2017 Classification Workshop

Aggressive Periodontitis

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Classification of Aggressive PDT:1999 report by the AAP committee on the classification of periodontal diseases

Aggressive periodontitis → **clinical presentation**.

Conclusion:

- all periodontal diseases were infectious in nature
- but could be categorized as either
  - slowly-progressing (chronic- CP), or,
  - rapidly-progressing (aggressive- AP) diseases.

(Armitage GC, 1999, Armitage GC, 2010)

Also concluded that ***many similarities*** were seen when CP and AP were compared

Then why Aggressive periodontitis? A separate disease entity?

Because,

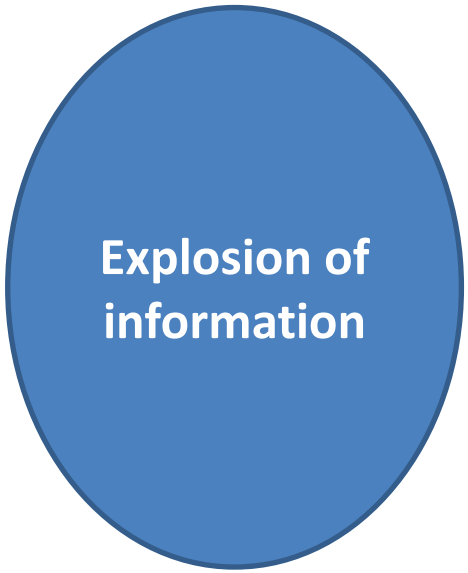
- aggressive nature
- location of the lesions
- familial tendencies
- thinness of its subgingival biofilm

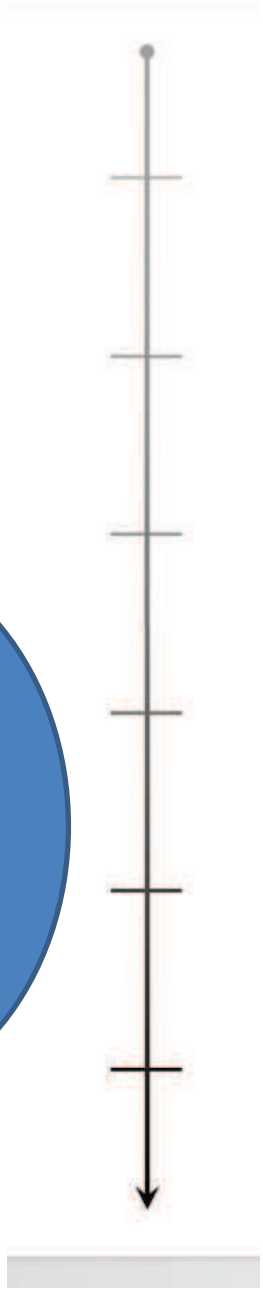
Further suggestions from data:

- could be provoked by specific bacteria in some well-defined cases.
- Immune responsiveness ⟹ disease manifestation and progression.
- Both systemic and local factors such as smoking and trauma were proposed as risk modifiers that could complicate diagnostic accuracy.

(Armitage GC, 2010)

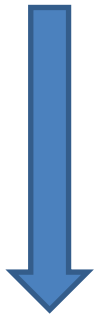
Time line





- roadblocks to a better understanding of “aggressive periodontitis” continue to exist
- work published since that time has
  - ➢ highlighted deficiencies in the definitions proposed in 1999
  - ➢ blurred the distinction between the localized (LAgP) and generalized version of disease (GAgP).

Review - 2018
Methods for literature search



- Time for a fresh look at the way in which we classify AgP
- LAgP needs *redefinition*
- LAgP need to be *distinguished from GAgP*

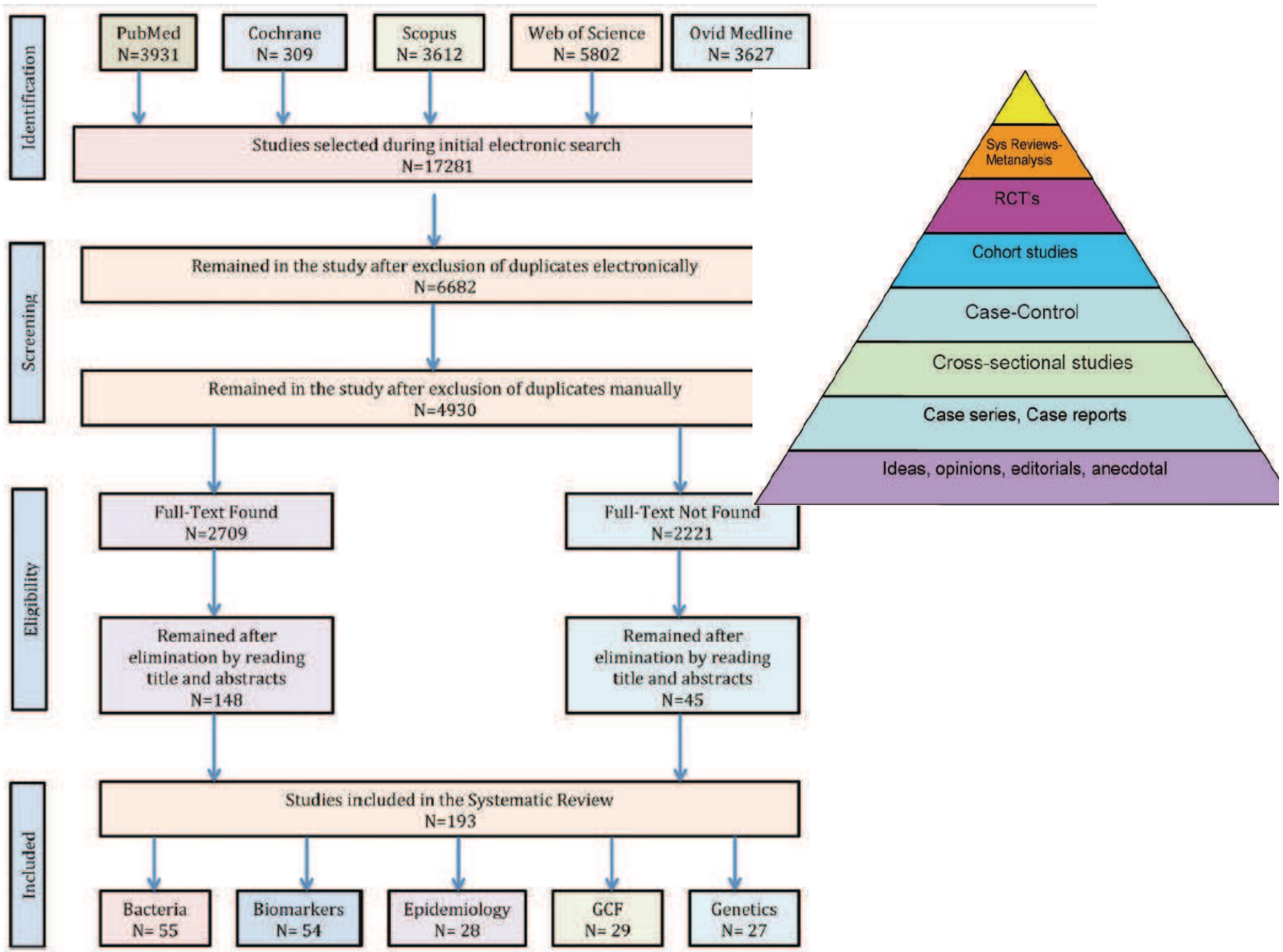


FIGURE 1B Flow-chart depicting the systematic review of the literature. A review of the literature was performed since the last official classification in 1999 was developed using the keywords; "Aggressive Periodontitis," "Severe Periodontitis," "Juvenile Periodontitis," "Localized Juvenile Periodontitis," "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

Microbiology : Relevant findings

Studies from 1998 forward examined a broad spectrum of bacteria using DNA technologies

- ½ the studies, Aggregatibacter actinomycetemcomitans - risk marker
- Other ½, Porphyromonas gingivalis

(Takeuchi Y, et al, 2003; GajardoM, et al. 2005; Faveri M, et al. 2009; Feng X, et al. 2014; Dahlen G, et al. 2014; Chahboun H, et al, 2015;Li Y, et al. 2015)

- Tannerella forsythia

(Faveri M, et al. 2009; Feng X, et al. 2014; Chahboun H, et al, 2015;Li Y, et al. 2015; Shaddox LM, Huang H, Lin T, et al.2012)

- Selenomonads

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.

- "in **younger individuals** A. A associated with disease whereas this was not the case in older subjects" study, 2017
- **3 longitudinal cohort studies** assessed disease progression.

(Shaddox LM, et al. 2012, Fine DH, et al. 2013; Haubek D, et al.2008)

All studies were performed in ***ethnically distinct and socio-economically disadvantaged*** populations

Haubek D, et al.2008

indicated that high leukotoxin producing and "more" virulent strains of A. actinomycetemcomitans might act as exogenous agents.

Shaddox LM, et al, 2012; Fine DH, et al 2013

Broad spectrum of bacteria

- temporal (time-related)
- topographic (site specific) levels of microbial deposits as they related to disease
- and indicated that A. a was associated with a consortium of other microbes but was;

1) present in **low abundance** prior to any periodontal destruction
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.

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(ethnic and geog differences in carriage of microbes) and sample processing, microbiologic identification, and statistical interpretation of data) in an unbiased manner 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.

Epidemiology

- data re-enforces differences seen in the prevalence of LAgP in various ethnic and racial populations

SYSTEMATIC review:

(Lopez et al. 2002;Collins J, Carpio AM et al, 2005;76: Levin L, Baev V et al 2006; Costa FO, Cota LOM et al, 2007; Eres G et al, 2009;Lopez R etal, 2009, Elamin AM et al, 2010, Sadeghi R.2010, Susin C et al, 2011, Kissa J et al, 2016)

- ↑ prevalence of LAgP was seen in individuals of *African and Middle Eastern descent* and
- Relatively ↓ prevalence was found in m individuals of *Caucasian descent*

(Levin L et al, 2006, Kissa J et al. 2016)

Critical evaluation

- In spite of differences in methods and endpoints used for the diagnosis and characterization of disease in these studies
- ➢ the data support the belief that both

  "genetic and perhaps ***socioeconomic*** factors"

  are related to disease susceptibility.
- 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, socio-economic factors , microbiologic and host factors need to be considered.

Host response elements
Relevant findings

- Host factor analysis was less consistent

1999

- model encouraged **(Gunsolley JC et al,1987)** researchers to **examine host/pathogen interactions** by

- Comparing Ab responsiveness to A. actinomycetemcomitans & other putative pathogens
- proposed that the aggressive form of disease went from **the**

- ***LAgP to GAgP 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

2017

- Workshop for the Classification of Periodontal Diseases highlights

- 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***

12 studies

- 9 studies ➡ multiple crevice sites within a patient population.
- Of these, 5 manuscripts reported multiple mediators at the local site.
- 2 cohort - found (MIP)1a, (IL)-1b, (TNF)a, to be elevated prior to disease.
- Restrictive 3 studies - individual pre-selected factors, i.e., lactic acid dehydrogenase & (MMPs), and thus had a built-in bias

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
Allant *et. al.*[44]; 2008	USA	LAgP 23	MMPs	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 = Matrixmetuloproteinases; 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* = *Prevotella intermedia*; AgP = Aggressive Periodontitis; LAgP = Localized Aggressive Periodontitis.

- Failure to identify the earliest microbial and host events that occur in AgP, roadblock to distinguishing between CP and AgP
- ⬆ Carefully done studies failed to support the relationship between serum Ab titers to pathogens and disease progression **(Hwang AM, etal, 2014)**
- ⬆Local gingival crevicular antibody responses to A.a antigens indicating a local antibody response. **(Ebersole JL, et al 2000)**

Critical evaluation

- Clear well defined associations between cytokines and disease are still lacking.
- 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

Many genetic studies were conducted

But,

- Most inadequate power
- few had either sufficient power or looked at multiple genes in AgP

22 studies

- 30 loci and genes were identified
- in which one or several genetic variants were associated with AgP
- Studies were based either on (CGA) or (GWAS)
- 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 not responsible for
- Many single nucleotide polymorphisms (SNPs) together with environmental and lifestyle factors may be deterministic in phenotypic expression of disease.

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[a]
Suzuki et. al.[53]; 2004	Japanese	*COL4A1*	Collagen Type IV Alpha 1 Chain	13	CGA	109661461[a]
Suzuki et. al.[53]; 2004	Japanese	*IL6ST*	Interleukin-6 Signal Transducer	5	CGA	55215302[a]
Nibali et. al.[54]; 2006	British	*CYBA (NADPH oxidase)*	NADPH Oxidase 4	11	CGA	rs6673
Nibali et. al.[55]; 2009	Caucasian	*IL6*	Interleukin-6	7	CGA	rs2069825[a] rs4719714[a]
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[b]
Schaefer et. al.[59]; 2010	German and Dutch	*DEFB1*	Beta-Defensin-1	8	CGA	rs1049031
Schaefer et. al.[61]; 2010	German and Dutch	*GLT6D1*	Glycosyltransferase-6 domain 1	9	GWAS	rs1537415 rs1103111 rs1333239 rs7466817 (rs1537415, rs1103111, rs1333239, rs7466817) (rs1103111, 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	rs1327127
Scapoli et. al.[62]; 2011	Italian	*TNFRSF1B* IL2*[†]	TNF Receptor Superfamily Member 1B * Interleukin-2	1 * 4	CGA	rs1061622 * rs2069762
Scapoli et. al.[62]; 2011	Italian	*TNFRSF1B* IL6*[†]	TNF Receptor Superfamily Member 1B * Interleukin-6	1 * 7	CGA	rs1061622 * rs2069825
Scapoli et. al.[62]; 2011	Italian	*SEPSECS (SEPS) * IL2*[†]	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase * Interleukin-2	15 * 4	CGA	rs1327127 * rs2069762
Scapoli et. al.[62]; 2011	Italian	*IL-6* IL18*[†]	Interleukin-6 * Interleukin-18	7 * 11	CGA	rs2069825 * rs1946518

(Continues)

Critical evaluation

Why 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 other inflammatory diseases.

- Though, several candidate loci/ 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.
- findings of nonsignificant associations for one selected SNP cannot rule out a potential disease association of the gene in question.(**Schaefer AS, et al, 2011;Schaefer AS, et al. 2015)**
- The loci and genes CDKN2B-AS1 (ANRIL), IL6, and GLT6D1, seem sufficiently validated.
- Also genetic analysis requires ***large and well-defined populations*** using unbiased methods (eg. GWAS)
- ***limited number of individuals diagnosed with the AgP***, individuals with the diagnosis AgP may form a heterogeneous group.
- Important to realize population specific genetic variants

Generalized aggressive periodontitis

- 18 papers were reviewed.
- **Case definitions** and methodologic approaches differed substantially
- Poor definitions of disease and conflicting results.
- **Microbiological studies :** two studies showed elevation for each of the following species: *Selenomonads, Eubaccteria, A. actinomycetemcomitans, P. gingivalis,* and *Tannerella*.
- ➢ The populations studied varied and included subjects from;
- ➢ Japan, Argentina, Egypt, Mexico, Taiwan, Sudan, Turkey, China, Thailand, Uganda, Israel, Chile, Iran, Dominican Republic, Sweden, Ghana, Morocco, USA and Brazil.
- As for **biomarkers**, among the markers examined, ***RANKL/OPG and IL-1b*** were the most studied. In one of the most stringent studies IL-1b/IL10 ratios showed some promise but once again *heterogeneous case definitions and marker selection bias* could have played a role.

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	1 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* = *Prevotella intermedia*; LAgP = Localized aggressive periodontitis

GAgP Conclusion

- Due to *poor definitions* and limited control of disease temporality (stage) and its *topography* (location)

"it is hard to make any definitive conclusions other than to say that it appears as though in GAgP host factors fail to contain and/or localize the disease"

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

- Age on onset **(Fine DH, et al. 2007)**
- Location of the lesions **(Diehl SR, et al. 2005, Brown LJ, et al 1996)**
- Rapidity of the breakdown **(Armitage GC, 2010 Brown LJ, et al 1996)**

Several added features that appear to be unique to LAgP. For example,

1) PMNs and macrophages show a level of hyperactivity **(Fredman G,et al.2011)**
2) Antibody responsiveness can be elevated either at a peripheral or local level **(Ebersole JL, etal, 2000)**
3) Specific subpopulations of bacteria are prevalent in specific populations **(Takeuchi Y, et al, 2003, Li Y, et al, 2015)**
4) Thin biofilm composed of Gram negative bacteria have been reported on root surfaces of LAgP subjects. **(Listgarten MA, 1976, Fine DH, et al, 1984)**

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)".

- Several hints also 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.

Roadblocks toward a better understanding

Major roadblocks in the current LAgP definition are:

- failure to id the ***early time-dependent issues*** related to disease
- A ***gold standard case definition*** is still lacking
- ***Classification is difficult*** if a gold standard is lacking as in the case of LAgP

- Current evidence does ***not support*** the distinction between CP & AP
- However, a ***substantial variation in clinical presentation*** exists with respect to extent and severity throughout the age spectrum, suggesting that there
- ***are population subsets with distinct disease trajectories due to differences in exposure and/or susceptibility.***
- specific ***etiologic or pathological elements*** that account for this distinct presentation are ***insufficiently defined.***

- Likewise, ***mechanisms accounting for the development of generalized periodontitis*** in young individuals are poorly understood
- the currently adopted ***classification is too broad***,
- the disease has not been studied from its ***inception***, and the low number of AgP individuals
- there is paucity of ***longitudinal studies*** including ***multiple time points*** and ***different populations***

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥5 mm	≥5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic/ no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes
Risk of systemic impact of periodontitis[a]	Inflammatory burden	High sensitivity CRP (hsCRP)	<1 mg/L	1 to 3 mg/L	>3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, gingival crevicular fluid, serum	?	?	?

A Restrictive definition

- ***advantage of modern methodologies to enhance knowledge on the diagnosis, pathogenesis, and management of this form of periodontitis***.
- based on
- clinical observations (med and dental Hx, clinical charting, and radiographic examinations + focus on
- obvious phenotypic indicators - age of onset, location of lesions in defined populations.
- factors such as host response elements, microbiology and many other confounding factors could be assessed for their role in the earliest stages of disease within a new definition
- a better understanding of the genes involved.