in establishing the multi-causal nature of this localized form of periodontal disease in young individuals.

CONCLUSIONS AND FUTURE DIRECTIONS

In the past, characterizations of the aggressive forms of periodontitis have been limited by; 1) the low number of individuals who have this form of disease, coupled with 2) inconsistency resulting from the broad definitions proposed in the past. Choosing a new definition should not only be based on clinical observations, like the usual medical and dental history, clinical charting, and radiographic examinations, but also it should focus on obvious phenotypic indictors such as age of onset, location of lesions in defined populations.

A new definition of aggressive periodontitis has been suggested; 1) to break the cycle of inertia that has occurred in the last 17 years, 2) to catch the disease in its earliest stages, and 3) to place a greater emphasis on the multi-causal model of disease. Factors such as host response elements, consortia of microorganisms, and many other confounding factors could be assessed for their role in the earliest stages of disease within a new definition. Using these parameters the multiplicity of inherited genes of minor effect can be related to the early stages of disease. To illustrate this point, inheritance of genes that lead to a hyper-inflammatory response may have a greater impact on the disease as it becomes the more generalized Löe and Brown form of disease. Moreover, a new definition could provide a better understanding of the genes involved in containing or limiting the extent of disease to its earliest stages (i.e., burned out form). However, substantiating this hypothesis and the pathophysiologic conditions that follow these parameters, will require populations that contain larger sample sizes using, as we suggest, a more restrictive definition.

The facts that (1) the phenotypic characteristics of what we have called LAgP, show very often alveolar bone loss at first molars as the initial site of destruction; and that (2) this disease occurs typically in an adolescent descending from Africa or the Middle East with strong hints that *A. actinomycetemcomitans* is part of the microbiome, suggests that longitudinal assessments are potentially possible. The fact that the disease we are attempting to define could be considered as an orphan disease (a disease affecting fewer than 200,000 individuals in the United States), that is also silent (presenting symptoms that are not noticed by the individual) makes it even more imperative that we make a vigorous attempt to create a restrictive definition so that we can catch it in its earliest stages.

In conclusion, the emergence of highly sophisticated and reproducible technologies has allowed us to use minimal amounts of plaque, saliva, and serum or crevice fluid to survey many microbiologic, host, and genetic factors simultaneously. In this manner disease related comparisons can be made in a relatively unbiased fashion. A new case definition helps to identify the earliest stages of disease. This should

enable significant progress in diagnosis, prevention, and treatment of this aggressive form of periodontal disease.

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The authors wish to thank all the research scholars who have contributed to our current and past knowledge base relative to these complex conditions we know as periodontal diseases. We did our best to select articles that highlight what we know and where we might go to pave our path to the future. We especially thank Dr. Gary Armitage who took on this enormous responsibility in the past and who provided many building blocks to our knowledge base by his meticulous review of the material during his tenure as the coordinator of this challenge. We also wish to apologize to the authors whom we omitted in our efforts to summarize the material to date. The volume of work related to this field has exploded in the last 17 years largely because of the groundwork provided by Dr. Armitage. This work has opened the door to the future and we extend our gratitude for his efforts. The authors report no conflicts of interest related to this review paper.

TO CLINICIANS

We hope this new definition will permit a more constrained definition that will lead to earlier and more rapid diagnosis that will provide more consistent and better treatment results.

TO RESEARCHERS

We hope this new definition will push the boundaries towards longitudinal cohort studies enrolling subjects in the earliest stages of disease that use the burgeoning research technology available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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