Staging and Grading of Periodontitis

Framework and Proposal of a new Classification and Case Definition

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Running title: Periodontitis case definition

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/JPER.18-0006.

Abstract

Background: Authors were assigned the task to develop case definitions for periodontitis in the context of the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases. The aim of this manuscript is to review evidence and rationale for a revision of the current classification, to provide a framework for case definition that fully implicates state of the art knowledge and can be adapted as new evidence emerges, and to suggest a case definition system that can be implemented in clinical practice, research and epidemiologic surveillance.

Methods: Evidence gathered in 4 commissioned reviews was analyzed and interpreted with special emphasis to changes with regards to the understanding available prior to the 1999 classification. Authors analyzed case definition systems employed for a variety of chronic diseases and identified key criteria for a classification/case definition of periodontitis.

Results: The manuscript discusses the merits of a periodontitis case definition system based on Staging and Grading and proposes a case definition framework. Stage I to IV of periodontitis is defined based on severity (primarily periodontal breakdown with reference to root length and periodontitis-associated tooth loss), complexity of management (pocket depth, infrabony defects, furcation involvement, tooth hypermobility, masticatory dysfunction) and additionally described as extent (localized or generalized). Grade of periodontitis is estimated with direct or indirect evidence of progression rate in 3 categories: slow, moderate and rapid progression (Grade A-C). Risk factor analysis is used as grade modifier.

Conclusions: The paper describes a simple matrix based on Stage and Grade to appropriately define periodontitis in an individual patient. The proposed case definition extends beyond description based on severity to include characterization of biological features of the disease and represents a first step towards adoption of precision medicine concepts to the management of periodontitis. It also provides the necessary framework for introduction of biomarkers in diagnosis and prognosis.

Keywords: Periodontitis, classification, case definition, periodontitis/stage, periodontitis/grade, diagnosis, standard of care, clinical attachment loss, radiographic bone loss, periodontal pocket, infrabony defect, furcation involvement, tooth hypermobility, masticatory dysfunction, risk factors, biomarkers, tooth loss, chronic periodontitis, aggressive periodontitis, necrotizing periodontitis, periodontitis as manifestation of systemic disease, stage I periodontitis, stage II periodontitis, stage III periodontitis, stage IV periodontitis, Grade A periodontitis, Grade B periodontitis, Grade C periodontitis, inflammatory burden.

1. Introduction: The 1999 Classification of Periodontitis

Periodontitis is characterized by microbially-associated, host-mediated inflammation that results in loss of periodontal attachment. The pathophysiology of the disease has been characterized in its key molecular pathways, and ultimately leads to activation of host-derived proteinases that enable loss of marginal PDL fibers, apical migration of the junctional epithelium and allows apical spread of the bacterial biofilm along the root surface. The bacterial biofilm formation initiates gingival inflammation; however periodontitis initiation and progression depend on dysbiotic ecological changes in the microbiome in response to nutrients from gingival inflammatory and tissue breakdown products that enrich some species and anti-bacterial mechanisms that attempt to contain the microbial challenge within the gingival sulcus area once inflammation has initiated. Current evidence supports multifactorial disease influences, such as smoking, on multiple immuno-inflammatory responses that make the dysbiotic microbiome changes more likely for some patients than others and likely influence severity of disease for such individuals.

Marginal alveolar bone loss – a key secondary feature of periodontitis - is coupled with loss of attachment by inflammatory mediators. Clinical presentation differs based on age of patient and lesion number, distribution, severity, and location within the dental arch. The level of oral biofilm contamination of the dentition also influences the clinical presentation.

In recent decades, attempts to classify periodontitis have centered on a dilemma represented by whether phenotypically different case presentations represent different diseases or just variations of a single disease. Lack of ability to resolve the issue is illustrated in the changes to the classification

system that progressively emphasized either differences or commonalities.[1, 2] Shortly before the 1999 International Workshop on Classification of periodontal diseases, research in the field emphasized individual features of periodontitis and thus differences in phenotype. These emerged from the identification of specific bacteria or bacterial complexes as etiologic agents of periodontitis,[3] the recognition of the existence of multiple modifiable risk factors,[4] and the identification of the relevance of genetic susceptibility[5, 6] and specific polymorphisms associated with disease severity.[7] The research perspective on the disease impacted the 1999 classification system that emphasized perceived unique features of different periodontitis phenotypes and led to the recognition of four different forms of periodontitis:

1. Necrotizing periodontitis
2. Chronic periodontitis
3. Aggressive periodontitis
4. Periodontitis as a manifestation of systemic diseases

The overall classification system aimed to differentiate the more common forms of periodontitis, i.e. chronic and aggressive periodontitis, from the unusual necrotizing form of the disease (characterized by a unique pathophysiology, distinct clinical presentation and treatment), and the rare major genetic defects or acquired deficiencies in components of host defense (characterized by a primary systemic disorder that also expresses itself by premature tooth exfoliation).

The 1999 group consensus report on aggressive periodontitis identified specific features of this form of disease and proposed the existence of major and minor criteria for case definition as well as distribution features to differentiate localized from generalized forms of periodontitis.[8] By default,

cases of periodontitis that would not satisfy the "aggressive" phenotype definition would be classified as "chronic" with the implication that latter cases could be managed more easily and, with appropriate therapy and maintenance care, would rarely jeopardize the retention of a functional dentition.[9] The rationale for differentiating between chronic and aggressive periodontitis included the ability to identify and focus on the more problematic cases: presenting with greater severity earlier in life, at higher risk of progression and/or in need of specific treatment approaches.

The 1999 International Classification workshop addressed a host of concerns with the clinical applicability and pathophysiologic rationale of previous classification systems (see Armitage 1999[10] for discussion), emphasized the need to capture differences between forms of the disease able to lead to edentulism, but did not clearly communicate differences between chronic and aggressive periodontitis. While the consensus report of the aggressive periodontitis working group articulated major and minor criteria required for the aggressive periodontitis diagnosis as well as specific definitions to identify patterns of distribution of lesions within the dentition (localized molar incisor vs. generalized, see Lang et al. 1999[8] for detailed discussion), the difficulty in applying the stipulated criteria in the everyday clinical practice and the substantial overlap between the diagnostic categories provided a barrier to clinicians in the application of the classification system. Furthermore, the validity of many of the criteria for aggressive periodontitis has not been confirmed in adequately designed studies.

Over the past two decades clinicians, educators, researchers and epidemiologists have voiced concern about their ability to correctly differentiate between aggressive and chronic periodontitis cases and these difficulties have been a major rationale for a new classification workshop.[11]

2. Summary and Interpretation of Evidence from Current Workshop Position Papers

To update evidence that has accumulated since the latest classification workshop, the organizing committee commissioned a review on acute periodontal lesions including necrotizing periodontitis,[12] a review of manifestations of systemic diseases that affect the periodontal attachment apparatus,[13] and three position papers that are relevant to the discussion of aggressive and chronic periodontitis[14 15 16].

The position papers that addressed aggressive and chronic periodontitis reached the following overarching conclusions relative to periodontitis:

1. There is no evidence of specific pathophysiology that enables differentiation of cases that would currently be classified as aggressive and chronic periodontitis or provides guidance for different interventions.

2. There is little consistent evidence that aggressive and chronic periodontitis are different diseases, but there is evidence of multiple factors, and interactions among them, that influence clinically observable disease outcomes (phenotypes) at the individual level. This seems to be true for both aggressive and chronic phenotypes.

3. On a population basis, the mean rates of periodontitis progression are consistent across all observed populations throughout the world.

4. There is evidence, however, that specific segments of the population exhibit different levels of disease progression, as indicated by greater severity of CAL in subsets of each age cohort relative to the majority of individuals in the age cohort.

5. A classification system based only on disease severity fails to capture important dimensions of an individual's disease, including the complexity that influences approach to therapy, the risk factors that influence likely outcomes, and level of knowledge and training required for managing the individual case.

Authors' Interpretation of Current Evidence Reviews

There is sufficient evidence to consider Necrotizing Periodontitis as a separate disease entity. Evidence comes from: i) a distinct pathophysiology characterized by prominent bacterial invasion and ulceration of epithelium; ii) rapid and full thickness destruction of the marginal soft tissue resulting in characteristic soft and hard tissue defects; iii) prominent symptoms; and iv) rapid resolution in response to specific antimicrobial treatment.

There is sufficient evidence to consider that periodontitis observed in the context of systemic diseases that severely impair host response should be considered a periodontal manifestation of the systemic disease and that the primary diagnosis should be the systemic disease according to International Statistical Classification of Disease (ICD).[13, 17] Many of these diseases are characterized by major functional impairment of host defenses and have multiple non-oral sequelae. At the moment there is insufficient evidence to

consider that periodontitis observed in poorly controlled diabetes is characterized by unique pathophysiology and/or requires specific periodontal treatment other than the control of both co-morbidities.[18]

Despite substantial research on aggressive periodontitis since the 1999 Workshop,[14] there is currently insufficient evidence to consider aggressive and chronic periodontitis as two pathophysiologically distinct diseases.

Current multifactorial models of disease applied to periodontitis appear to account for a substantial part of the phenotypic variation observed across cases as defined by clinical parameters. Multiple observational studies in populations with long-term exposure to microbial biofilms on the teeth have shown that a small segment of the adult population expresses severe generalized periodontitis and most express mild to moderate periodontitis.[19, 20] It is also well documented using twin studies that a large portion of the variance in clinical severity of periodontitis is attributable to genetics.[5, 6, 21, 22]

It is reasonable to expect that future research advances will increase our knowledge of disease-specific mechanisms in the context of the multifactorial biological interactions involved in specific phenotypes. That pursuit may be valuable in guiding better management of complex cases and may lead to novel approaches that enhance periodontitis prevention, control, and regeneration. Multi-dimensional profiles that combine biological and clinical parameters are emerging that better define phenotypes and may guide deeper understanding of the mechanisms that lead to differences in phenotypes.[23-26]

There is clinical value in individualizing the diagnosis and the case definition of a periodontitis patient to take into account the known dimension of the multifactorial etiology to improve

prognosis, account for complexity and risk, and provide an appropriate level of care for the individual.

3. Integrating Current Knowledge to Advance Classification of Periodontitis

3.1 Clinical Definition of Periodontitis

Periodontitis is characterized by microbially-associated, host-mediated inflammation that results in loss of periodontal attachment. This is detected as clinical attachment loss (CAL) by circumferential assessment of the erupted dentition with a standardized periodontal probe with reference to the cemento-enamel junction.

It is important to note:

a. Some clinical conditions other than periodontitis present with clinical attachment loss.

b. Periodontitis definitions based on marginal radiographic bone loss suffer from severe limitations as they are not specific enough and miss detection of mild to moderate periodontitis.[27] Periodontitis definitions based on radiographic bone loss should be limited to the stages of mixed dentition and tooth eruption when clinical attachment level measurement with reference to the CEJ are impractical.[28] In such cases periodontitis

assessments based on marginal radiographic bone loss may use bitewing radiographs taken for caries detection.

3.2 Objectives of a Periodontitis Case Definition System

A case definition system should facilitate the identification, treatment and prevention of periodontitis in individual patients. Given current knowledge, a periodontitis case definition system should include three components:

- One that allows identification of a patient as a periodontitis case,
- A second that identifies the specific form of periodontitis, and
- A third that describes the clinical presentation and other elements that affect clinical management, prognosis, and potentially broader influences on both oral and systemic health.

Furthermore, case definitions may be applied in different contexts: patient care, epidemiological surveys and research on disease mechanisms or therapeutic outcomes, as discussed in Appendix B in the online *Journal of Periodontology*. In the various contexts, case definitions may require different diagnostic characteristics based on the objectives of the specific application, as is discussed below.

3.3 Definition of a Patient as a Periodontitis Case

Given the measurement error of clinical attachment level with a standard periodontal probe, a degree of misclassification of the initial stage of periodontitis is inevitable and this affects diagnostic accuracy. As disease severity increases, clinical attachment loss is more firmly established, and a periodontitis case can be identified with greater accuracy. Decreasing the threshold of CAL increases sensitivity. Increasing the threshold, requiring CAL at more than one site, and excluding causes of CAL, other than periodontitis, increases specificity.

We should anticipate that, until more robust methods, potentially salivary biomarkers or novel soft-tissue imaging technologies, are validated, the level of training and experience with periodontal probing will greatly influence the identification of a case of initial periodontitis.

It should be noted that periodontal inflammation, generally measured as bleeding on probing (BOP), is an important clinical parameter relative to assessment of periodontitis treatment outcomes and residual disease risk post-treatment.[29-32] However BOP itself, or as a secondary parameter with CAL, does not change the initial case definition as defined by CAL or change the classification of periodontitis severity.

Multiple periodontitis case definitions have been proposed in recent years. The AAP/CDC case definition for epidemiologic surveillance and the EFP case definition for the purpose of risk factors research have been widely utilized.[33, 34] Although the AAP/CDC and the sensitive EFP definition share similarities there are some important differences.

In the context of the 2017 World Workshop it is suggested that a single definition be adopted.

A patient is a periodontitis case in the context of clinical care if:

1. Interdental CAL is detectable at 2 or more non-adjacent teeth, or

2. Buccal or oral CAL ≥ 3mm with pocketing greater than 3 mm is detectable at 2 or more teeth

but the observed CAL cannot be ascribed to non-periodontal causes such as: i) gingival recession of traumatic origin; ii) dental caries extending in the cervical area of the tooth; iii) the presence of CAL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, iv) an endodontic lesion draining through the marginal periodontium; and v) the occurrence of a vertical root fracture.

Key to periodontitis case definition is the notion of "detectable" interdental CAL: the clinician being able to specifically identify areas of attachment loss during periodontal probing or direct visual detection of the interdental CEJ during examination, taking measurement error and local factors into account.

It is recognized that "detectable" interdental attachment loss may represent different magnitudes of CAL based upon the skills of the operator (e.g. specialist or general practitioner) and local conditions that may facilitate or impair detection of the CEJ, most notably the position of the gingival margin with respect to the CEJ, the presence of calculus or restorative margins. The proposed case definition does not stipulate a specific threshold of detectable CAL to avoid misclassification of initial periodontitis cases as gingivitis and maintain consistency of histological and clinical definitions. There is also a need to increase specificity of the definition and this is accomplished requiring detection of CAL at two non-adjacent teeth. Setting a specific threshold of CAL for periodontitis definition (e.g. 2 mm) to address measurement error with CAL detection with a periodontal probe would result in misclassification of initial periodontitis cases as gingivitis. Specific considerations are

needed for epidemiological surveys where threshold definition is likely to be based on numerical values dependent on measurement errors.

3.4 Identification of the Form of Periodontitis

Based on pathophysiology, three clearly different forms of periodontitis have been identified:

A. Necrotizing periodontitis

B. Periodontitis as a direct manifestation of systemic diseases

C. Periodontitis

Differential diagnosis is based on history and the specific sign and symptoms of necrotizing periodontitis and the presence or absence of an uncommon systemic disease that definitively alters the host immune response. Necrotizing periodontitis is characterized by history of pain, presence of ulceration of the gingival margin and/or fibrin deposits at sites with characteristically decapitated gingival papillae, and, in some cases, exposure of the marginal alveolar bone. With regards to periodontitis as a direct manifestation of systemic disease, the recommendation is to follow the classification of the primary disease according to the respective International Statistical Classification of Diseases and Related Health Problems (ICD) codes.

The vast majority of clinical cases of periodontitis do not have the local characteristics of necrotizing periodontitis or the systemic characteristics of a rare immune disorder with a secondary manifestation of periodontitis. It is the majority of clinical cases of periodontitis that present with a range of phenotypes that require different approaches to clinical management and offer different

complexities that define the knowledge and experience necessary to successfully manage various cases.

3.5 Additional Elements Proposed for Inclusion in the Classification of Periodontitis

Since the 1999 International Classification Workshop, it has become apparent that additional information beyond the specific form of periodontitis and the severity and extent of periodontal breakdown is necessary to more specifically characterize the impact of past disease on an individual patient's dentition and on treatment approaches needed to manage the case. Clinical diagnosis needs to be more all-encompassing in expressing the effects of periodontitis and should account not only for the oral effects but also for potential systemic implications of the disease.

Severity

The degree of periodontal breakdown present at diagnosis has long been used as the key descriptor of the individual case of periodontitis. The 1999 case definition system is also based on severity. Rationale of classification according to severity encompasses at least two important dimensions: complexity of management and extent of disease. Important limitations of severity definitions are worth discussing also in the context of recent therapeutic improvements that have enabled successful management of progressively more severe periodontitis.[35] Conventional definitions of severe periodontitis need to be revised to better discriminate the more severe forms of periodontitis. Another important limitation of

current definitions of severe periodontitis is a paradox: whenever the worst affected teeth in the dentition are lost, severity may actually decrease. Tooth loss attributable to periodontitis needs to be incorporated in the definition of severity.

Complexity of management

Factors such as probing depths,[36] type of bone loss (vertical and/or horizontal),[37] furcation status,[38] tooth mobility,[39-41] missing teeth, bite collapse,[42] and residual ridge defect size, increase treatment complexity, need to be considered and should ultimately influence diagnostic classification. Explicit designation of case complexity factors help define level of competence and experience that a case is likely to require for optimal outcomes.

Extent

The number and the distribution of teeth with detectable periodontal breakdown has been part of current classification systems. The number of affected teeth (as a percentage of teeth present) has been used to define cases of chronic periodontitis in the 1999 classification[9, 10] while the distribution of lesions (molar incisor vs generalized pattern of breakdown) has been used as a primary descriptor for aggressive periodontitis.[8, 28] Rationale for keeping this information in the classification system comes from the fact that specific patterns of periodontitis (e.g. the molar-incisor pattern of younger subjects presenting with what was formerly called localized juvenile periodontitis, provide indirect information about the specific host-biofilm interaction.

Rate of progression

One of the most important aspects for a classification system is to properly account for variability in the rate of progression of periodontitis. The importance of this criteria has been well recognized in the 1989 AAP classification that identified a rapidly progressing form of periodontitis.[43] Concern about this criterion has been mostly on how to assess the rate of progression at initial examination in the absence of direct evidence (e.g. an older diagnostic quality radiograph allowing comparison of marginal bone loss over time).

Risk Factors

Recognized risk factors have not been previously included formally in the classification system of periodontitis but have been used as a descriptor to qualify the specific patient as a smoker or a patient with diabetes mellitus. Improved knowledge of how risk factors affect periodontitis (higher severity and extent at an earlier age) and treatment response (smaller degrees of improvements in surrogate outcomes and higher rates of tooth loss during supportive periodontal therapy[40, 41, 44] indicate that risk factors should be considered in the classification of periodontitis.

Interrelationship with general health

Since the 1999 workshop considerable evidence has emerged concerning potential effects of periodontitis on systemic diseases. Various mechanisms linking periodontitis to multiple systemic diseases have been proposed.[45, 46] Specific oral bacteria in the periodontal pocket may gain bloodstream access through ulcerated pocket epithelium. Inflammatory mediators from the periodontium may enter the bloodstream and activate liver acute phase proteins, such as C-reactive protein (CRP), which further amplify systemic inflammation levels. Case-control[47-50] and pilot intervention studies[51, 52] show that periodontitis contributes to the overall inflammatory burden of

the individual which is strongly implicated in coronary artery disease, stroke and Type 2 diabetes.[53-58] Initial evidence also supports the potential role of overall systemic inflammatory burden on risk for periodontitis.[59]

Modestly sized periodontitis treatment studies of uncontrolled Type 2 diabetes have shown value in reducing hyperglycemia, although reductions in hyperglycemia have not been supported in some larger studies where the periodontal treatment outcomes were less clear.[18, 60, 61] Although intriguing health economics analyses have shown a reduction in cost of care for multiple medical conditions following treatment for periodontitis,[62] little direct periodontitis intervention evidence, beyond the diabetes experience, has convincingly demonstrated the potential value of effectively treating periodontitis relative to overall health benefits. **Current evidence that effective treatment of certain cases of periodontitis can favorably influence systemic diseases or their surrogates, although limited, is intriguing and should be definitively assessed.**

Other factors that need to be considered in formulating a diagnostic classification include the medical status of the patient and the level of expertise needed to provide appropriate care. If the patient has severe systemic disease, as indicated by their American Society of Anesthesiologists (ASA) status, this can seriously affect the clinician's ability to control disease progression due to the patient's inability to withstand proper treatment or their inability to attend necessary maintenance care.

4. Framework for Developing a Periodontitis Staging and Grading System

New technologies and therapeutic approaches to periodontitis management are now available such that clinicians with advanced training can manage moderate and severe periodontitis patients to achieve clinical outcomes that were not previously possible.

The other dimension not previously available in our classification is the directed identification of individual patients who are more likely to require greater effort to prevent or control their chronic disease long-term. This explicitly acknowledges the evidence that most individuals and patients respond predictably to conventional approaches to prevent periodontitis and conventional therapeutic approaches and maintenance, while others may require more intensive and more frequent preventive care or therapeutic interventions, monitoring and maintenance.[19, 20, 63-65]

Staging, an approach used for many years in oncology, has been recently discussed relative to periodontal disease[66] and affords an opportunity to move beyond the one-dimensional approach of using past destruction alone and furnishes a platform on which a multidimensional diagnostic classification could be built. Furthermore, a uniform staging system should provide a way of defining the state of periodontitis at various points in time, can be readily communicated to others to assist in treatment, and may be a factor in assessing prognosis. Periodontitis staging should assist clinicians in considering all relevant dimensions that help optimize individual patient management and thus represents a critical step towards personalized care (or precision medicine).

Staging relies on the standard dimensions of severity and extent of periodontitis at presentation but introduces the dimension of complexity of managing the individual patient.

As it is recognized that subjects presenting with different severity/extent and resulting complexity of management may present different rates of progression of the disease and/or risk factors, the information derived from the staging of periodontitis should be supplemented by information on the inherent biological grade of the disease. This relies on three sets of parameters: i) rate of periodontitis progression; ii) recognized risk factors for periodontitis progression; and iii) risk of an individual's case affecting the systemic health of the subject.

The concept and value of "staging" has been extensively developed in the oncology field. Staging of tumors is based on current observable clinical presentation including size or extent and whether it has metastasized. This may be an example of how one might communicate current severity and extent of a disease, as well as the clinical complexities of managing the case. To supplement staging, that provides a summary of clinical presentation, grade has been used as an assessment of the potential for a specific tumor to progress, i.e. to grow and spread, based on microscopic appearance of tumor cells. In addition, current molecular markers often guide selection of specific drug therapies, and thereby incorporate biological targets that increase the granularity of the grade and thus may increase the probability of a favorable clinical outcome. These concepts have been adapted to periodontitis, as summarized in Table 1, and as described in detail below.

While devising a general framework, it seems relevant from a patient management standpoint to differentiate four stages of periodontitis. Each of these stages is defined by unique disease presentation in terms of disease severity and complexity of management. In each stage of severity, it may be useful to identify subjects with different rates of disease progression and it is foreseen that,

in the future, stage definition will be enriched by diagnostic tests enabling definition of the biological "grade" and/or susceptibility of periodontitis progression in the individual patient. The addition of grade may be achieved by refining each subject's stage definition with a Grade A, B or C, in which increasing grades will refer to subjects with direct or indirect evidence of different rates of periodontal breakdown and presence and level of control of risk factors.

An individual case may thus be defined by a simple matrix of Stage at presentation (severity and complexity of management) and Grade (evidence or risk of progression and potential risk of systemic impact of the patient's periodontitis; these also influence the complexity of management of the case). Table 2 illustrates this concept and provides a general framework that will allow update and revisions over time as specific evidence becomes available to better define individual components, particularly in the biological grade dimension of the disease and the systemic implications of periodontitis.

Stage I Periodontitis

Stage I Periodontitis is the borderland between gingivitis and periodontitis and represents the early stages of attachment loss. As such, subjects with Stage I Periodontitis have developed periodontitis in response to persistence of gingival inflammation and biofilm dysbiosis. They represent more than just an early diagnosis: if they show a degree of clinical attachment loss at a relatively early age, these subjects may have heightened susceptibility to disease onset. Early diagnosis and definition of a population of susceptible subjects offers opportunities for early intervention and monitoring that may prove more cost-effective at the population level as shallow lesions may provide specific options for both conventional mechanical biofilm removal and pharmacological agents delivered in oral hygiene aids. It is recognized that early diagnosis may be a formidable challenge in general

dental practice as periodontal probing to estimate early clinical attachment loss – the current gold standard for defining periodontitis – may be inaccurate. Assessment of salivary biomarkers and/or new imaging technologies may increase early detection of Stage I Periodontitis in a variety of settings.

Stage II Periodontitis

Stage II Periodontitis represents the stage of established periodontitis in which a carefully performed clinical periodontal examination identifies the characteristic damages that periodontitis has caused to tooth support. At this stage of the disease process, however, management remains relatively simple for many cases as application of standard treatment principles involving regular personal and professional bacterial removal and monitoring is expected to arrest disease progression at this stage. Careful evaluation of the Stage II patient's response to standard treatment principles is essential, and the case Grade plus treatment response may guide more intensive management for specific patients.

Stage III Periodontitis

At Stage III, periodontitis has produced significant damage to the attachment apparatus and, in the absence of advanced treatment, some teeth may be at risk of being lost. The stage is characterized by the presence of deep periodontal lesions that extend to the middle portion of the root whose management is complicated by the presence of deep intrabony defects, furcation involvement, history of periodontal tooth loss/exfoliation, presence of localized ridge defects that complicate implant tooth replacement. In spite of the possibility of tooth loss, masticatory function is preserved, and treatment of periodontitis does not require complex rehabilitation of function.

Stage IV Periodontitis

At the more advanced Stage IV, periodontitis has caused considerable damage to the periodontal support and may have caused significant tooth loss; this translates in loss of masticatory function. In the absence of proper control of the periodontitis and adequate rehabilitation, the dentition is at risk of being lost.

This stage is characterized by the presence of deep periodontal lesions that extend to the apical portion of the root and/or history of multiple tooth loss; it is frequently complicated by tooth hypermobility due to secondary occlusal trauma and the sequelae of tooth loss: posterior bite collapse and drifting. Frequently, case management requires stabilization/restoration of masticatory function.

Grade of Periodontitis

Irrespective of the Stage at diagnosis, periodontitis may progress with different rates in individual subjects, may respond less predictably to treatment in some patients, and may or may not influence general health or systemic disease. This information is critical for precision medicine but has been an elusive objective to achieve in clinical practice. In recent years, validated risk assessment tools,[25, 67] and presence of any one of three individually validated risk factors[65] have been associated with tooth loss, indicating that it is possible to estimate risk of periodontitis progression and tooth loss.

In the past, grade of periodontitis progression has been incorporated into the classification system by defining specific forms of periodontitis with high(er) rates of progression or presenting with more severe destruction relatively early in life.[28] One major limitation in the implementation of this

knowledge has been the assumption that such forms of periodontitis represent different entities and thus focus has been placed on identification of the form rather than the factors contributing to progression. The systematic reviews informing this workshop have indicated that there is no evidence to suggest that such forms of periodontitis have a unique pathophysiology, rather the complex interplay of risk factors in a multifactorial disease model may explain the phenotypes of periodontitis in exposed patients. In this context, it seems useful to provide a framework for implementation of biological grade (risk or actual evidence of progression) of periodontitis in the individual patient.

Recognized risk factors, such as cigarette smoking or metabolic control of diabetes, affect the rate of progression of periodontitis and, consequently, may increase the conversion from one stage to the next. Emerging risk factors like obesity, specific genetic factors, physical activity or nutrition may one day contribute to assessment and a flexible approach needs to be devised to ensure that the case-definition system will adapt to the emerging evidence.

Disease severity at presentation/diagnosis as a function of patient age has also been an important indirect assessment of the level of individual susceptibility. While not ideal – as it requires significant disease at early age or minimal disease at advanced age – this concept has been used in clinical practice and risk assessment tools to identify highly susceptible or relatively resistant individuals. One approach has been the assessment of bone loss in relation to patient age by measuring radiographic bone loss in percentage of root length divided by the age of the subject. This approach was originally applied in a longitudinal assessment of disease progression assessed in intraoral radiographs[68, 69] and was later incorporated in the theoretical concept that led to development of the periodontal risk

assessment (PRA) system.[31, 70] More recently, an individual's severity of CAL has been compared to their age cohort.[16] This information from large and diverse populations could be considered an age standard for CAL, with the assumption that individuals who exceed the mean CAL threshold for a high percentile in the age cohort would be one additional piece of objective information that may represent increased risk for future progression. The CAL must be adjusted in some way based on number of missing teeth to avoid biasing the CAL based on measuring only remaining teeth after extraction of the teeth with the most severe periodontitis. Such challenges again require a framework that will adapt to change as more precise ways to estimate individual susceptibility become available.

Integrating Biomarkers in a Case Definition System

Clinical parameters are very effective tools for monitoring the health-disease states in most patients, likely because they respond favorably to the key principles of periodontal care, which include regular disruption, and reduction of the gingival and subgingival microbiota. Current evidence suggests, however, that some individuals are more susceptible to develop periodontitis; more susceptible to develop progressive severe generalized periodontitis; less responsive to standard bacterial control principles for preventing and treating periodontitis; and theoretically more likely for their periodontitis to adversely impact systemic diseases.

If due to multiple factors, such individuals are more likely than others to develop and maintain a dysbiotic microbiota in concert with chronic periodontal inflammation, it is unclear whether current clinical parameters are sufficient to monitor disease development and treatment responses in such patients. For those individuals, biomarkers, some of which are currently available, may be valuable to augment information provided by standard clinical parameters.

Biomarkers may contribute to improved diagnostic accuracy in the early detection of periodontitis and are likely to provide decisive contributions to a better assessment of the Grade of periodontitis. They may assist both in staging and grading of periodontitis. The proposed framework allows introduction of validated biomarkers in the case definition system.

Integrating Knowledge of the Interrelationship between Periodontal Health and General Health in a Case Definition System

At present there is only emerging evidence to identify specific periodontitis cases in which periodontal treatment produces general health benefits. it is important to identify approaches to capture some dimensions of the potential systemic impact of a specific periodontitis case and its treatment to provide the basis for focusing attention on this issue and beginning to collect evidence necessary to assess whether effective treatment of certain cases of periodontitis truly influence systemic disease in a meaningful way.

Specific considerations for use of the Staging and Grading of Periodontitis with epidemiological and research applications are discussed in Appendix B in the online *Journal of Periodontology*.

5. Incorporation of Staging and Grading in the Case Definition System of Periodontitis

A case definition system needs to be a dynamic process that will require revisions over time in much the same way the tumor, node, metastasis (TNM) staging system for cancer has been shaped over many decades. It needs to be:

i) Simple enough to be clinically applicable but not simplistic: additional knowledge has distinguished dimensions of periodontitis, such as complexity of managing the case to provide the best level of care

ii) Standardized in order to be able to support effective communication among all stakeholders

iii) Accessible to a wide range of people in training and understood by members of the oral health care team around the world

It is suggested that a case definition based on a matrix of periodontitis stage and periodontitis grade be adopted. Such multidimensional view of periodontitis would create the potential to transform our view of periodontitis. And the powerful outcome of that multidimensional view is the ability to communicate better with patients, other professionals, and third parties.

Stage of Periodontitis (Table 3)

At present, relevant data are available to assess the two dimensions of the Staging process: severity and complexity. These can be assessed in each individual case at diagnosis by appropriate anamnestic, clinical and imaging data.

The severity score is primarily based on interdental CAL in recognition of low specificity of both pocketing and marginal bone loss, although marginal bone loss is also included as an additional

descriptor. It follows the general frame of previous severity based scores and is assigned based on the worst affected tooth in the dentition. Only attachment loss attributable to periodontitis is used for the score.

The complexity score is based on the local treatment complexity assuming the wish/need to completely eliminate local factors and takes into account factors like presence of vertical defects, furcation involvement, tooth hypermobility, drifting and/or flaring of teeth, tooth loss, ridge deficiency and loss of masticatory function. Besides the local complexity, it is recognized that individual case management may be complicated by medical factors or comorbidities.

The diagnostic classification presented in Table 3 provides definitions for four stages of periodontitis. In using the table, it is important to use clinical attachment loss as the initial Stage determinant in the Severity dimension. It is recognized that in clinical practice application some clinicians may prefer to use diagnostic quality radiographic imaging as an indirect and somehow less sensitive assessment of periodontal breakdown. This may be all that is necessary to establish the stage. However, if other factors are present in the Complexity dimension that influence the disease then modification of the initial stage assignment may be required. For example, in case of very short common root trunk a CAL of 4 mm may have resulted in class II furcation involvement, hence shifting the diagnosis from Stage II to Stage III periodontitis. Likewise, if posterior bite collapse is present then the Stage IV would be the appropriate Stage diagnosis since the complexity is on the Stage IV level.

Evidence for defining different stages based on CAL loss/bone loss in relation to root length is somewhat arbitrary.

Patients who have been treated for periodontitis may be periodically staged to monitor them. In most of successfully treated patients, complexity factors that might have contributed to baseline staging will have been resolved through treatment. In such patients CAL and RBL will be the primary stage determinants. If a stage shifting complexity factor(s) were eliminated by treatment, the stage should not retrogress to a lower stage since the original stage complexity factor should always be considered in maintenance phase management. A notable exception is successful periodontal regeneration that may, through improvement of tooth support, effectively improve CAL and RBL of the specific tooth.

Grade of Periodontitis (Table 4)

Grading adds another dimension and allows rate of progression to be considered. Table 4 illustrates periodontitis grading based on primary criteria represented by the availability of direct or indirect evidence of periodontitis progression. Direct evidence is based on longitudinal observation available for example in the form of older diagnostic quality radiographs. Indirect evidence is based on the assessment of bone loss at the worst affected tooth in the dentition as a function of age (measured as radiographic bone loss in percentage of root length divided by the age of the subject). Periodontitis grade can then be modified by the presence of risk factors.

The objective of grading is to use whatever information is available to determine the likelihood of the case progressing at a greater rate than is typical for the majority of the population or responding less predictably to standard therapy.

Clinicians should approach grading by assuming a moderate rate of progression (Grade B) and look for direct and indirect measures of actual progression in the past as a means of improving the establishment of prognosis for the individual patient. If the patient has risk factors that have been

associated with more disease progression or less responsiveness to bacterial reduction therapies, the risk factor information can be used to modify the estimate of the patient's future course of disease. A risk factor, should therefore shift the grade score to a higher value independently of the primary criterion represented by the rate of progression. For example, a Stage and Grade case definition could be characterized by moderate attachment loss (Stage II), the assumption of moderate rate of progression (Grade B) modified by the presence of poorly controlled Type II diabetes (a risk factor that is able to shift the Grade definition to rapid progression or Grade C).

In summary a periodontitis diagnosis for an individual patient should encompass 3 dimensions:

1. Definition of a periodontitis case based on detectable CAL loss at two non-adjacent teeth
2. Identification of the form of periodontitis: necrotizing periodontitis, periodontitis as a manifestation of systemic disease or periodontitis
3. Description of the presentation and aggressiveness of the disease by Stage and Grade (see Appendix A in online *Journal of Periodontology*)

6. Conclusions

The proposed Staging and Grading of periodontitis provides an individual patient assessment that classifies patients by two dimensions beyond severity and extent of disease that identify patients as to **complexity** of managing the case and **risk** of the case exhibiting more progression and/or responding less predictably to standard periodontal therapy. The proposed risk stratification is based

on well-validated risk factors including smoking, uncontrolled Type 2 diabetes, clinical evidence of progression or disease diagnosis at an early age, and severity of bone loss relative to patient age.

The proposed Staging and Grading explicitly acknowledges the potential for some cases of periodontitis to influence systemic disease. The current proposal does not intend to minimize the importance or extent of evidence supporting direct distal effects of periodontal bacteremia on adverse pregnancy outcomes and potentially other systemic conditions; but focuses on the role of periodontitis as the second most frequent factor (obesity being the most frequent) that is well-documented as a modifiable contributor to systemic inflammatory burden.

The proposed staging and grading is designed to avoid the paradox of improvement of disease severity observed after loss/extraction of the more compromised teeth. This is achieved by incorporating, whenever available, knowledge about periodontitis being the predominant reason for loss of one or more teeth.

Finally, one of the strong benefits of the Staging and Grading of Periodontitis is that it is designed to accommodate regular review by an ad hoc international task force to ensure that the framework incorporates relevant new knowledge within an already functioning clinical application.

Table 1. Primary Goals in Staging and Grading a Periodontitis Patient

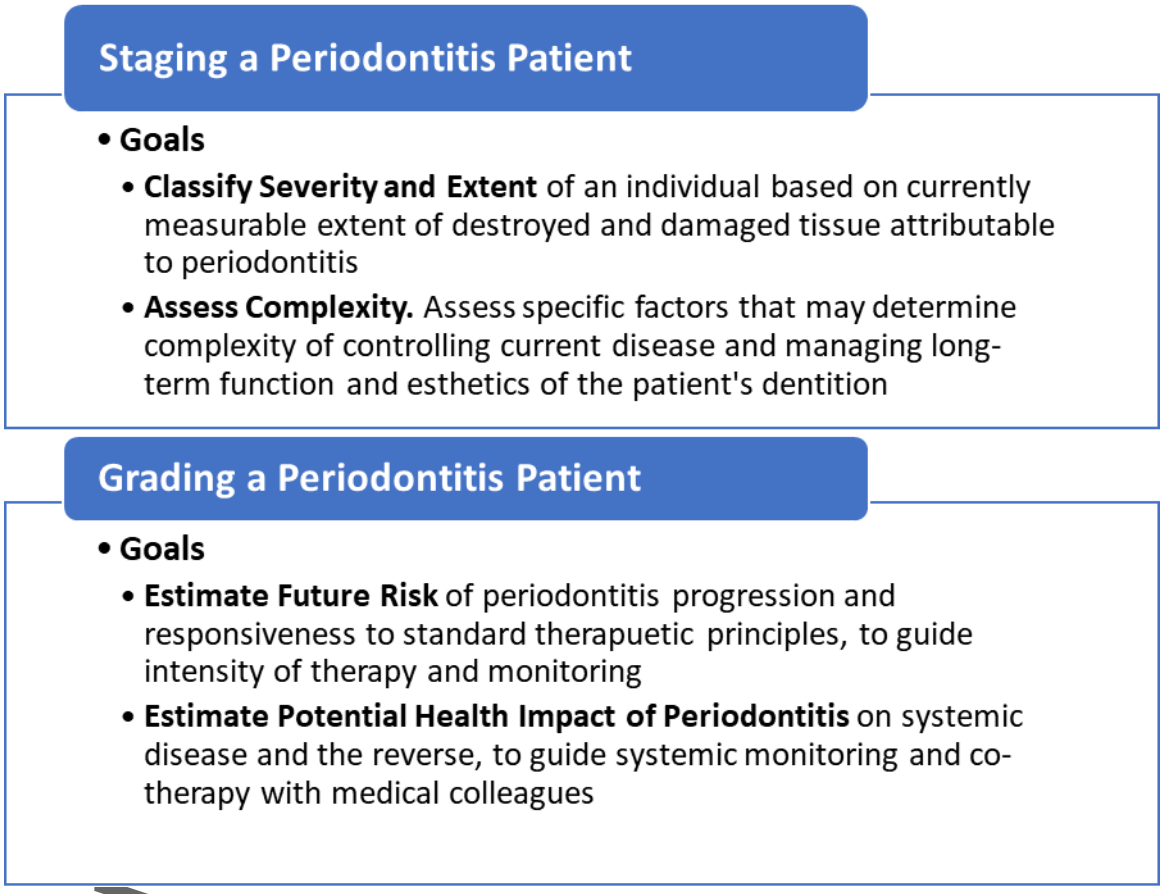

Table 2 – Framework for Staging and Grading of Periodontitis

		Disease Severity and Complexity of Management			
		Stage I Initial Periodontitis	Stage II Moderate Periodontitis	Stage III Severe Periodontitis with potential for additional tooth loss	Stage IV Advanced Periodontitis with extensive tooth loss and potential for loss of dentition
Evidence or risk of rapid progression, anticipated treatment response and effects on systemic health	Grade A	**Individual Stage and Grade Assignment**			
	Grade B				
	Grade C				

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Table 3 – Periodontitis Stage – Please see text and appendix A (in online *Journal of Periodontology*) for explanation

Periodontitis stage		**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Severity	Interdental CAL at site of greatest loss	1-2 mm	3-4 mm	≥ 5 mm	≥ 8 mm
	Radiographic bone loss	Coronal third (< 15%)	Coronal third (15-33%)	Extending to Middle third	Extending to Apical third
	Tooth loss	No Perio Tooth Loss		Perio tooth loss ≤ 4 teeth	Perio tooth loss ≥ 5 teeth
Complexity	Local	Probing depth ≤ 4mm Mostly horizontal bone loss	Probing depth ≤ 5mm Mostly horizontal bone loss	In addition to Stage II Complexity: Probing depth 6-7mm Vertical bone loss ≥ 3 Furcation 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 ≥ 2) Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs); Probing depth ≥ 8mm Severe ridge defect

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Extent & distribution	Add to Stage as descriptor	For each Stage, describe extent as localized (<30% of teeth involved), generalized or molar incisor pattern

The initial Stage should be determined using CAL; if not available then RBL should be used. Information on tooth loss that can be attributed primarily to periodontitis – if available – may modify stage definition. This is the case even in the absence of complexity factors. Complexity factors may shift the Stage to a higher level, for example furcation II or III would shift to either Stage III or IV irrespective of the CAL. The distinction between Stage III and Stage IV is primarily based on complexity factors. For example, a high level of tooth mobility and/or posterior bite collapse would indicate a Stage IV diagnosis. For any given case only some, not all, complexity factors may be present, however, in general it only takes 1 complexity factor to shift the diagnosis to a higher Stage. It should be emphasized that these case definitions are guidelines that should be applied using sound clinical judgment to arrive at the most appropriate clinical diagnosis.

For post-treatment patients CAL and RBL are still the primary stage determinants. If a stage shifting complexity factor(s) were eliminated by treatment, the stage should not retrogress to a lower stage since the original stage complexity factor should always be considered in maintenance phase management.

Abbreviations: CAL – clinical attachment loss; RBL = radiographic bone loss.

Table 4 – Periodontitis Grade – Please see text and appendix A (in online *Journal of Periodontology*) for explanation

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 (PA radiographs or CAL loss)	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	0.25-1.0	> 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 Diabetes	Non-Smoker Normoglycaemic with or without prior diagnosis of diabetes	Smoker <10 cigarettes/day HbA1c < 7.0 in diabetes patient	Smoker ≥10 cigarettes/day HbA1c ≥ 7.0 in diabetes patient
Risk of systemic impact of periodontitis*	Inflammatory Burden	High sensistivity CRP (hsCRP)	< 1 mg/L	1-3 mg/L	> 3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, GCF, serum	?	?	?

Grade should be used as an indicator of the rate of periodontitis progression. The primary criteria are either direct or indirect evidence of progression. Whenever available, direct evidence is used; in its absence indirect estimation is made using bone loss as a function of age at the most affected tooth or case presentation (radiographic bone loss expressed as percentage of root length divided by the age of the subject, RBL/age). Clinicians should initially assume Grade B disease and seek specific evidence to shift towards grade A or C, if available. Once grade is established based on evidence of progression, it can be modified based on the presence of risk factors.

*Refers to Increased risk that periodontitis may be an inflammatory co-morbidity for the specific patient. CRP values represent a summation of the patient's overall systemic inflammation, which may be in part influenced by periodontitis, but otherwise is an "unexplained" inflammatory burden that be valuable to assess in collaboration with the patient's physicians. The grey color of the table cells refers to the need to substantiate with specific evidence. This element is placed in the table to draw attention to this dimension of the biology of periodontitis. It is envisaged that in the future it will be possible integrate the information into periodontitis Grade to highlight the potential of systemic impact of the disease in the specific case.

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