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Principles of Periodontology

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Abstract

Periodontal diseases are among the most common diseases affecting humans. Dental biofilm is a contributor to the etiology of most periodontal diseases. It is also widely accepted that immunological and inflammatory responses to biofilm components are manifested by signs and symptoms of periodontal disease. The outcome of such interaction is modulated by risk factors (modifiers), either inherent (genetic) or acquired (environmental), significantly affecting the initiation and progression of different periodontal disease phenotypes. While definitive genetic determinants responsible for either susceptibility or resistance to periodontal disease have yet to be identified, many factors affecting the pathogenesis have been described, including smoking, diabetes, obesity, medications, and nutrition. Currently, periodontal diseases are classified based upon clinical disease traits using radiographs and clinical examination. Advances in genomics, molecular biology, and personalized medicine may result in new guidelines for unambiguous disease definition and diagnosis in the future. Recent studies have implied relationships between periodontal diseases and systemic conditions. Answering critical questions regarding host-parasite interactions in periodontal diseases may provide new insight in the pathogenesis of other biomedical disorders. Therapeutic efforts have focused on the microbial nature of the infection, as active treatment centers on biofilm disruption by non-surgical mechanical debridement with antimicrobial and sometimes anti-inflammatory adjuncts. The surgical treatment aims at gaining access to periodontal lesions and correcting unfavorable gingival/osseous contours to achieve a periodontal architecture that will provide for more effective oral hygiene and periodontal maintenance. In addition, advances in tissue engineering have provided innovative means to regenerate/repair periodontal defects, based upon principles of guided tissue regeneration and utilization of growth factors/biologic mediators. To maintain periodontal stability, these treatments need to be supplemented with long-term maintenance (supportive periodontal therapy) programs.

Periodontology has been defined as ‘the scientific study of the periodontium in health and disease’ (6). The periodontium includes the gingiva, alveolar bone, periodontal ligament and root cementum, i.e. the tissues that support the teeth. The anatomy, histology and physiology of the normal periodontium have been described in great detail elsewhere.³⁴⁷ They will not be covered in this context.

People exhibiting periodontal abnormalities, for example impairments of tissue integrity or function, are said to have periodontal diseases. These comprise a variety of phenotypes; defined by clinical signs and symptoms, they constitute the periodontal syndrome.^{44, 397, 404} The most frequently observed phenotype is inflammation of the gingiva (gingivitis) induced by dental plaque (biofilm), and includes changes in tissue color, volume, temperature, crevicular exudate and bleeding upon gentle provocation with a probe.²⁵¹ The clinical signs of biofilm-associated gingivitis are reversible when adequate oral hygiene is implemented and maintained.²³² Less prevalent than gingivitis, but still observed in many persons, are the clinical signs of biofilm-associated periodontitis. They include periodontal pockets, attachment loss, bleeding upon probing, and radiographic bone loss.¹¹⁷ Therapeutic efforts are directed towards elimination of the suspected underlying infection, typically leading to resolution of the signs of inflammation, tissue repair, and restoration of function and esthetics. The results of periodontal therapy may be stable over a long time period, but signs of disease may return unpredictably in terms of location, frequency and severity.

Many other phenotypes, frequently disease forms with severe signs and symptoms, have been described and classified.^{145, 201} They are much less prevalent than typical biofilm-associated gingivitis or periodontitis. Some of the rare forms are related to systemic conditions; others are components of genetic syndromes. Diagnostic criteria frequently used to characterize the various phenotypes of periodontal syndrome are listed in [Table 1](#).

Table 1. Diagnostic criteria used for periodontal diseases. A diagnosis can be made if two or more diagnostic signs are present. The initial diagnosis is further characterized using two or more modifiers

Diagnostic signs and symptoms
Gingival color (or texture, volume or contour)
Gingival necrosis
Gingival enlargement
Gingival recession
Bleeding on provocation
Bleeding on probing
Pockets
Attachment loss
Bone loss
Tooth mobility
Lateral migration
Pain
Modifiers
Age of onset (early or adult)
Progression (chronic or rapid)
Response to treatment (stable or recurrent)
Severity (mild, moderate or severe)
Extent (localized or generalized)

The objective of this overview of principles of periodontology is presentation of current and established concepts. Aspects of the history, classification, etiology, pathogenesis, epidemiology and treatment modalities of the most common periodontal diseases are discussed.

History

Early Observations

Periodontal diseases, unlike caries, are not a by-product of modern civilization. Manifesting themselves as *ante mortem* loss of alveolar bone, signs indicative of periodontal pathology were discovered in human specimens attributed to the Middle Pleistocene stage. For instance, indications of alveolar bone resorption were found in the 640- to 735,000-year-old Mauer mandible (*Homo heidelbergensis*) in Germany, and in a 169- to 191,000-year-old mandible that was unearthed at the Bau de l'Aubésier, Vaucluse, France^{91, 224} Such findings support the theory that periodontal diseases have plagued humans and their phylogenetic ancestors for a very long time.

Chinese physicians were probably first to describe signs of periodontal diseases. Diagnoses and treatments were presented in the earliest known textbook of Chinese medicine, *Nei Ching*, attributed to Huang Di (approximately 2700–2600 BC).³⁵⁷ The ancient Egyptian Ebers Papyrus was written approximately 1000 years later (approximately 1550 BC). It is one of the oldest fully preserved medical documents, and contains several passages on remedies to cure conditions such as loose teeth and swollen gums ('flesh').¹³⁹ In Ancient India, Sushruta (approximately 6th century BC) illustrated a large number of surgical instruments, and explained 300 surgical procedures in the treatise *Samhita*. Sushruta taught a holistic approach to medical therapy. In pursuit of his philosophy, he described four periodontal conditions, offering probably the first classification of periodontal diseases.³⁵⁷

In 1563, the Italian Renaissance anatomist and physician Bartolomeo Eustachi (1514–1574) completed '*Libellus de Dentibus*', the first book dedicated exclusively to the description of teeth.¹²⁷ He was the first to describe the periodontal ligament, as well as the deciduous and permanent dentitions. Eustachi's profound understanding of head anatomy and his amazing eye for the detail led him to link increased tooth mobility at an advanced age with widening of the space between the root and the alveolar bone. Similarly remarkable, he prescribed the removal of calculus and granulation tissue using scalers and curettes, respectively, to encourage re-attachment of periodontal tissues to loose teeth.³⁵⁸

From scurvy of the gum to Riggs' disease

Almost two centuries after Eustachi, the French surgeon-dentist Pierre Fauchard (1678–1761) published '*Le Chirurgien Dentiste*', a two-volume book dedicated to the practice of dentistry. Fauchard's comprehensive work profoundly influenced the practice of dentistry. He pointed out that any dental disease can be allocated to one of only three classes, namely: (1) diseases with external cause, (2) (hidden) diseases that attack those tooth parts embedded in the periodontium, and (3) (symptomatic) diseases caused by the teeth.¹¹³ Critical of the theories accepted by most physicians of his time, Fauchard postulated a humoral etiology of periodontal disease that is modulated by local factors, e.g. calculus. To prevent 'gum disease', he recommended cleaning the teeth, massaging the gingiva with an astringent liquid, and washing the mouth with wine and water. Because of the spongy appearance of the gingiva that had similarity to gingiva he observed in patients with scurvy, Fauchard called the phenotype 'scurvy of the gums'.

Fifty years later, the Scottish surgeon and scientist John Hunter (1728–1793) published '*A Practical Treatise on the Diseases of the Teeth intended as a supplement to the Natural History of those Parts*', his second and less popular book on teeth and tooth-related structures. Hunter postulated that gradual loss of alveolar bone, associated pocket formation and gingival recession would inevitably result in tooth loss. He considered the process to be disease when it occurred early in life, but the result of natural aging in the elderly. Among gingival diseases, Hunter distinguished between cases that resembled Fauchard's 'scurvy of the gums' and cases of overgrown fibrotic tissue.¹⁷⁶

Achievements in microbiology, a novel scientific discipline in the 19th century, changed the way periodontal diseases were viewed. Two German physicians, Robert Ficinus (1809–1852) and Adolph Witzel (1847–1906), deserve credit for associating bacteria with periodontal tooth loss.⁶³ In Europe, the term ‘alveolar pyorrhea’ was coined to describe any form of periodontal disorder unrelated to the aging process. According to Witzel, in patients exhibiting alveolar pyorrhea, the gingiva forms a pocket that allows bacteria to infect and destroy the underlying periosteum and ultimately alveolar bone. In the USA, John M. Riggs (1810–1885), also known as the father of periodontics, treated diseased pockets by painstakingly thorough calculus removal, curettage of soft tissues, and implementation of meticulous individual oral hygiene. He was convinced that all stages of periodontal disease, from the earliest signs of inflammation to tooth loss, were attributable to the same local etiology, i.e. calculus. Reportedly, Riggs’ rigorous procedure healed more than 90% of his patients, a huge improvement over any previously known treatment. His success was soon recognized. In 1869, the Connecticut Valley Dental Association passed a resolution acknowledging Riggs as the first person ever to treat gum inflammation successfully.²⁶⁴ Riggs’ achievement also had a lasting effect on dental terminology; in the USA, the term ‘scurvy of the gums’ was replaced by ‘Riggs disease’. Not for long, however. At the 1877 meeting of the American Dental Association, the Germany-born physician Frederick H. Rehwinkel (1825–1889) presented a paper on ‘pyorrhea alveolaris’, and ever since has been credited for introducing the European term to the American dental literature.²⁶³ The term ‘pyorrhea alveolaris’ was quickly adopted by the dental community. It persisted deep into the 20th century, despite being rather a poor choice for the disease it purported to describe.

Focal infection theory

Willoughby D. Miller (1853–1907), whose work was very much influenced by Robert Koch, is best known for his groundbreaking ideas on the etiology of caries. He also postulated a role for bacteria in the etiology of alveolar pyorrhea,²⁷⁰ and concluded that, in the presence of predisposing factors, many bacteria found normally in the mouth can cause periodontal disease (e.g., non-specific plaque hypothesis). Miller advocated that such bacteria could also play a role in the etiology of many other diseases in humans. He coined the expression ‘focus of infection’.²⁷¹ but stopped short of promoting eradication of infected teeth to prevent or treat systemic illnesses. This step was made by Frank Billings (1854–1932), a highly respected American physician and academic leader. Billings and his student and colleague Edward C. Rosenow (1875–1966) promoted the theory of focal infection in the USA.^{51, 331} Like Miller, Billings spent time in Europe, where the germ theory of disease, initiated by the groundbreaking discoveries of Koch, Lister, Pasteur and other luminaries, was heavily debated. According to Billings’ theory, the germ carrier harbors pleiomorphic microorganisms that may cause disease at any time. Dissemination of such germs from a latent localized infection to a distant organ would occur through the blood and lymphatic systems. The focal infection paradigm was quickly adopted by many dentists and physicians, especially surgeons in the USA. Its clinical implementation, which was further promoted by substantial improvements in asepsis, led to uncountable unwarranted tooth extractions, tonsillectomies and other surgical procedures.¹³⁵ In 1928, Holman publicly questioned the validity of the focal infection theory.¹⁶⁴ Its importance started to decline in the 1930s as evidence accumulated indicating that surgical removal of suspected foci has no beneficial effect on the medical status of affected patients.^{65, 326} It is tempting to speculate about apparent similarities between the focal infection theory and the so-called ‘systemic link’. However, a closer look at the basis of the two paradigms reveals fundamental discrepancies, especially with regard to bacterial pleiomorphism and tissue lesion latency.

Periodontal disease classifications

Times of transition and consolidation

At the dawn of the 20th century, the realization that alveolar pyorrhea can be treated led to recognition of 'periodontia' as a dental specialty. The professional organization of periodontists now known as the American Academy of Periodontology was established in 1914 as the American Academy of Oral Prophylaxis and Periodontology. In Germany, the 'Arbeitsgemeinschaft für Parodontosen Forschung' was formed in 1924 with the goal of establishing an open communication platform for academicians and practitioners. However, the much needed information exchange was impeded by decidedly inconsistent terminology. Over subsequent decades, periodontists on both sides of the Atlantic met repeatedly to develop countless classification systems that reflected scientific progress as well as clinical utility. As a result of this effort, new nomenclatures were published at arbitrary intervals by professional bodies such as the American Academy of Periodontology, the American Dental Association, the Arbeitsgemeinschaft für Parodontosen Forschung and the World Dental Federation, among others. In addition, classifications were also contributed by individual authors.

One of the major biomedical accomplishments of the 20th century was the recognition that formal hypotheses can be tested in the clinic. Application of quantitative methods to clinical problem solving, albeit implemented slowly in most dental disciplines, had profound effects on the classification of periodontal diseases. The paucity of scientific evidence in support of periodontosis and occlusal trauma as classes of periodontal disease was initially acknowledged at the 1966 World Workshop in Periodontics,¹ and formalized 11 years later at the International Conference on Biology of Periodontal Disease. Only two classes of periodontal disease remained – juvenile periodontitis and chronic marginal periodontitis⁴¹⁷ – and these constituted the 1977 American Academy of Periodontology classification system.

In the meantime, the studies on experimental gingivitis by Harald Löe and his collaborators at the Royal Dental College in Aarhus, Denmark, ushered in the 'plaque era' of periodontology. Using novel index systems to assess plaque and gingivitis,^{231, 360} they provided unequivocal experimental evidence for a direct relationship between the presence of dental bacterial plaque and gingivitis.^{232, 233, 390} In addition, they demonstrated the full reversibility of all clinical signs of gingival pathology when oral hygiene was re-established. There is no question that the nature and results of these ground-breaking studies had a profound effect on most aspects of clinical periodontology.

Moreover, a destructive form of periodontal disease, most frequently observed around the central incisors and first molars in young people, initiated renewed interest in the disease class previously known as periodontosis. Baer⁴⁵ and Manson & Lehner²⁴⁸ published initial clinical reports that were followed by studies of host defense mechanisms.^{74, 77, 406} Because it was frequently diagnosed in adolescent patients, the form was re-named juvenile periodontitis. At the time of the 1977 International Conference on Biology of Periodontal Disease, the majority opinion among dentists was that, without treatment, gingivitis progresses to periodontitis, at a relatively constant rate, ultimately resulting in tooth loss. This view was challenged when Löe et al.²³⁴ presented their results on the natural history of periodontal diseases. Performed in Sri Lanka in a population with no access to dental services and virtually no home care, the longitudinal study suggested the presence of three distinct sub-populations exhibiting clearly discernible patterns of disease progression: a cohort with no or minimal disease progression over time, a cohort with moderate disease progression, and a cohort with rapid disease progression. In most subjects, the presence of plaque and gingivitis did not lead to severe periodontitis or tooth loss. The centuries-old belief that linked alveolar bone and tooth loss to ageing was finally disproved.

These and other findings were reflected in a new classification that was first suggested at the 1986 World Workshop in Clinical Periodontics and modified at the World Workshop in Clinical Periodontics in 1989.² The revised system distinguished five classes of periodontal disease. In comparison to the 1986 taxonomy, a new class was introduced for periodontal diseases linked to systemic conditions. Moreover, criteria for disease onset and rate of progression were considered. One of the more obvious shortcomings of the 1989 classification was the absence of a category for gingival diseases. Also, many practicing periodontists felt that the emphasis of the classification on patient age at disease onset was not suitable for long-term patient care.

Finally, in 1993, the European Academy of Periodontology (now the European Federation of Periodontology) was founded at the 1st European Workshop on Periodontology. The European Academy of Periodontology adopted the American Academy of Periodontology's 1989 classification but suggested that an improved system should be considered based on three major classes: early-onset periodontitis, adult periodontitis and necrotizing periodontitis. Each of these was further defined by secondary descriptors (distribution within dentition, progression rate, treatment response, relation to systemic disease, microbiological characteristics, etc.).³²

1999 International Workshop for Classification of Periodontal Diseases and Conditions

The currently used classification (2010) was implemented based on recommendations by the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions ([Table 2](#)).²⁹ In addition to increasing the number of disease classes from five to eight, the revision included several substantial deviations from preceding classifications. Briefly, gingival diseases were included as an independent entity (class I). Chronic periodontitis (class II) and aggressive periodontitis (class III) replaced adult periodontitis and early-onset periodontitis, respectively, thus eliminating the classifier 'age'. The refractory class was abandoned, periodontitis as manifestation of systemic diseases (class IV) was modified and restricted to include only genetic and hematological diseases, and necrotizing periodontal diseases (class V) replaced necrotizing ulcerative periodontitis. Categories for abscesses of the periodontium (class VI), periodontitis associated with endodontic lesions (class VII) and developmental or acquired deformities and conditions (class VIII) completed the new classification system. Although not perfect, it reflects the current scientific understanding of the nature of periodontal

diseases, as well as the practice of periodontics. In the subsequent sections, the terminology of the 1999 classification will be used as appropriate.

Table 2. 1999 Classification of periodontal diseases and conditions

I: Gingival diseases
A Dental plaque-induced gingival diseases
B Non-plaque-induced gingival lesions
II: Chronic periodontitis
A Localized
B Generalized (>30% of sites are involved)
III: Aggressive periodontitis
A Localized
B Generalized (>30% of sites are involved)
IV: Periodontitis as a manifestation of systemic diseases
A Associated with hematological disorders
B Associated with genetic disorders
C Not otherwise specified
V: Necrotizing periodontal diseases
A Necrotizing ulcerative gingivitis
B Necrotizing ulcerative periodontitis
VI: Abscesses of the periodontium
A Gingival abscess
B Periodontal abscess
C Pericoronal abscess
VII: Periodontitis associated with endodontic lesions
A Combined periodontic–endodontic lesions
VIII: Developmental or acquired deformities and conditions
A Localized tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis
B Mucogingival deformities and conditions around teeth

C Mucogingival deformities and conditions on edentulous ridges
D Occlusal trauma

Classification limitations and next steps

Periodontal disease classification has evolved over a long time period. As such, it is the result of major paradigm shifts³⁰ that collectively have defined modern periodontology. Needless to say, all classifications have had their shortcomings, which exposed them to considerable criticism.^{44, 175, 300, 323, 404} Armitage³⁰ probably put it best when he concluded that: ‘Any attempt to group the entire constellation of periodontal diseases into an orderly and widely accepted classification system is fraught with difficulty, and inevitably considerable controversy. No matter how carefully the classification is developed, and how much thought and time are invested in the process, choices need to be made between equally unsatisfactory alternatives’.

The purpose of disease classification is to unambiguously link clinical phenotypes, defined by clinical observations and simple laboratory investigations, with diagnoses and ultimately disease-specific therapy (Table 3). The currently used system is a combination of broadly defined classification elements such as location, etiology and pathology. Some disease classes (II and III) are further refined using rule-based criteria, e.g. slight chronic periodontitis is defined by the inclusion criterion ‘1–2 mm of clinical attachment loss’. Other classes (I, IV and VIII) use relationship definitions rather than operational definitions for allocation of cases to sub-classes, e.g. periodontitis as a ‘manifestation of’ Down syndrome. Technically, allocation of a clinical phenotype to a disease class is achieved using information collected in a standard periodontal examination. Due to the inherent simplicity of the required clinical procedures, classification is an easy task for specialists in periodontics.

Table 3. Typical general characteristics of an ideal classification system

• The classification corresponds to the nature of the disease being classified
• Every member of the universe of periodontal diseases (‘periodontal syndrome’) will fit in one and only one class/sub-class in the classification system
• The classification is useful
• The number of sub-classes is not excessive
• The set of classes can be constructed using a systematic procedure

However, as mentioned above, the current classification has also received challenges. Of general concern is that some clinical phenotypes do not meet the classification criteria of any particular disease class. Examples have been described in the literature,^{175, 300} and concern non-inflammatory destructive periodontal disease or atrophy. A weakness of many disease classifications is substantial overlap among classes. This occurs when the key properties of classes are too broadly defined. In such situations, clinical phenotypes cannot be allocated unequivocally, and mis-classification is possible. An example is the definition of aggressive periodontitis (class III) as ‘rapid attachment loss and bone destruction’. Here the critical identifier refers to a subjective, temporal interpretation of a cross-sectional finding rather than objective information that can be obtained from patient examinations and records.

However, there is no universal agreement on threshold rates for rapid attachment loss and bone destruction. To mitigate the risk of mis-classification, selected biochemical (e.g. interleukin-1 β and prostaglandin E₂) and microbiological (e.g. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*) secondary identifiers have been proposed.²²¹ Another concern is the sensitivity and specificity of the methods used to collect patient information. Data on change in probing depth, clinical attachment and radiographic bone level are collected as the result of disease history. The methods used to generate such information lack the sensitivity required to detect the subtle sub-clinical changes that occur before tissue damage is clinically obvious. In addition, they are associated with substantial measurement error, which affects diagnostic specificity.

Our understanding of the fundamental mechanisms involved in onset and progression of most diseases, including those affecting the periodontium, remains incomplete. The already substantial amount of knowledge acquired from clinical and laboratory research regarding the etiology and pathomechanisms responsible for periodontal diseases has not yet paid off in terms of development of potent preventive and therapeutic measures for the *individual patient*. However, this situation will change. Progress achieved in the post-genomic disciplines of transcriptomics, proteomics, metabolomics and systems biology will permit a much more accurate and precise characterization and definition of disease at the phenotype level. In the not so distant future, such information could be used for identification of phenotypic differences among patients suffering from the same disease, subsequently leading to individualized, patient-specific therapies.²³⁹

Etiology

It is accepted that dental plaque microorganisms existing in the form of biofilms are primary etiological agents of periodontal diseases. Biofilms are matrix-enclosed bacterial communities that adhere to each other and to surfaces or interfaces. Enormous advances in biology and technology have provided ever more sophisticated tools for the investigation of dental biofilms. Introduction of the GasPak system⁵⁹ and the anaerobic glove box²⁷ allowed discovery of numerous fastidious anaerobic planktonic species in the oral cavity.^{274, 365} Due to this advancement in anaerobiosis, coupled with epidemiological data, it was possible to associate a population shift toward certain gram-negative anaerobic species in dental plaque biofilms with the initiation and progression of periodontal diseases. However, it was the application of DNA-based assays, polymerase chain reaction and confocal microscopy^{71, 206, 212, 217, 304, 366} that deepened our understanding of the formation, maturation and ecology of dental plaque biofilms.

The epithelia lining the mouth and the exposed tooth surfaces constitute the adherence substrate for oral biofilms (Fig. 1). Oral bacteria are initially acquired by contact with an infected family member at birth or at later life stages.⁴⁰¹ The conditions for bacteria to initiate successful colonization vary greatly depending on tissue type, location, and exposure to external shear forces. The gingival sulcus, and especially the col region, which forms the bridge between adjacent gingival papillae, offer protected niches that favor bacterial settling. Pioneer colonizers include oral species of the genera *Streptococcus*, *Veillonella*, *Prevotella*, *Neisseria*, *Gemella*, *Actinomyces* and others.³⁰² During biofilm maturation, bacteria interact with each other within and between species via surface-associated structures (co-aggregation), leading to a unique spatial organization.²²⁹ As part of a sophisticated ecological system, biofilm residents communicate through exchange of genetic information and quorum sensing, a mechanism that allows coordination of their gene expression according to population density.^{47, 379} In addition, biofilm bacteria facilitate processing and uptake of nutrients, and protect themselves from other species (by producing bacteriocins), the host and harsh environments,²⁴⁵ allowing them to establish stable communities.²¹⁴

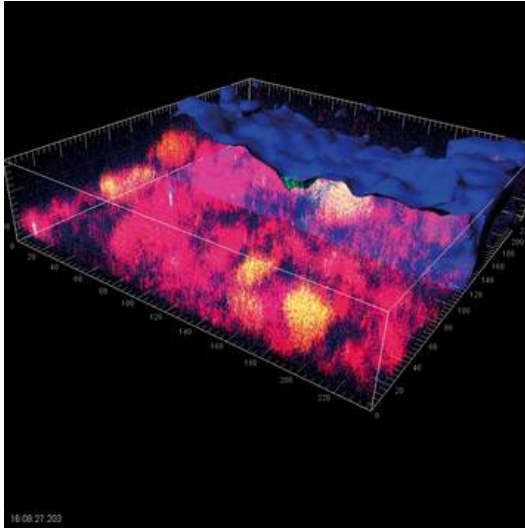


Figure 1. Properties of bacterial biofilms. Bacterial cells in a biofilm are held together by a matrix composed of extracellular polysaccharides, proteins, and other compounds. Biofilm development occurs in response to extracellular signals, both environmental and self-produced. Biofilms protect bacteria from a wide array of insults as diverse as antibiotics, predators, and the human immune system. The biofilm shown in the figure was grown for 3 days on a human enamel sliver worn by a healthy volunteer in the region of the maxillary premolars and molars. The surface to be imaged was facing towards the natural teeth to simulate retention areas. The biofilm was stained using fluorescent in situ hybridization (FISH) to show streptococci (yellow) and all bacteria (red). Reflected imaging (blue) was used to show the surface of the plaque and the slime matrix between the bacteria in the biofilm. The plaque biofilm was composed of dense clusters of streptococci interspersed with clusters formed by other bacteria. The scales on the x, y and z axes are in 1 μm increments. Biofilm image courtesy of Drs. Christiane von Ohle (Department of Conservative Dentistry, Tübingen, Germany) and Paul Stoodley (National Centre for Advanced Tribology Southampton, Southampton University, UK).

Mature dental biofilms can host a large variety of bacterial genera. Molecular detection of the microflora in the oral cavity has led to identification of approximately 700 bacterial species or phylotypes.^{12, 212, 304} Approximately 50–60 species can be identified in a typical plaque sample when 16S rRNA probes are used.³²⁹ 16S rRNA is a highly conserved gene sequence that permits estimation of evolutionary distance and relatedness of organisms.⁷⁸ Species compositions of dental biofilms vary greatly from sample to sample and are site-specific.³⁰⁵ From initial colonization to formation of mature and potentially pathogenic supra- and subgingival communities, dental biofilms pass through several stages, including colonization, growth of commensal bacteria, and integration and invasion of pathogenic species.²⁰⁷ Such opportunistic pathogens co-exist with other biofilm residents until changed environmental conditions favor their expansion and expression of their pathogenic properties. The bacterial composition of mature biofilms sampled in the gingival sulcus of periodontally healthy subjects over an extended time period shows a high level of temporal stability. In contrast, in subjects whose clinical status changes from health to disease or *vice versa*, many bacterial species disappear or emerge.^{213, 368, 384} Likewise, periodontal diseases are considered to be opportunistic polymicrobial infections. Putative bacterial pathogens associated with periodontal diseases have been identified in subgingival biofilms. These include *A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Eikenella corrodens*, *Campylobacter rectus*, *Parvimonas micra* (previously *Peptostreptococcus micros*) and *Streptococcus intermedius*. Three species, *P. gingivalis*, *T. forsythia* and *T. denticola*, have been

designated as 'the red complex',³⁶⁷ and are implicated in progression of chronic periodontitis. Numerous virulence factors, which can initiate and modulate pathways of the host response, were identified and characterized from these species.^{165, 386} *P. gingivalis* (previously *Bacteroides gingivalis*), a gram-negative black-pigmented, immotile obligate anaerobe, is a late or secondary colonizer that depends on the presence of other biofilm species.²⁸¹ Its virulence potential is characterized by: (1) adhesion and co-aggregation mediated by fimbriae, vesicles, several hemagglutinins and outer membrane proteins, (2) evasion of host responses mediated by capsule lipopolysaccharides, and immunoglobulin and complement proteases, and (3) tissue damage mediated by a large number of peptidases that enable tissue invasion and destruction, and production of toxic metabolic end-products.²⁸¹ *T. forsythia* (previously *Bacteroides forsythus*) is a fastidious, non-motile, spindle-shaped, obligate anaerobic gram-negative rod whose growth in biofilms depends on co-aggregation with *P. gingivalis* or *F. nucleatum*. It secretes proteolytic enzymes and sialidase, and can induce apoptosis. Furthermore, *T. forsythia* can adhere to and invade epithelial cells and extracellular matrix components via the cell surface-associated BspA protein. The invasion is enhanced in the presence of *P. gingivalis*.¹⁷⁷ In addition, *T. forsythia* possesses a unique surface structure called a surface (S-) layer that is involved in hemagglutination and adherence/invasion of epithelial cells.³³⁵ *T. denticola* is a gram-negative, aero-tolerant anaerobic spirochete. It is a late colonizer, and adheres readily to other bacteria, such as *P. gingivalis*, *T. forsythia* and *F. nucleatum*, using various adhesins. *T. denticola* also possesses numerous proteinases and peptidases. The functions of selected virulence factors identified from these periodontal pathogens have been validated by construction of isogenic mutants and animal studies.¹⁶⁶

Aggregatibacter actinomycetemcomitans (previously *Actinobacillus actinomycetemcomitans*)²⁸⁵ is a putative pathogen that has been associated with aggressive (previously known as 'juvenile') forms of periodontitis.^{115, 363, 429} The oral cavity is its only known natural habitat. It is isolated regularly and in large numbers from various oral mucosal surfaces, even in toddlers and in the absence of periodontal pathology.^{218, 385} Serotype b, one of five defined serotypes, can be isolated primarily from periodontal pockets in subjects with localized aggressive periodontitis.⁴²⁸ In addition to its ability to colonize, *A. actinomycetemcomitans* can invade epithelial cells,²⁶⁵ secrete a leukotoxin^{42, 157} and induce apoptosis.¹⁹² *A. actinomycetemcomitans* shows clonality in virulence, as leukotoxin production is greatly increased in clone JP2.¹⁹⁹ This clone belongs to serotype b and has a 530 bp deletion in the promoter region of the leukotoxin gene operon. This deletion is most likely responsible for the increased toxin production. Originally discovered in an 8-year-old Moroccan child with aggressive periodontitis,¹⁴⁹ the clone has also been isolated from Africans with a history of aggressive periodontitis in other parts of the world. The restriction of infection with JP2 to individuals of West- and North-African descent implies great colonization stability and a vertical transmission pathway from mother to child. Moreover, this allowed the investigators to track JP2's emergence on the African continent back in time for hundreds of years.¹⁹⁹ While infection with JP2 is a somewhat unique finding, it sheds light on the importance of specific bacteria in certain forms of periodontal disease, as well as the potential value of microbiological screening³⁰⁹ for early detection in susceptible subjects.

Pathogenesis

The characteristic gingival and periodontal lesions are the result of biofilm-induced, orchestrated inflammatory responses involving the innate and adaptive arms of the immune system. Inflammation that remains limited to the gingiva is the outcome of a well-balanced symbiosis between biofilms and the host tissues, while periodontitis is the result of breakdown of this symbiosis. Moreover, it may be speculated that even the most common forms of periodontal diseases are merely analogous phenotypes of different pathogenetic pathways, initiated by biofilm products, of which only a few lead to tissue destruction in susceptible hosts. Much progress has been made at all levels of inquiry towards

understanding these pathways.^{209, 295, 296, 298} [Figure 2](#) shows a highly simplified model of the inflammatory pathway that can lead to tissue destruction, and it is explained below.

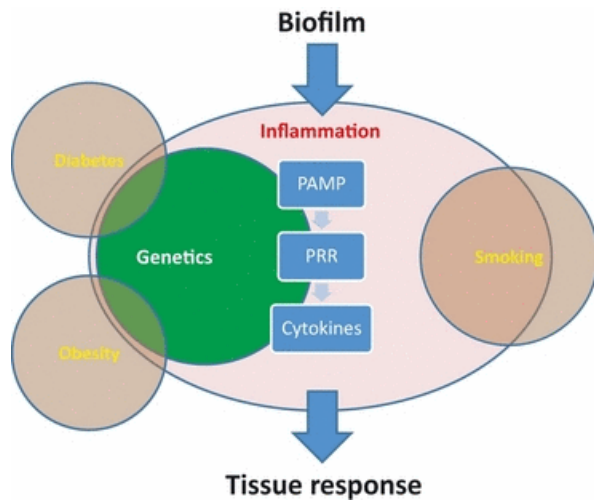


Figure 2. Inflammatory pathways are initiated by biofilm bacteria or products, and ultimately produce a tissue response, i.e. gingivitis or periodontitis. The type and strength of the response are determined by pathogen-associated molecular patterns (PAMPs) and the subject's genetic make-up, and modulated by the presence or absence of modifying factors, including diabetes, obesity, smoking, and others. For example, the PAMP lipopolysaccharide from gram-negative bacteria (e.g. Porphyromonas gingivalis or Tannerella forsythia), first binds via the CD14 receptor to Toll-like receptor 4, a pattern recognition receptor (PRR) that is expressed on polymorphonuclear leukocytes, as well as gingival and junctional epithelia. Activation of Toll-like receptor 4 also requires the presence of protein MD2, and engages a set of response proteins. Subsequently, intracellular signal cascades are turned on, resulting in a Toll-like receptor-specific reaction. Transition from the innate to the adaptive response is initiated by Toll-like receptor-triggered cytokine and chemokine production, and involves activation of antigen-presenting cells, as well as T-cell differentiation and regulation.

Basically, dental plaque biofilms are in constant interaction with their underlying substrates, i.e. the tooth surface, junctional epithelium, gingival epithelium and pocket epithelium. They receive nutrients from the saliva, crevicular fluid, cell debris and food. Considering biofilms a nuisance, without any benefit to the host, may be a big mistake. Not only do biofilms affect the host, there is mounting evidence that the host's responses similarly influence the metabolism and composition of biofilms. In a healthy person, host defense and biofilms co-exist in a mutually beneficial symbiotic state.^{167, 253}

Bacteria are released continuously from dental biofilms, and to a large extent are eliminated before they elicit any host response. Significant bacterial invasion is not observed in subjects with clinically healthy periodontal tissues. Various physiological mechanisms are in place to maintain tissue integrity; bacterial products are rinsed off by the continuous saliva flow, crevicular fluid flushes the gingival sulcus, and the high turnover of the junctional and gingival epithelia eliminates bacteria-loaded superficial cells.^{60, 348}

In addition to the mechanical cleansing action, highly potent first-line antimicrobial defense systems can sense and destroy intruders. Such systems include peptides found in the saliva (histatins, cathelicidins and others), epithelium, neutrophils,⁹³ and molecules described as pattern recognition receptors (PRRs).⁷³ α -defensins are observed in the junctional epithelium, where they are associated with polymorphonuclear leukocytes. These cells constantly migrate towards the gingival sulcus, responding

to a gradient of interleukin-8 that is expressed in the junctional and sulcus epithelium.³⁹⁵ β -defensins are found in gingival and pocket epithelia, where they are constitutively expressed.²¹¹ In addition to exhibiting excellent antibacterial properties, defensins can activate the complement cascade, up-regulate production of the chemokine interleukin-8 in epithelial cells, and attract immune cells.²⁵⁴ PRRs are typically found on the surface of polymorphonuclear leukocytes, macrophages, dendritic cells, endothelial cells, mucosal epithelium cells and lymphocytes.¹⁸⁹ They include two functional families. Endocytic PRRs are located on the surface of phagocytes. They facilitate the attachment of microorganisms, leading to their engulfment and destruction. Signaling PRRs are located on the surface of a greater variety of cells. They recognize structurally highly conserved pathogen-associated molecular patterns (PAMPs) on microorganisms. PAMPs include lipopolysaccharide, teichoic acids, sugar residues, *N*-formyl peptides and others. Binding of PAMPs to PRRs promotes the synthesis and secretion of intracellular regulatory molecules such as cytokines that are crucial for initiating innate immunity and adaptive immunity.

Recently, Toll-like receptors, a subgroup of the signaling family of PRRs, were identified in periodontal tissues.²⁴⁶ Interaction between a PRR and its PAMP leads to a rapid cascade of events, including formation of a PRR–ligand complex that can be internalized, activation of Toll-like receptors and NF κ B, and transcriptional activation resulting in the synthesis of reactive oxygen species, reactive nitrogen species, cytokines (interleukin-1, interleukin-12 and tumor necrosis factor- α), and chemokines (interleukin-8, monocyte chemoattractant protein-1, regulated on activation, normal T cell expressed and secreted (RANTES)). These compounds trigger an immediate inflammatory response, and enable migration of additional leukocytes from the blood to the site of inflammation. CD14 is another PRR that is expressed on polymorphonuclear leukocytes, macrophages and monocytes. It enhances the ability of Toll-like receptor 4 to respond to lipopolysaccharide. The complex formed of CD14, lipopolysaccharide and Toll-like receptor 4 increases the production of cytokines and chemokines, leading to inflammation and activation of the complement cascade and the coagulation pathway. Finally, Toll-like receptors instruct dendritic cells to initiate a highly differentiated, specific T-cell response.¹⁴ Thus, defensins and PRRs not only neutralize microbial components, they also constitute an important link between innate and adaptive immune responses.

Increased vascular leakage and activation of serum protein systems potentiate the local acute inflammatory response. Gingival crevicular fluid flows at an increased rate.^{108, 134} During early phases of lesion development, a dense polymorphonuclear leukocyte-dominated infiltrate is found in the biofilm-adjacent gingival compartment. To destroy potential intruders, polymorphonuclear leukocytes release proteases, prostaglandins and other inflammation-enhancing molecules, as well as highly potent reactive oxygen and nitrogen species. These effectors do not discriminate between host and bacteria, resulting in collateral damage to gingival connective tissue. A successful inflammatory response eliminates the infectious agent and initiates tissue repair. However, if the infection prevails, as a result of persisting inflammation and instructed by macrophages and dendritic cells, cells of the adaptive immune system appear, and the lesion takes on chronic traits. T-cells and B-cells start to accumulate, and ultimately dominate the lesion. Their proportions are determined by the type of immune response elicited by the antigens and the presence of modulating cytokines. Plasma cells develop from B cells and produce antibodies in response to bacterial antigens and mitogens. In a typical gingival lesion, T cells predominate. T-helper cell subsets (Th1 or Th2) develop from T cells depending on the types and amount of cytokines released. The balance between T-helper cell subsets is critical for the immunoregulation of periodontal disease.³⁵⁶ Th1 cells predominate in stable periodontal lesions, but a strong presence of Th2 cells indicates a shift towards lesion progression, with a predominance of plasma cells.³⁵⁵

The local physiological defense mechanisms are very robust and exhibit substantial redundancy. In fact, many people show minimal or no periodontal destruction despite experiencing gingivitis as a result of lifelong poor oral hygiene.²³⁴ However, robust systems are weak when their non-redundant components are attacked,²⁰⁴ resulting in deficiencies in the immune system. Such attacks may have critical consequences for periodontal tissue integrity, as illustrated in patients with (genetic or acquired) immune deficiencies. In particular, class IV.B cases of periodontal disease have been associated with mutations in the genes encoding for polymorphonuclear leukocyte elastase (severe congenital neutropenia), Chediak–Higashi syndrome 1 protein (Chediak–Higashi syndrome), integrin-β2 (leukocyte adhesion deficiency), cathepsin C (Papillon–Lefèvre syndrome) and others.¹⁴⁵

Resorption of the alveolar bone is a defining characteristic of many periodontal diseases. Several inflammatory pathways can result in bone destruction.³⁸⁷ Macrophages, in addition to processing and presenting antigens for activation of the specific immune response, also produce cytokines and enzymes that induce bone resorption. Recently, an alternative mechanism was described that involves three members of the tumor necrosis factor receptor family: the receptor activator of NFκB (RANK), the receptor activator of NFκB ligand (RANKL) and osteoprotegerin.^{193, 230} The ligand RANKL is found on osteoblasts, but is also expressed by lymphocytes present in the inflammatory infiltrate. RANK is expressed on mature osteoclasts and their precursors, and osteoprotegerin is synthesized by mesenchymal cells. The interaction of RANK and RANKL initiates the differentiation and activation of bone-resorbing osteoclasts, and can be blocked by the decoy ligand osteoprotegerin. RANKL and osteoprotegerin are found in crevicular fluid, and their relative levels appear to predict disease.⁵⁴

Epidemiology

General trends

Gingival and periodontal diseases occur globally and among virtually all populations that have been studied to date.¹⁹ Clinical signs of periodontal destruction may be absent in individuals of any age, but there is little evidence supporting the existence of periodontitis-resistant populations. However, two defined apparently resistant cohorts with no access to dental care were described in Namaqualand and Crossroads (South Africa).^{13, 324} They showed minimal clinical periodontal breakdown at any age, despite the presence of a heavy plaque load and gingivitis.

The World Health Organization performed extensive surveys of the periodontal status of potentially under-served populations around the globe, especially in developing countries.³⁰⁷ Using the Community Periodontal Index for Treatment Needs to assess prevalence, a majority of subjects examined had gingivitis and 10–15% of adults had periodontal pockets ≥6 mm deep. In contrast to common belief, periodontal diseases are not the most important factor for tooth loss in many Asian and most African populations. In fact, surveys have indicated that, in Africa, most people retain the majority of their teeth throughout their lives.^{43, 83}

In the USA, based on estimates obtained from the National Health and Nutrition Examinations Surveys performed from 1988 to 1994 (NHANES III),²⁷⁸ the overall prevalence of moderate to severe signs of periodontitis among adults was 7.3%, corresponding to one affected adult person in 14.^{19, 53} Approximately one in five adults had slight periodontitis, one in ten had moderate periodontitis, and one in 30 showed signs of severe periodontitis. The prevalence of periodontitis increased with population age, but the prevalence of more severe forms peaked at 70 years and leveled off thereafter.¹⁹ Periodontitis was more frequently diagnosed in men than in women. Substantial racial and ethnic disparities were observed. Adult black people were almost twice as likely to exhibit periodontitis as white adults, suggesting a significant racial gap.⁵³

In the analysis of the more recent NHANES 1999–2000 data,⁵³ the overall prevalence of moderate to severe periodontitis was only 4.2% (compared to 7.3%), suggesting a potentially substantial reduction in disease burden over the past decade. Surveys performed in Europe have corroborated the suspected ‘secular trend’ of prevalence reduction in periodontal diseases among adults.^{334, 362} A comparison over a 30-year period of the prevalence of various clinical signs of periodontal disease in Swedish subjects aged 20–70 years revealed remarkable changes (Fig. 3).¹⁶⁹ Over the surveyed period, the proportion of periodontally healthy individuals improved from 8% to 44%. The increment compensated for the decrease in the proportion of individuals with gingivitis or moderate alveolar bone loss. In contrast, the proportion of subjects exhibiting signs of severe periodontal disease was small and did not change over time. Improvements in oral hygiene, changes in lifestyle and adoption of less risky behavior, in particular recognition of deleterious smoking effects, have been proposed to explain the unexpected decline. However, much more work is undoubtedly required to confirm and understand this highly desirable trend.

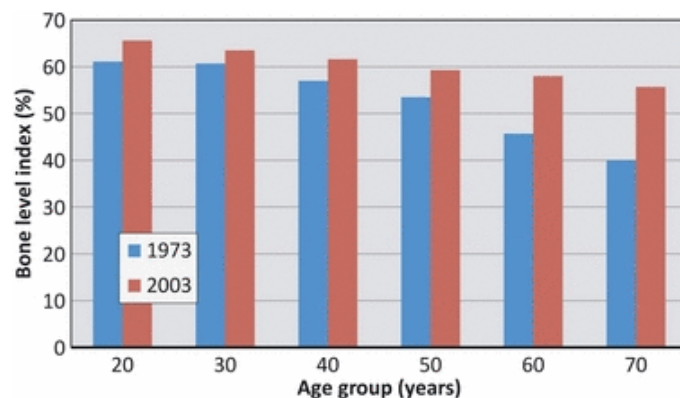


Figure 3. An improvement in alveolar bone index was observed over a 30-year time period in Scandinavians, as indicated by the blue (1973) and red (2003) bars. Mean alveolar bone indices were estimated from radiographs obtained in cross-sectional studies performed in 1973 and 2003. Age groups from 20 to 70 years are shown. Data from.¹⁶⁹

Aggressive forms of periodontitis

Aggressive forms of periodontitis are defined by rapid localized or generalized loss of the supportive periodontal structures, and occur in family clusters in otherwise medically healthy subjects.²²¹

Aggressive forms can affect the primary or permanent dentition. Typically, susceptible patients are less than 30 years old at disease onset.¹⁶ The similar phenotypes of aggressive periodontal disease are probably the clinical expression of multiple disease forms with discrete etiologies.

The reported prevalence of early-onset aggressive periodontitis varies from study to study. The comparability of the data is affected by the somewhat ambiguous disease definitions and the various diagnostic techniques used. A review concluded that aggressive forms of periodontitis have a low prevalence in most regions of the world, occurring in 0.1–1.0% of the population.²⁰ For reasons that are unclear at present, this disease form is seen substantially more frequently among young black subjects. A prevalence of 2.6% was reported in a sample representative of high school students in the USA.¹⁵

Even higher disease prevalences of 6.5% and 7.6% were observed in two cohorts of adolescents and young adults in Uganda¹⁸ and Morocco,¹⁴⁹ respectively. These subjects were carriers of *A. actinomycetemcomitans* clone JP2, which is endemic in Morocco. Carriers of the JP2 clone, who

were free of clinical disease signs at the first examination, had a relative risk of 18.0 (95% CI 7.8–41.2) of experiencing periodontal attachment loss during the 5-year observation period.¹⁵⁰

Although earlier reports by Saxén³³⁸ showed a female majority among subjects with early-onset aggressive periodontitis, a more recent national survey conducted in the USA did not corroborate this observation.²³⁵ Furthermore, based on the results of a genetic segregation analysis performed in 100 families in the USA, the aggressive disease trait has an autosomal dominant inheritance pattern.²⁴⁹ This contrasts with the autosomal recessive inheritance pattern identified in northern Europe,³³⁹ suggesting a different pathway to disease for each of the two populations.

Necrotizing periodontal diseases

Necrotizing periodontal diseases feature ulceration and necrosis of the interdental papillae, spontaneous bleeding, pain and a removable pseudomembrane.⁴ Advanced cases involve alveolar bone resorption, may be generalized, and may lead to fever, malaise and lymphadenopathy.²⁷⁶ Necrotizing periodontal diseases are observed frequently in parts of Africa, Asia and Latin America, mainly in socially disadvantaged children. For example, in an urban South African clinic population, the prevalence of acute necrotizing ulcerative gingivitis was 3%. Males were more frequently affected than females. Seventy-three per cent of the patients were children between 5 and 12 years old. The seasonal occurrence varied greatly, with most cases diagnosed in the summer (relative risk 6.57; 95% CI 4.96–8.70).²⁸ In contrast, necrotizing periodontal disease is now rarely observed in the general population of Europe and North America, as confirmed in a recent study among 18- to 22-year-old military recruits in Switzerland.⁸²

A high prevalence of necrotizing periodontal disease has been observed in HIV-infected subjects.^{223, 306, 314} Based on this finding, the presence of necrotizing periodontal disease has been recommended for use as a surrogate marker of HIV-associated immune deficiency and AIDS.¹²⁵

Risk modifiers

Development and progression of periodontal disease in an individual are ‘personalized’ by a number of endogenous and exogenous factors (Table 4). Assessment, knowledge and proper management of these factors facilitate the prevention of disease or its containment in the case of an existing periodontal condition. An intelligent algorithm that estimates the risk for periodontal disease based on easily accessible clinical information was developed, validated and implemented in practice.^{299, 301}

Table 4. A selection of risk modifiers of chronic and aggressive periodontitis

Risk modifier
Age of patient
Bleeding on probing
Diabetes mellitus
Furcation involvement
History of periodontal surgery
Probing (pocket) depth

Radiographic bone level
Restoration below the gingival margin
Root calculus
Single-nucleotide polymorphisms
Smoking history
Vertical bone lesions

Smoking

An association between smoking and alveolar bone loss was first reported by Waerhaug's group in the late 1950s.³¹ Cigarette smoking was identified to be an age-independent risk indicator for periodontal disease in the Tecumseh Community Health Study in Michigan.³⁷⁸ This greatly increased risk of smokers experiencing periodontal breakdown was confirmed in many studies.^{36, 104, 163, 255, 315} An analysis of the NHANES III survey data concluded that smokers have a four times greater risk of periodontitis than non-smokers.¹⁷ The data suggest a dose-effect relationship between the number of cigarettes smoked per day and the likelihood of developing periodontitis. The research further estimated that more than 40% of cases of periodontitis among adults can be attributed to current cigarette smoking. Of major clinical relevance is the observation that smoking impairs wound healing following scaling and root planning,^{137, 182, 403} periodontal surgery^{24, 111, 376, 396} and guided tissue regeneration procedures.²⁴⁰ Mechanisms for smoking-induced adverse effects have been postulated, but the precise molecular pathways remain to be identified.^{46, 49} Smoking is unquestionably a major risk modifier for most inflammatory periodontal diseases.

Genetics

It has been well established from twin studies that genetic factors contribute substantially to the risk of chronic periodontitis.^{84, 266, 267} A population-based study²⁷⁵ in more than 10,000 Swedish twin pairs estimated that genetics-attributable contributions to the cumulative risk of periodontal disease amounted to 39% (95% CI 31–47%) and 33% (95% CI 24–42%) in women and men, respectively. Furthermore, the magnitude of the effect was strongly influenced by age and smoking status, suggesting substantial gene-environment interaction.

Based on the currently available evidence, chronic and aggressive forms of periodontitis are not associated with single gene mutations or acquired molecular abnormalities. However, DNA sequence variations in genes that result from alteration of a single nucleotide can substantially affect the disease phenotype. Single-nucleotide polymorphisms are thought to play a role in periodontal diseases.¹⁰ The commercial availability of high-throughput, low-cost technology has boosted research in genome-based risk factors for complex diseases. As a result, the association of numerous polymorphisms with specific forms of periodontal disease was investigated.^{58, 114, 120, 130, 181, 208, 380, 383, 422, 423} Examples of single-nucleotide polymorphisms that were considered in such studies include those in interleukin-1, interleukin-6, interleukin-10, interleukin-12RB2, Fc- γ , matrix metalloproteinase-9 and tumor necrosis factor- α , to name but a few. In addition to obtaining a better understanding of the disease process, such polymorphisms may be used as diagnostic or prognostic markers. The PST™ genetic test (Interleukin Genetics Inc., Waltham, MA, USA) has been offered to patients with periodontitis. It tests for single-nucleotide polymorphisms of interleukin-1 genes, and has shown moderate sensitivity and specificity in

predicting disease progression in non-smokers. The test's cost-effectiveness was investigated using a mathematical model.¹⁶⁰ The authors' conclusion that more benefits would result if risk-specific treatments were available is very much to the point.

Epigenetic alterations to the genome may also play a significant role in disease expression. These changes involve both methylation of DNA and post-translational modification of histone proteins. The epigenetic profile is modified by the environment over time, and may have substantial implications for periodontal disease expression.⁴²¹

Diabetes

Estimates suggest that approximately 7% of the total population in the USA have diabetes, and the prevalence is increasing.⁶⁶ Subjects with a history of type 2 diabetes mellitus have a higher prevalence and severity of periodontitis, as shown in Pima Indians.¹¹⁰ In another study, 25- to 74-year-old diabetics had significantly increased likelihood of experiencing attachment loss.¹³⁶ Recently, an increased prevalence of periodontitis was shown in children and teenagers with type 1 diabetes compared to age-matched controls.²¹⁷ Subjects with poor glycemic control showed faster recurrence of periodontal pockets after periodontal treatment than non-diabetic controls.³⁸⁹ Westfelt et al.⁴¹⁶ compared the outcomes of periodontal surgical treatment in subjects with well-controlled type 1 and 2 diabetes with those in sex- and age-matched controls over a 5-year period. All subjects had moderate to advanced forms of chronic periodontitis. The results showed no difference between the two treatment groups, suggesting that well-controlled diabetics can maintain healthy periodontal conditions. There has been increased interest in the question of whether or not treatment of periodontal diseases leads to improved glycemic control in diabetic patients.¹⁷⁸ Nine controlled clinical trials were performed in an attempt to answer this important question, and the results were summarized meta-analytically.⁹⁴ The overall results indicated that periodontal treatment led to a statistically significant reduction in the surrogate marker glycosylated hemoglobin (HbA1c). However, the authors' enthusiasm about this favorable finding was guarded because of the small size of the reduction (<1%) and its lack of robustness. They therefore concluded that there is still insufficient evidence for global recommendation of periodontal treatment as an effective measure to reduce glycosylated hemoglobin (HbA1c) in adult subjects.

Obesity

Obesity is a major risk contributor to disease and death worldwide. More than 60% of adults in the USA are overweight, and approximately 30% are obese.¹⁵¹ Close relationships have been established between obesity and diabetes, hypertension, coronary heart disease and stroke, and cancer.¹⁴⁶ Body fat, which is accumulated to excess in obese people, is produced by adipocytes. In addition to producing fat, these cells also release molecules that affect insulin resistance, and secrete hormones and cytokines, leading to a hyperinflammatory state. In a brief editorial note, Saito et al.³³⁶ described their observation that apparently healthy Japanese subjects with a BMI > 25 kg/m² had a significantly higher relative risk of periodontitis than subjects with a BMI < 20 kg/m². The association between obesity and periodontitis was subsequently substantiated by more extensive studies in various populations.^{227, 310, 424}

Pregnancy

The female body is subject to substantial hormonal fluctuations, especially during pregnancy. The most remarkable hormonal change during pregnancy is the increasing production of estrogens and progesterone, which levels off approximately one month before delivery. By that time, estrogen blood levels have risen more than 100-fold. In addition, the type of estrogen secreted changes from estradiol to the less potent estriol. These hormones are mostly produced by the placenta, and the levels revert to pre-pregnancy levels within a few days after delivery. An increased prevalence and severity of gingival

inflammation were reported in pregnant women.^{231, 247, 375} These changes appear to be independent of changes in plaque amount¹⁶⁸ and are reversible.¹⁴⁰ About one pregnant woman in 20 develops a highly vascular, edematous lesion known as pyogenic granuloma. The lesion occurs typically during the first two trimesters, and has a strong tendency to recur if excised during pregnancy. Although hormones are likely to play a significant role in the development of pyogenic granuloma, its etiology remains largely unknown.²¹⁶

Medications

Early studies on the effect of oral contraceptives on parameters of periodontal health reported an increased prevalence and severity of gingivitis in subjects who were taking contraceptives than in controls.²⁵⁰ The contraceptives used by study participants contained high doses of estrogen, progestin, or both. In contrast, the most frequently used products at the present time are low-dose combination preparations of estrogen (≤ 50 μg) and progestin (≤ 1 mg). A more recent study³⁸² used information collected in NHANES I and III to investigate the relationship between oral contraception use and periodontal parameters. The thorough analysis rejected the previously held notion that women on oral contraception are at higher risk of experiencing clinical signs of gingivitis or periodontitis.

Certain anticonvulsants (e.g. phenytoin), immunosuppressants (cyclosporine) and calcium channel blockers (e.g. nifedipine) have been associated with gingival enlargement.⁷ The prevalence of this side-effect varies from 5% to 50% in adults.⁷⁹ For cyclosporine, the highest prevalence of gingival overgrowth was observed in children¹⁹¹ and decreased with increasing patient age.¹⁵² The severity ranged from small single lesions to massive growths that impaired function and esthetics.¹⁴⁷ The pathogenesis of drug-influenced gingival enlargement remains unresolved, although a multitude of contributing factors appear to be involved, including integrins, cytokines and matrix metalloproteinases. An interesting hypothesis proposed involvement of single-nucleotide polymorphisms of the *MDR1* gene, which encodes the drug-efflux pump P-glycoprotein. This effect was observed in a clinical study⁹⁸ that found severe cyclosporine-induced overgrowth in patients carrying the *MDR1* C3435T mutation.

Nutrition

For many centuries, a deficient diet was considered a cardinal factor in the development of periodontal diseases. The hypothesis was based on anecdotal evidence, and held up to its premise until animal experiments permitted its scientific test. Glickman¹²⁶ was among the first to investigate the effect of vitamin C on the periodontium in guinea pigs. His experiments confirmed that diets lacking certain vitamins or minerals can affect the development of periodontal tissues and bone. Specifically, the author concluded that a diet deficient in vitamin C resulted in generalized alveolar changes but was not responsible for periodontal pocket formation. Recently, Nishida et al.²⁸⁴ reassessed the relationship between dietary vitamin C intake and periodontal disease using the powerful NHANES III database. They found that persons with low vitamin C intake (<30 mg/day) had a slightly increased likelihood of developing periodontitis when compared to a reference group with elevated intake (>180 mg/day).

Diets rich in whole grain have been associated with lower risk of diabetes and cardiovascular disease.²²⁶ This desirable effect is probably the result of improved insulin sensitivity and improved glycemic control.¹⁸⁰ Merchant et al.²⁶² used information gathered in the Health Professionals Follow-up Study (HPFS) to investigate the relationship between intake of whole grain, refined grain or cereal fiber and risk of periodontitis. After 14 years of follow-up, men who consumed 3.4 servings per day (median) of whole grains were 23% less likely to be diagnosed with periodontal disease than those who consumed 0.3 servings per day (median). These intriguing results were further confirmed in a study using data from NHANES III that found an inverse association between serum total antioxidant capacity and periodontitis.^{69, 70}

Systemic effects of periodontal disease

After several decades of relative absence from the scientific literature, new reports linking indicators of dental health with an increased risk for a variety of systemic diseases emerged in the 1980s and 1990s. Examples include associations with myocardial infarction,^{257, 361} stroke,^{236, 381} cardiovascular disease,¹⁰² peripheral vascular disease,²⁶¹ adverse pregnancy outcomes^{95, 289} and pneumonia.^{118, 340, 341} The possibility that periodontal and other diseases of the human body could be linked created broad-based excitement among the dental community and beyond, and ushered in the era of periodontal medicine.⁴¹⁸ As a result, in a worldwide effort, hundreds of clinical and laboratory studies have been performed, leading to a much deeper understanding of periodontal diseases as part of overall health.

The foundation for an etiological role of periodontal diseases in general health is based on two assumptions. First, bacteria released from biofilms located in periodontal pockets can enter the bloodstream through ulcerations of the pocket epithelium and colonize other body parts, especially in patients with compromised immunity.^{200, 342} Second, periodontal pathogens elicit inflammatory reactions in the affected tissues, stimulating the release of pro-inflammatory cytokines or acute-phase proteins, and contributing to systemic inflammation, possibly atherogenesis, and other pathology.^{96, 200, 303}

Although many published (frequently small-scale) studies have reported statistical associations between parameters of oral health and systemic disease, the all-important cause/effect relationship awaits confirmation in large-scale longitudinal epidemiological and interventional studies. Examinations of the link between periodontitis and coronary heart disease using information collected in NHANES I did not show the expected strong association.^{171, 172} Furthermore, a review of nine cohort studies found no or only weak associations after controlling for smoking or lifestyle factors.¹⁷⁴ The concern that confounding could mask the study outcome received additional support in the 6-month pilot trial of the National Institutes of Health-sponsored Periodontitis and Vascular Events (PAVE) study.²⁹³ The trial showed that a beneficial effect of periodontal treatment on the surrogate marker hs-C-reactive protein was achieved only in non-obese subjects with cardiovascular disease, whereas it was not observed in obese subjects. Another National Institutes of Health-funded multi-centered study, the randomized controlled Obstetrics and Periodontal Therapy (OPT) trial, investigated the effect of non-surgical periodontal treatment on pre-term birth rates in more than 800 pregnant women exhibiting clinical signs of chronic periodontitis.²⁶⁸ The investigation confirmed the safety and effectiveness of standard periodontal treatment in pregnant women, but did not detect significant treatment-induced reductions in the rate of pre-term birth or other birth-related outcomes.

It is too soon to draw a final conclusion as to whether the so-called 'systemic link' is of major public health relevance, or not. Caution is warranted. The biological plausibility model of the systemic link assumes that the larger the wound surface area, the greater the chances of bacteremia, and that the large wound surface persists over substantial time periods. Are some of the model assumptions overly optimistic? For example, the combined contact surface area between biofilms and pocket epithelium in patients with generalized periodontitis was estimated as up to 70 cm²,²⁹⁷ potentially resulting in an impressively large wound surface.²⁹⁰ However, the overwhelming majority of patients with chronic periodontitis do not show signs of disease activity in all pockets simultaneously,³⁶⁴ and phases of such activity are typically short-term. Indeed, detection of active periodontal disease is a daunting task in most patients because of its elusive character. The disease is often present at only a few sites, which could mean that the effective wound size is considerably smaller than previously estimated, possibly just a few square centimeters.^{173, 282} Although not impossible, detection of remote effects of such a small wound is a formidable challenge.

Treatment modalities for gingivitis and periodontitis

Historical overview

Local mechanical debridement of the teeth and root surfaces has been advocated for centuries as a treatment for diseases of the periodontium, with descriptions of calculus removal being found in the ancient writings of almost all known civilizations. Various other therapies such as cauterization using thermal or chemical agents, use of astringents on the soft and hard tissues, as well as soft-tissue removal using curettes or surgical blades have been advocated at various times and in various cultures as treatments for periodontal diseases.^{127, 128} Scientific and technical progress in the 19th and 20th centuries, including better understanding of the histopathology of the disease and its microbial etiology, as well as the development of radiography, local anesthesia and analgesia, made diagnosis and treatment of periodontal diseases more standardized although not truly cause-related.

After the seminal work by Löe et al.,²³² demonstrating the cause and effect relationship between bacterial plaque/biofilms and gingival inflammation, the second half of the 20th century saw an explosion of research on cause-related therapy for gingivitis and the most common phenotypes of periodontitis. These centered on mechanical and chemical methods to attack the microbial origins of disease. Later observations of differential host susceptibility to disease^{162, 234} and the discovery of molecular mechanisms of tissue destruction in the periodontium²⁴³ suggested anti-inflammatory or host modulation approaches as potential means to address periodontal syndromes.²⁰² Today it is universally agreed that effective periodontal therapy for plaque-related disease requires elimination of inflammation through re-establishment of a biologically acceptable 'clean' root surface. Current therapeutic approaches all aim to achieve that end with minimal removal of cementum. Antimicrobials and host-modulating agents may be used as adjuncts to this basic and arguably ancient mechanical approach to therapy. How, when and why these approaches fit into therapy is discussed below in the context of treatment sequence, with emphasis on the most common form of disease: chronic periodontitis.

Systemic and acute phases of treatment

General guidelines for dental treatment planning have been published³⁷⁷ based on five treatment phases: systemic, acute, cause-related, surgical corrective and maintenance (Table 5). The systemic treatment phase is concerned with prevention of treatment complications, particularly in subjects in whom periodontitis is associated with systemic disease, as well as with protection against disease transmission. Another goal of the systemic phase is to optimize treatment outcomes by addressing important subject-based risk factors, such as smoking^{163, 315} and diabetes.^{389, 416} Although the systemic treatment phase is crucial in many periodontal disease phenotypes, the acute treatment phase is usually only implemented for symptomatic forms of periodontal disease, such as necrotizing periodontal diseases, abscesses of the periodontium, and sometimes in cases of periodontitis associated with endodontic lesions. In acute situations, the systemic treatment phase may be abbreviated, but cannot be ignored. For such situations, control of pain and infection is paramount. Basic treatment approaches for some common acute periodontal conditions are outlined in Fig. 4. As the majority of gingivitis and tissue-destructive periodontal diseases are non-painful, most of the treatment for these conditions occurs in the context of overall restoration of oral health during the active treatment phases.

Table 5. Guidelines for sequencing the treatment for periodontal patients. Modified and reproduced with permission from³⁷⁷

I: Systemic phase

A Consultation with patient's physician
B Pre-medication
C Stress/fear management
D Any necessary treatment considerations for systemic disease
II: Acute phase
A Emergency treatment for pain and infection
B Addressing the urgent chief complaint
III: Cause-related phase
A Oral hygiene education, patient motivation and risk assessment
B Mutual goal-setting for acceptable outcomes/endpoints of therapy
i: Implementation of strategies for risk reduction
C Excavation of deep carious lesions
i: Determine restorability
D Extraction of hopeless teeth along with non-surgical periodontal debridement
E Removal of plaque retentive factors
F Necessary endodontic and occlusal therapy
G Post-treatment re-evaluation
i: Objective assessment of endpoints of therapy
IV: Surgical corrective phase
A Resective/regenerative and implant surgical procedures
B Post-surgical re-evaluation
i: Objective assessment of endpoints of therapy
C Definitive prosthodontic restoration
V: Maintenance phase
A Periodic professional supportive care
B Reinforcement of oral hygiene instruction and motivation
C Annual multi-pronged periodontal stability and risk re-assessment
D Comprehensive professional supra- and subgingival plaque removal

E Radiographic updates and therapeutic interventions (as needed)

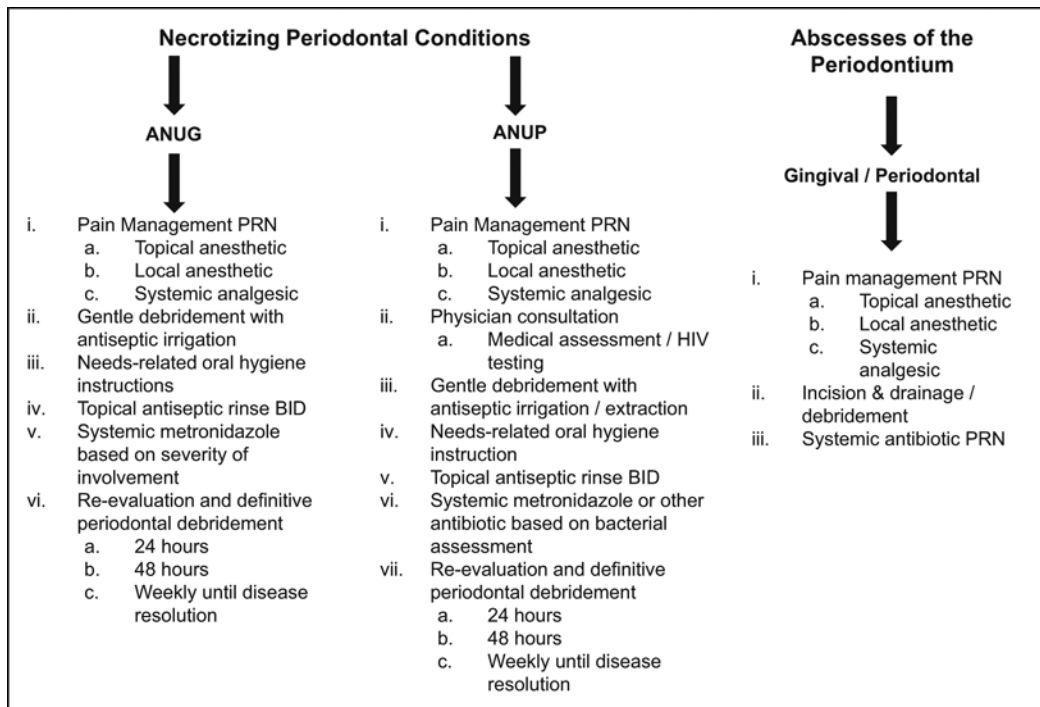


Figure 4. Common treatment strategies for acute periodontal conditions. ANUG: acute, necrotizing, ulcerative gingivitis. ANUP: acute, necrotizing, ulcerative periodontitis. PRN: as needed. BID: twice a day.

Active treatment and maintenance

Periodontal treatment is often divided into disease control, surgical and maintenance phases. While variations in the therapeutic approach are necessary for different forms of periodontal disease, these three phases are generally applicable to asymptomatic periodontitis patients. The disease control phase has also been termed the 'initial' or 'cause-related' phase of treatment because it is primarily focused on elimination of pathogenic subgingival biofilms as well as removal of factors that promote biofilm formation and subsequent destructive inflammation. An overview of common treatment strategies for gingivitis is presented in [Fig. 5](#). For plaque-induced gingivitis, the treatment centers on professional and personal plaque removal, with proper training in needs-related oral hygiene measures being critical. Antiseptics can also play a role in reducing plaque and gingivitis. For non-plaque-induced gingivitis, it is important to identify the source of inflammation and reduce or eliminate it whenever possible. Common treatment approaches for chronic and aggressive periodontitis, in which tissue destruction has occurred, are outlined in [Fig. 6](#). In each case, active treatment centers on disruption of the pathogenic biofilm by non-surgical mechanical debridement using antimicrobial and sometimes anti-inflammatory adjuncts, and, as with all biofilm-mediated oral disease, patient-specific instruction in daily plaque removal.

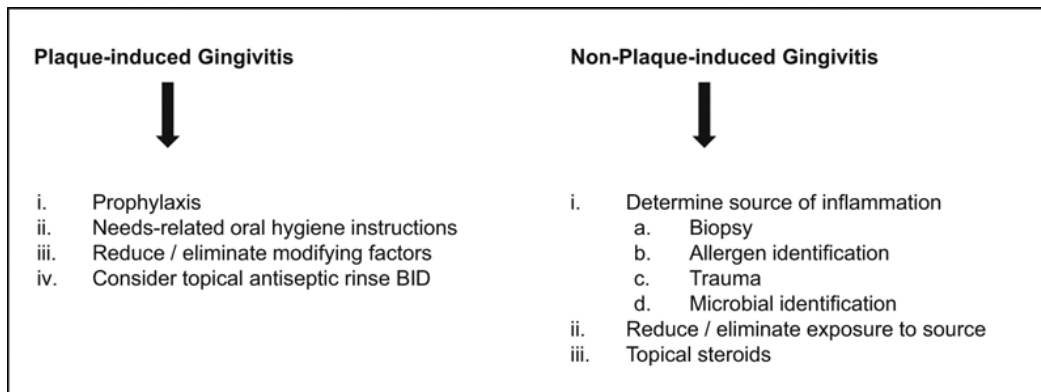


Figure 5. Common treatment strategies for gingivitis. BID: twice a day.

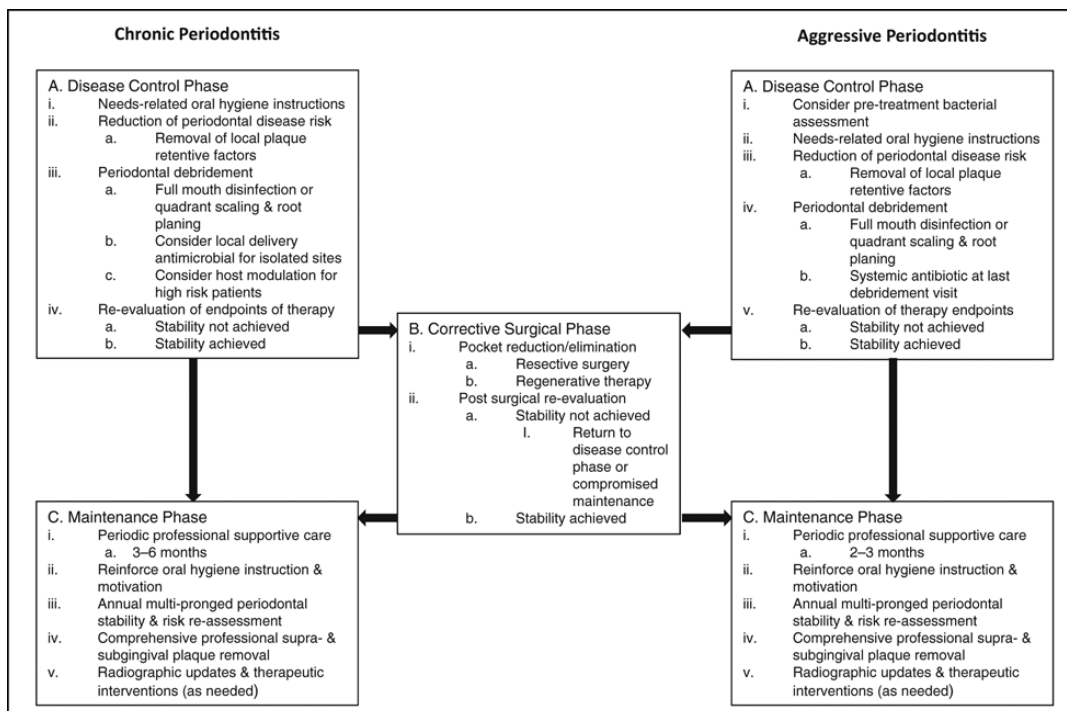


Figure 6. Comparison of active treatment strategies for chronic and aggressive periodontitis.

While traumatic occlusion is not an etiological factor for periodontal disease, it is considered to be a potential disease modifier. It is often addressed during initial therapy.⁵ Management of other potential disease modifiers, such as psychological stress, osteoporosis and poor dietary habits, is often advocated. Such interventions can be beneficial. However, little research has been performed to clarify the effects of these other potential risk indicators on disease susceptibility, and even less research has been performed regarding intervention.¹⁵⁵

Success in the cause-related phase is achieved when disease progression is halted or significantly reduced, as determined by measurements taken upon re-evaluation (Table 6). Important clinical benchmarks for assessment of treatment success include reduction in bleeding on probing and probing depth, together with gains in clinical attachment levels and optimization of needs-related plaque control. There is insufficient evidence to support the utility of microbial diagnostics as a tool in the management of chronic periodontitis, although microbial assessment may play a useful role in guiding

therapy for aggressive periodontitis and phenotypes of disease that are non-responsive to conventional therapy.²³⁷

Table 6. Prediction of periodontal stability defined as a change in clinical attachment level of 0 ± 1 mm and no change in radiological bone level

Predictor	Level	Decision criterion	Long-term stability	Reference
Diabetes (HbA _{1c})	Patient	HbA _{1c} \geq 9% (poor control)	Unfavorable	388
Obesity (BMI)	Patient	BMI \geq 30 kg/m ²	Unfavorable	310
Smoking	Patient	Current smoker	Unfavorable	258 , 316 , 396
Oral hygiene (HI)	Full mouth	HI>30% consistently	Unfavorable	41
Radiographs	Site	Crestal lamina dura consistently present	Favorable	322
	Site	Loss in crestal bone height	Unfavorable	322
Bleeding on probing	Site	Bleeding on probing = 0 consistently	Favorable	185 , 220
	Site	Bleeding on probing > 0 consistently	Questionable	41 , 76 , 219
	Full mouth	Bleeding on probing > 30% consistently	Unfavorable	185
Gingival inflammation (GI)	Tooth	All tooth sites GI \leq 1 consistently	Favorable	222
	Tooth	All tooth sites 1 < GI \leq 2 consistently	Questionable	222
	Tooth	All tooth sites GI \geq 2 consistently	Unfavorable	222

Predictor	Level	Decision criterion	Long-term stability	Reference
Probing depth (PD)	Site	Change in PD = 0 ± 1 mm	Favorable	41, 75, 76
	Site	Change in PD ≥ 2 mm since previous visit	Unfavorable	41, 75, 76
	Site	Eight or more sites with PD ≥ 5 mm	Unfavorable	76, 258
	Site	PD ≥ 6 mm	Unfavorable	258

For definitions of long-term stability criteria, see [215](#)

The surgical/corrective phase of therapy is performed only after thorough re-evaluation of initial therapy has suggested that residual infection/inflammation exists, and compliant patients are still at risk for disease progression ([Fig. 6](#)). In the surgical phase of therapy, periodontal regeneration or resection may be attempted, depending on the bone and soft-tissue architecture. Useful treatment algorithms have been published recently and will not be detailed here.¹⁹⁰ A combination of resective and regenerative procedures is often used at a single surgical site ([Fig. 7](#)). However, surgical therapy is best avoided in patients whose plaque control is inadequate^{228, 287} or who are heavy smokers.³¹⁶



Figure 7. Periodontal surgical intervention for severe chronic periodontitis that combines resective and regenerative strategies to reduce pocket depth and achieve a healthy and maintainable periodontium. (A) Chronic periodontal abscess showing exudate on palpation of teeth 24 and 25. (B) Probing confirms a 12 mm mucogingival/osseous defect. (C) Pre-treatment periapical radiograph showing advanced bone loss. (D) Surgical flap after defect and root debridement and prior to bone graft and Emdogain®. (E) The tissues have been positioned apically and sutured. (F) Probing depths are stable and maintainable. (G) Healthy but receded gingival tissues are seen five years after treatment. (H) Periapical radiograph suggesting some improvement in bone level after 5 years.

The supportive or maintenance phase of therapy involves secondary prevention of periodontal disease.³ Ideally, this phase is entered only after all signs of disease have been eliminated or substantially reduced and the long-term stability of periodontal health is highly probable. A multi-pronged approach to regular reassessment of periodontal health during the supportive phase is critical to long-term success in preventing disease recurrence (Table 6).¹⁰⁰ Although absence of bleeding on probing is a useful indicator of health,²²⁰ increasing pocket depth over time, or pockets deeper than 6 mm coupled with consistent bleeding on probing, are still the best predictors of disease progression.^{41, 75, 258} These measures have been proven useful and are easy to record, and so have become important clinically.³⁹⁸ Recently, Offenbacher et al.^{291, 292} proposed what they call the ‘biofilm–gingival interface classification’, based on classic clinical disease markers coupled with microbial and host molecular markers for disease, to describe different biological phenotypes of periodontitis. The molecular markers may turn out to be useful adjuncts to the standard clinical markers of probing depth and bleeding on probing.

Efforts continue in the hope of developing saliva- or crevicular fluid-based diagnostic systems that may help to distinguish between health and disease based on microbial or host inflammatory markers.⁵⁴ As yet, no system is in wide use, perhaps due to the fact that detailed multi-pronged clinical observations continue to be very effective.

Non-surgical cause-related treatment

Plaque control

The first step in treatment of any form of periodontitis is training the patient in proper plaque removal. Although effective oral hygiene provides limited but positive changes in signs of disease, such as reductions in probing depths and bleeding on probing,^{39, 40, 67, 238} optimal daily plaque control is the most important determinant for long-term success in periodontal therapy.^{35, 38, 354} A systematic review on the effects of a prophylaxis combined with a single episode of oral hygiene instruction emphasizing use of a manual toothbrush demonstrated a small but consistent reduction in gingivitis, even though it was clear that plaque reduction in these studies was not optimal.⁴⁰⁵ More focused training in needs-related plaque removal, such as flossing, the use of woodsticks or other interdental hygiene aids, can be extremely effective in reducing disease long-term when combined with regular professional mechanical cleaning.^{33, 34, 38, 210} Combining interdental plaque removal with an already existing habit of toothbrushing has been strongly advocated.³⁷

Powered toothbrushes have been shown in systematic reviews to provide a modest additional short-term benefit over manual toothbrushing.^{330, 359} Compliance is an issue over the long-term, and even the best powered brushes have yet to demonstrate clinically relevant proximal plaque removal. It is clear that repeated instruction and motivation on interdental cleaning by any means is necessary for long-term success, particularly in the high-risk posterior teeth.^{369, 370} When interproximal soft tissue has receded, use of interdental brushes is of particular value.^{72, 197, 409}

Removing plaque-retentive factors

The removal of plaque-retentive factors as part of initial periodontal therapy is clearly important. Multiple retrospective cross-sectional studies as well as short-term longitudinal studies have confirmed the negative microbiological and clinical effects of subgingival and otherwise non-ideal restoration margins.²⁹⁴

Scaling and root planing

Mechanical root cleaning as a treatment for periodontitis has been advocated for centuries, and scaling and root planing is still the 'gold standard' treatment for chronic periodontitis. This cause-related approach is aimed at removal of pathogenic biofilms, toxins and calculus, and re-establishment of a biologically acceptable root surface. Shrinkage of the periodontal pocket occurs as a combination of soft tissue reattachment to the clean root surface and recession of the soft-tissue margin as a result of a decrease in the inflammatory infiltrate in the periodontal tissues.^{39, 40} Significant reductions in the levels of motile rods and spirochetes are a common finding in areas that show clinical improvements after treatment.^{142, 161, 327} Evidence for clinical improvement includes positive changes in tissue color, contour and consistency, as well as in reductions of bleeding on probing and pocket depth, and gain in attachment.

Badersten et al.⁴⁰ proposed that, for non-molar teeth, there is no true threshold pocket depth where non-surgical periodontal therapy becomes ineffective. However, others have suggested that the ability to adequately remove biofilm and calculus to achieve a biologically acceptable root surface depends on the depth of the pocket, the root anatomy, the instrumentation, the experience of the operator and the approach used.^{57, 61, 62, 106, 116, 374} Systematic reviews have indicated that powered instruments, such as

magnetostrictive and piezoelectric ultrasonic scalers and sonic scalers, are at least as effective as curettes in mechanical debridement, but the powered instruments tend to be more efficient.^{402, 414} There is some evidence that powered instruments may be more effective in areas that are difficult to access, such as furcations and deeper pockets.^{50, 256} When used properly, the powered instruments appear to remove less root structure.³⁴⁶

Adjunctive treatments during initial-phase therapy

Systemic antibiotics

Use of systemic antibiotics as an adjunct to scaling and root planing has become the standard of care in aggressive and non-responsive forms of periodontitis. However, the decision to use a systemic antibiotic must be made based on the patient's medical and dental history. Performing microbial culture and obtaining antibiotic sensitivity data are recommended.⁸

Systemic antimicrobials have also shown some benefit with regard to clinical attachment level gains in short-term treatment studies of chronic and aggressive periodontitis, with the benefit being more pronounced in deeper sites.^{141, 142} However, as mechanical treatment alone is quite often effective, and development of antibiotic-resistant bacterial strains is a growing problem, widespread use of such adjunctive therapy for chronic periodontitis cannot be justified.^{141, 411} Many systemic antimicrobials and combinations of agents were tested in clinical trials, with tetracyclines, metronidazole and combinations of metronidazole with amoxicillin being most frequently reported.¹⁴¹ Systemic use of antibiotics as an adjunct to non-surgical periodontal therapy may have at least a short-term positive effect on systemic levels of inflammation.³⁵² and on glycemic control in diabetics.¹³⁸

Local antimicrobial treatment

The delivery of high levels of antimicrobial directly to the disease site has advantages over systemic antibiotics, including fewer side-effects and non-compliance issues. Several systems have been approved by the Food and Drug Administration for use in the USA, and in other countries. By and large, systems showing ease of use, consistent retention at the site of placement, and slow, steady release of high concentrations of antimicrobial have become popular adjunctive therapies. Non-setting gel preparations have fared poorly, presumably due to unfavorable release characteristics.^{87, 392} Several large randomized, multi-center clinical trials have demonstrated modest short-term clinical benefits of antimicrobials as an adjunct to scaling and root planning.^{107, 109, 179, 419} Test agents with favorable pharmacodynamics included tetracycline fibers, chlorhexidine chips, minocycline microspheres and doxycycline gel. Their use in the initial stage of therapy has shown statistically significant improvements in probing depth reduction, and clinical attachment level gains in some cases. However, reviews have suggested that the magnitude of the changes is of questionable clinical relevance.^{52, 88, 133, 144} Moreover, the cost/benefit ratio remains unproven.^{99, 158} Currently, the most accepted indication for local antimicrobial treatment is in chronic periodontitis patients with isolated pockets of moderate disease that have not responded to mechanical therapy alone (Fig. 6).¹¹

Recent trials using locally delivered minocycline microspheres as part of 'intensive periodontal therapy' demonstrated short-term alterations in several systemic inflammatory markers in addition to providing local clinical benefits that lasted for several months.^{92, 399}

Host modulation

The concept of modulating the inflammatory response as a way to reduce or prevent periodontal breakdown has been investigated since Golub et al. observed that minocycline inhibited collagenase activity in a germ-free rat model.¹²⁹ As periodontal bone and attachment loss are the result of destructive inflammation, it stands to reason that a reduction of the host response should provide a

useful adjunct to typical mechanical and chemical antimicrobial approaches during disease control or maintenance phases of treatment (Fig. 6). Host modulation approaches have been based primarily on damping down effector molecules such as matrix metalloproteinases and prostanoids, although more recent efforts to inhibit destructive inflammation have targeted upstream mediators, such as p38 MAPK (203), as well as novel downstream lipid mediators, lipoxins and resolvins, that actually appear to resolve the chronic inflammatory response rather than simply suppress it.^{148, 407, 408} An additional approach, focused on alterations of bone metabolism by bisphosphonates, has also been studied.¹²⁴

While studies of non-steroidal anti-inflammatory drugs, bisphosphonates, and most recently p38MAPK inhibitors, lipoxins and resolvins, have shown proof of concept, only low-dose doxycycline has obtained US Food and Drug Administration approval for treatment of periodontal disease. In several large, randomized multi-center clinical trials, investigators demonstrated modest clinical benefits with adjunctive low-dose doxycycline after scaling and root planing in subjects with moderate to severe generalized chronic periodontitis.^{64, 286, 317} In addition, a systematic review concluded that adjunctive use of low-dose doxycycline, together with non-surgical scaling and root planing, provided a statistically significant improvement over non-surgical therapy alone.³²⁵ However, the clinical relevance of the adjunctive benefits demonstrated for this therapy has been questioned.¹³³ Moreover, compliance is always an issue when patients are required to take frequent medication for prolonged periods of time, and a modified version of low-dose doxycycline (40 mg everyday) was introduced in response to such issues.³¹⁹ Controversy remains regarding the effect of low-dose doxycycline in smokers.^{280, 318} From a microbiological viewpoint, there is a growing body of evidence suggesting that the standard regimen low-dose doxycycline (20 mg twice a day) has no detrimental effects on the commensal flora of the oral cavity or the gastrointestinal tract.^{391, 412, 413}

However, caution remains regarding application of low-dose doxycycline. Matrix metalloproteinases are ubiquitous and necessary for normal physiological processes, and the potential consequences of long-term matrix metalloproteinase inhibition on other systems are not yet clear. Host modulation therapeutic agents under development show promise, but a magic bullet isn't on the horizon.^{202, 203, 408} Further advances in this area of therapy await better classification of diseases and identification of the multi-faceted molecular basis for the biofilm/host imbalances that produce destructive inflammation. A glimpse into the future was provided by the observation that use of resolvins, but not aspirin-triggered lipoxins, have a positive effect on human neutrophils from subjects with localized aggressive periodontitis, and that topical resolvins reverse periodontal inflammation in the rabbit periodontal disease model.¹⁴⁸ Scientists have expressed great hope in pharmacogenomics,¹²¹ in which the individual genetic and epigenetic make-up of the patient will guide efforts to modulate the host response via drugs and even diet. DNA microarray analysis will be useful in this endeavor.²⁰⁹ Using these molecular approaches, we may finally begin to develop individualized therapies with predictable outcomes for various periodontal diseases.

Full-mouth disinfection

The concept of same-day full-mouth 'disinfection' (antiseptics) was introduced in 1995³²⁰ as a potentially more effective non-surgical periodontal therapy than the conventional quadrant-by-quadrant scaling approach. Many follow-up studies have been performed, with varied results.^{25, 26, 205, 273} The idea of radically reducing the levels of bacterial pathogens from all intra-oral niches, including the gingival crevice and periodontal pockets, is conceptually sound. However, variations in study designs have prevented a clear answer as to whether the concept will effectively translate into a widely accepted clinical approach. The pertinent evidence was assessed at the 6th European Workshop of Periodontology. The reviewers concluded that full-mouth scaling and root planing with or without adjunctive antiseptics does not provide significant clinical benefit beyond conventional, staged

debridement. It was concluded that any of the three treatment approaches are valid ways to accomplish debridement in the cause-related treatment phase for chronic periodontitis.³³⁷

Lasers

The use of laser light to disinfect the periodontal pocket more efficiently has been another area of intense research.^{22, 90, 393} A recent review of the available evidence⁸⁰ concluded that results are inconsistent, and that the radiation parameters and techniques have not been reported in enough detail to make useful recommendations. According to Schwartz et al.,³⁴⁹ use of the Er-YAG laser as a monotherapy may be useful in the cause-related phase of therapy, as it appears to provide similar clinical outcomes to conventional mechanical debridement, but the evidence is weak. Other lasers such as the CO₂, Nd:YAG and Nd:YAP lasers have higher potential for thermal damage to the root surface, and have not shown a clinical benefit, and as such are not recommended.³³⁷ The technology appears to require more development and testing before it can be considered a substitute for classic mechanical debridement.⁸⁰

Photodynamic therapy is another technology of great potential.¹⁸⁴ The essence of photodynamic therapy is to load bacteria with a photoreactive dye, such as toluidine blue, and subsequently expose the dye–bacteria complex to tissue-penetrating light. The combination of dye and light energy leads to formation of singlet oxygen reactive species that can cause cell death. Photodynamic therapy could be an interesting adjunct to scaling and root planing, but this approach is still in development.^{23, 97}

Surgical phase of treatment

When therapeutic targets are not achieved following appropriate cause-related treatment, a surgical approach may be indicated ([Fig. 6](#)). Several surgical procedures have been well documented as a means to gain access to facilitate instrumentation of the root surfaces, reducing pocket depths and restoring clinical attachment. These surgical approaches have been utilized in treatment of periodontal disease for decades, and are broadly classified as access, resective or regenerative procedures. The pocket depth and bone architecture will dictate which surgical approach is indicated.

Access treatment

There have been vigorous debates over the past century concerning the relative merits of surgical and non-surgical treatment for periodontitis.¹²⁸ In the 1980s, several groups published longitudinal clinical trials comparing scaling and root planing to various surgical procedures with or without osseous recontouring. In general, the non-surgical treatments compared reasonably well to more invasive approaches when surrogate outcomes, such as change in probing depth and clinical attachment level, were used.^{186-188, 228, 308, 321} Unfortunately, the vast majority of these trials used a split-mouth design, which has serious deficiencies, including carry-across effects.^{101, 170, 225} This design is no longer recommended for comparative efficacy studies of periodontal treatments.

A more recent 12-year, randomized, parallel-group clinical trial compared scaling and root planing to surgical access. It showed that surgical access resulted in fewer teeth being lost over time as well as fewer subjects showing continued disease progression. This was particularly evident over the first three years of the study.³⁵⁴ Over this period, approximately 80% of the subjects who received only scaling and root planing reached a stable endpoint, while 20% continued to show signs of significant clinical attachment loss. However, recognizing the 20% of patients who do not reach a stable endpoint after non-surgical therapy remains a formidable challenge for the clinician. In addition, the study only assessed single-rooted teeth,³⁵⁴ and did not consider the more difficult furcation areas in multi-rooted teeth.

Resective procedures

Resective procedures are designed to reduce or eliminate periodontal probing depths and establish favorable gingival and osseous contours that will allow more efficient oral hygiene and periodontal maintenance. Two soft tissue resective procedures that have been employed in periodontal treatment for many years are gingivectomy and gingivoplasty.^{89, 105, 410} Both have been shown to be effective for reducing probing depths and contouring enlarged gingival tissues. However, these surgical techniques are limited to areas where only soft-tissue contours need to be addressed. They are not indicated when access to or modification of underlying bone contours is necessary.

As a result of the limitations of gingivectomy, use of mucogingival flaps became favored, and is more conducive to gaining access, pocket reduction and elimination of osseous defects. Resective mucogingival flaps described in the literature include apically positioned flaps with and without osseous re-contouring.^{119, 183, 288, 345} Studies have demonstrated that the effects of apically positioned flaps with and without osseous resection are predictable in terms of pocket reduction and long-term stability. In a systematic review of randomized controlled trials comparing surgical to non-surgical therapy, it was observed that surgical therapy consistently provided greater pocket depth reduction and clinical attachment gain at deeper sites (≥ 6 mm pocket depth) compared to non-surgical therapy.¹⁵⁴

Even back in the 1950s, it was a concern that deeper pockets might leave a nidus for re-infection. This was corroborated by more recent findings that periodontal pathogens such as *P. gingivalis* and spirochetes are more prevalent in deeper pockets,^{198, 272} and subjects with a higher prevalence of deeper pockets have a tendency to show greater disease progression over time.^{76, 258} Compared with non-surgical therapy, osseous resective and modified Widman surgical procedures result in a reduction of probing depths and clinical attachment gains for periods from one to 12 years.^{48, 187, 354}

When periodontal resective procedures are utilized in the treatment of Class II and III furcations, long-term success is uncertain. Treatment of furcated teeth is challenging. As a result, they are likely to lose more attachment than non-furcated teeth. Surgical techniques that have demonstrated long-term success in treatment of furcated teeth include root resection,^{143, 332} tooth hemisection and tunneling,^{143, 156} however, root caries is a frequently seen reason for failure. With the increased use of dental implants, these types of resective therapies are performed much less often.

Regenerative procedures

Regeneration, not repair, is the optimal treatment outcome for patients with significant bone and clinical attachment loss. However, obtaining predictable regeneration is challenging. An early surgical modality that resulted in periodontal regeneration was the use of bone grafts³⁴³ for treating periodontal infra-bony defects. Over the years, numerous grafting materials have been reported to have potential for true regeneration, including autogenous intra-oral and extra-oral grafts^{333, 344} and allografts (Fig. 7).^{159, 353} This property is due to their osteogenic, osteoinductive and osteoconductive properties. However, alloplastic grafting materials such as tricalcium phosphate,^{55, 371} porous¹⁹⁴⁻¹⁹⁶ and non-porous⁴²⁵⁻⁴²⁷ hydroxyapatite, xenografts and composites have been shown to have limited regenerative potential, and act mainly as a filler.⁹

Guided tissue regeneration and biological agents

The concept of selectively isolating the epithelium and gingival connective tissues by use of resorbable and non-resorbable barrier membranes^{56, 131, 132, 244, 312, 313, 372, 373} to allow re-population of cells from the periodontal ligament, cementum and bone²⁵⁹ has led to clinical techniques described as guided tissue regeneration. The literature suggests that when treating two- or three-wall osseous defects, as well as Class II furcations, clinical results are achieved using guided tissue regeneration that are more predictable and durable than simple access flap surgery.²⁶⁰ Systematic reviews have confirmed the

clinical benefits observed for bone grafting and/or guided tissue regeneration in both intra-bony defects and buccal Class II furcation involvements.^{277, 328} In addition, specific flap designs such as the modified papilla preservation technique⁸⁵ and the simplified papilla preservation technique in areas with narrow inter-dental papillae have improved regenerative results due to better flap adaptation, tension-free closure and wound stability post-surgically.^{86, 394} For technically demanding multi-tooth recession defects, use of a coronally positioned flap via a tunneling procedure is widespread.²¹ As for any surgical approach, intensive post-operative care influences the outcomes of these regenerative procedures.

Recent advances in understanding of the wound healing effects of growth factors and biological mediators,³¹¹ such as platelet-derived growth factor-BB, insulin-like growth factor,^{123, 241, 242, 341} enamel matrix derivative (e.g., Emdogain®),^{153, 350} and bone morphogenetic proteins on the periodontal tissues have given promise to the possibility of obtaining enhanced and predictable periodontal regeneration.⁴¹⁵ Studies utilizing growth factors and biological mediators have demonstrated significant improvement in clinical attachment and periodontal regeneration.^{68, 112, 279}

For confined (three-wall) intra-bony defects, there is robust evidence for the use of enamel matrix derivative in promoting tissue regeneration.⁴⁰⁰ From animal studies, it appears that there is little benefit of addition of bone grafting materials to enamel matrix derivative or use of a guided tissue regeneration membrane in such three-wall defects and class II furcation defects. However, as the number of bony walls decreases, there is evidence of superior regeneration when a combination of membrane and graft material is used to surgically repair the defect.³⁵¹ Much more research must be performed to assess the range of materials available and their most efficient and cost-effective application in various defect architectures.

A systematic review of studies on root conditioning during surgical exposure suggested that such treatment does not result in any significant improvement in periodontal regeneration, and provides little clinical advantage other than removal of a smear layer.²⁵²

Mucogingival procedures

A significant current focus is on improving oral-facial esthetics, creating an emphasis on mucogingival surgery to enhance the periodontal gingival complex. A more appropriate and contemporary term for such surgery is periodontal plastic surgery. Periodontal plastic surgery is designed to correct the dimensions and amount of gingival tissue in the esthetic zone, provide root coverage lost due to soft-tissue recession, preserve the bone height of an extraction socket, and perform ridge augmentation. A detailed history of these procedures is beyond the scope of this review, and readers are referred to a review on the development of periodontal plastic surgery.²⁶⁹

Supportive phase of treatment

Following completion of active periodontal therapy, it is essential that a periodontal maintenance schedule be established. Studies have shown that tooth loss in periodontal patients is related to the frequency and quality of their maintenance care.^{38, 420} In addition, periodontal surgical therapy may fail in patients who are seen at infrequent maintenance intervals.^{103, 287} A recent systematic review confirmed that patients who are seen at regular intervals for supportive periodontal therapy experience less attachment loss and lose fewer teeth.¹²² Therefore, it is very important for each periodontal patient to receive comprehensive periodontal maintenance treatment at appropriate intervals after active periodontal therapy as outlined in [Table 5](#) and [Fig. 6](#). The periodontal disease status should be evaluated and communicated to the patient using the same multi-pronged approach to re-assessment as used after active treatment ([Table 6](#)). Intervals between periodontal maintenance visits should range from 2–

6 months depending on the patient's disease phenotype and history, among other things. Shorter intervals decrease the likelihood of progression of the disease.⁸¹

Concluding remarks

Periodontal diseases are arguably among the most ancient and common infectious diseases affecting humans, leading to permanent destruction of the supporting structures of the dentition and ultimately tooth loss. It has been established that dental biofilm ("plaque"), consisting of many microbial species and their products, is an etiological agent of periodontal disease. It is widely accepted that immunological and inflammatory responses to dental plaque via host-parasite interaction are manifested by clinical signs and symptoms of periodontal diseases. The outcome of this interaction can be modulated by other components known as risk factors (modifiers), either inherent (genetic) or acquired (environmental) in nature, significantly affecting the initiation and progression of periodontal diseases of different types. While definitive genetic factors responsible for either susceptibility or resistance to periodontal diseases await definitive identification and verification, a small number of environmental factors affecting the pathogenesis of periodontal diseases have been described. They include, among others, smoking, diabetes, medication, and nutrition.

Currently, periodontal diseases are classified based upon clinically observed disease traits using radiographs and clinical examination: gingivitis; chronic periodontitis; aggressive periodontitis; periodontitis as manifestation of systemic diseases; necrotizing ulcerative periodontitis; abscesses of the periodontium; periodontitis associated with endodontic lesions; and developmental or acquired deformities and conditions. Advances in genomics, molecular science, and personalized medicine may result in guidelines for unambiguous disease definition and diagnosis in the future (Fig. 8). Recent studies have implied that periodontal diseases and several systemic conditions, such as diabetes, cardiovascular disease, and pre-term delivery are interconnected, although concrete relationships still await to be ascertained. Therefore, by answering critical questions about the physiology of host-parasite interactions in periodontal diseases, scientists may be able to generate new information regarding the pathogenesis of systemic medical disorders, and vice versa.



Figure 8. Example of a case of periodontal disease that is not captured by the current classification system. (Top) Intra-oral photographs of a 52-year-old Caucasian male who presented with a low plaque index (10%), low full-mouth bleeding on probing index (<5%), and a lifelong history of hard-bristle toothbrush use. There was no history of scaling and root planing or surgical debridement, and only recent free soft-tissue grafts on teeth 22 and 27 for recession coverage. The overly aggressive hygiene probably accounted for some recession and abrasion. (Bottom) Significant generalized horizontal bone loss is seen in the radiographs. Its etiology is unknown. This may represent a non-inflammatory destructive periodontal disease phenotype³⁰⁰ modified by traumatic toothbrush abrasion.

The therapeutic efforts for controlling periodontal diseases focus on the removal of dental biofilm from the affected lesion, as active treatment centers on non-surgical mechanical debridement with antimicrobial and sometimes anti-inflammatory adjuncts. The surgical therapy aims at gaining access to the lesion and correcting unfavorable gingival/osseous contours to achieve a periodontal architecture that will provide for more efficient oral hygiene and periodontal maintenance. In addition, recent advances in tissue engineering have provided an efficient means to regenerate/repair periodontal defects, based upon principles of guided tissue regeneration and utilization of growth factors/biologic mediators. To maintain periodontal stability, these therapies must be supplemented by a long-term maintenance program (supportive periodontal therapy).

References

- 1 American Academy of Periodontology. Committee Report and Discussion. The Etiology of Periodontal Disease. In: *World Workshop in Periodontics (Proceedings)*. Chicago, IL: American Academy of Periodontology, 1966: 167–177.
- 2 American Academy of Periodontology. Consensus Report. In: Nevins M, Becker W, Kornman K, editors. *Proceedings of the World Workshop in Clinical Periodontics*. Chicago, IL: American Academy of Periodontology. 1989:1/23–1/24
- 3 American Academy of Periodontology. Position paper. Supportive periodontal therapy (SPT). *J Periodontol* 1998; **69**: 502–506.
- 4 American Academy of Periodontology. Consensus report. Necrotizing periodontal diseases. *Ann Periodontol* 1999; **4**: 78.
- 5 American Academy of Periodontology. Parameters of care. Parameter on occlusal traumatism in patients with chronic periodontitis. *J Periodontol* 2000; **71**: 873–875.
- 6 American Academy of Periodontology. *Glossary of Periodontal Terms*, 4th edition. Chicago, IL: American Academy of Periodontology, 2001.
- 7 American Academy of Periodontology. Academy report/Informational paper. Drug-associated gingival enlargement. *J Periodontol* 2004; **75**: 1424–1431.
- 8 American Academy of Periodontology. Position paper. Systemic antibiotics in periodontics. *J Periodontol* 2004; **75**: 1553–1565.
- 9 American Academy of Periodontology. Position paper. Periodontal regeneration. *J Periodontol* 2005; **76**: 1601–1622.
- 10 American Academy of Periodontology. Academy report. Implications of genetic technology for the management of periodontal diseases. *J Periodontol* 2005; **76**: 850–857.
- 11 American Academy of Periodontology. Local delivery of sustained or controlled release antimicrobials as adjunctive therapy for the treatment of periodontitis. *J Periodontol* 2006; **77**: 1458.
- 12 Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol* 2005; **43**: 5721–5732.
- 13 Africa CW, Parker JR, Reddy J. Bacteriological studies of subgingival plaque in a periodontitis-resistant population. *J Periodontal Res* 1985; **20**: 1–7.
- 14 Agrawal S, Agrawal A, Doughty B, Gerwitz A, Blenis J, van Dyke T, Pulendran B. Cutting edge: different Toll-like receptor agonists instruct dendritic cells to induce distinct Th responses via differential modulation of extracellular signal-regulated kinase-mitogen-activated protein kinase and c-Fos. *J Immunol* 2003; **171**: 4984–4989.
- 15 Albandar JM, Baghdady VS, Ghose LJ. Periodontal disease progression in teenagers with no preventive dental care provisions. *J Clin Periodontol* 1991; **18**: 341–345.
- 16 Albandar JM, Brown LJ, Löe H. Clinical features of early-onset periodontitis. *J Am Dent Assoc* 1997; **128**: 1393–1399.
- 17 Albandar JM, Streckfus CF, Adesanya MR, Winn DM. Cigar, pipe, and cigarette smoking as risk factors for periodontal disease and tooth loss. *J Periodontol* 2000; **71**: 1874–1881.
- 18 Albandar JM, Muranga MB, Rams TE. Prevalence of aggressive periodontitis in school attendees in Uganda. *J Clin Periodontol* 2002; **29**: 823–831.
- 19 Albandar JM, Rams TE. Global epidemiology of periodontal diseases: an overview. *Periodontol 2000* 2002; **29**: 7–245.
- 20 Albandar JM, Tinoco EMB. Global epidemiology of periodontal diseases in children and young persons. *Periodontol 2000* 2002; **29**: 153–176.
- 21 Allen EP, Miller PD Jr. Coronal positioning of existing gingiva: short-term results in treatment of shallow marginal tissue recession. *J Periodontol* 1989; **60**: 316–319.

- 22 Ambrosini P, Miller N, Briançon S, Gallina S, Penaud J. Clinical and microbiological evaluation of the effectiveness of the Nd:Yap laser for the initial treatment of adult periodontitis. A randomized controlled study. *J Clin Periodontol* 2005; **32**: 670–676.
- 23 Andersen R, Loebel N, Hammond D, Wilson M. Treatment of periodontal disease by photodisinfection compared to scaling and root planing. *J Clin Dent* 2007; **18**: 34–38.
- 24 Andia DC, Martins AG, Casati MZ, Sallum EA, Nociti FH. Root coverage outcome may be affected by heavy smoking: a 2-year follow-up study. *J Periodontol* 2008; **79**: 647–653.
- 25 Apatzidou DA, Kinane DF. Quadrant root planing versus same-day full-mouth root planing. I. Clinical findings. *J Clin Periodontol* 2004; **31**: 132–140.
- 26 Apatzidou DA, Riggio MP, Kinane DF. Quadrant root planing versus same-day full-mouth root planing. II. Microbiological findings. *J Clin Periodontol* 2004; **31**: 141–148.
- 27 Aranki A, Syed SA, Kenney EB, Freter R. Isolation of anaerobic bacteria from human gingival and mouse cecum by means of a simplified glove box procedure. *Appl Microbiol* 1969; **17**: 568–576.
- 28 Arendorf TM, Bredekamp B, Cloete CA, Joshipura K. Seasonal variation of acute necrotizing ulcerative gingivitis in South Africans. *Oral Dis* 2001; **7**: 150–154.
- 29 Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol* 1999; **4**: 1–6.
- 30 Armitage GC. Classifying periodontal diseases – a long-standing dilemma. *Periodontol 2000* 2002; **30**: 9–23.
- 31 Arno A, Schei O, Lövdal A, Waerhaug J. Alveolar bone loss as a function of tobacco consumption. *Acta Odontol Scand* 1959; **17**: 3–8.
- 32 Attström R, van der Velden U. Consensus report (epidemiology). In: Lang NP, Karring T, editors. *Proceedings of the 1st European Workshop on Periodontics, 1993*. London: Quintessence Publishing Co. Inc., 1994: 120–126.
- 33 Axelsson P, Lindhe J. Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. *J Clin Periodontol* 1978; **5**: 239–248.
- 34 Axelsson P, Lindhe J. Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. Results after six years. *J Clin Periodontol* 1981; **8**: 133–151.
- 35 Axelsson P, Lindhe J, Nyström B. On the prevention of caries and periodontal disease. Results of a 15-year longitudinal study in adults. *J Clin Periodontol* 1991; **18**: 182–189.
- 36 Axelsson P, Paulander J, Lindhe J. Relationship between smoking and dental status in 35-, 50-, 65-, and 75-year-old individuals. *J Clin Periodontol* 1998; **25**: 297–305.
- 37 Axelsson P, Albandar JM, Rams TE. Prevention and control of periodontal diseases in developing and industrialized nations. *Periodontol 2000* 2002; **29**: 235–246.
- 38 Axelsson P, Nyström B, Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. *J Clin Periodontol* 2004; **31**: 749–757.
- 39 Badersten A, Nilvéus R, Egelberg J. Effect of nonsurgical periodontal therapy. I. Moderately advanced periodontitis. *J Clin Periodontol* 1981; **8**: 57–72.
- 40 Badersten A, Nilvéus R, Egelberg J. Effect of nonsurgical periodontal therapy. II. Severely advanced periodontitis. *J Clin Periodontol* 1984; **11**: 63–76.
- 41 Badersten A, Nilvéus R, Egelberg J. Scores of plaque, bleeding, suppuration and probing depth to predict probing attachment loss. 5 years of observation following nonsurgical periodontal therapy. *J Clin Periodontol* 1990; **17**: 102–107.
- 42 Baehni P, Tsai CC, McArthur WP, Hammond BF, Taichman NS. Interaction of inflammatory cells and oral microorganisms. VIII. Detection of leukotoxic activity of a plaque-derived gram-negative microorganism. *Infect Immun* 1979; **24**: 233–243.
- 43 Baelum V, Scheutz F. Periodontal diseases in Africa. *Periodontol 2000* 2002; **29**: 79–103.

- 44 Baelum V, Lopez R. Defining and classifying periodontitis: need for a paradigm shift? *Eur J Oral Sci* 2003; **111**: 2–6.
- 45 Baer PN. The case for periodontosis as a clinical entity. *J Periodontol* 1971; **42**: 516–520.
- 46 Barbour SE, Nakashima K, Zhang JB, Tangada S, Hahn CL, Schenkein HA, Tew JG. Tobacco and smoking: environmental factors that modify the host response (immune system) and have an impact on periodontal health. *Crit Rev Oral Biol Med* 1997; **8**: 437–460.
- 47 Bassler BL. How bacteria talk to each other: regulation of gene expression by quorum sensing. *Curr Opin Microbiol* 1999; **2**: 582–587.
- 48 Becker W, Becker BE, Ochsenein C, Kerry G, Caffesse R, Morrison EC, Prichard J. A longitudinal study comparing scaling, osseous surgery and modified Widman procedures after one year. *J Periodontol* 1988; **59**: 351–365.
- 49 Bergström J. Tobacco smoking and chronic destructive periodontal disease. *Odontology* 2004; **92**: 1–8.
- 50 Beuchat M, Busslinger A, Schmidlin PR, Michel B, Lehmann B, Lutz F. Clinical comparison of the effectiveness of novel sonic instruments and curettes for periodontal debridement after 2 months. *J Clin Periodontol* 2001; **28**: 1145–1150.
- 51 Billings F. Chronic focal infections and their etiologic relations to arthritis and nephritis. *Arch Intern Med* 1912; **9**: 484–498.
- 52 Bonito AJ, Lux L, Lohr KN. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. *J Periodontol* 2005; **76**: 1227–1236.
- 53 Borrell LN, Burt BA, Taylor GW. Prevalence and trends in periodontitis in the USA: from the NHANES III to the NHANES, 1988 to 2000. *J Dent Res* 2005; **84**: 924–930.
- 54 Bostanci N, Ilgenli T, Emingil G, Afacan B, Han B, Toz H, Atilla G, Hughes FJ, Belibasakis GN. Gingival crevicular fluid levels of RANKL & OPG in periodontal diseases: implications of their relative ratio. *J Clin Periodontol* 2007; **34**: 370–376.
- 55 Bowers GM, Vargo JW, Levy B, Emerson JR, Bergquist JJ. Histologic observations following the placement of tricalcium phosphate implants in human intrabony defects. *J Periodontol* 1986; **57**: 286–287.
- 56 Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, Stevens M, Romberg E. Histologic evaluation of new attachment apparatus formation in humans. Part I. *J Periodontol* 1989; **60**: 664–674.
- 57 Brayer WK, Mellonig JT, Dunlap RM, Marinak KW, Carson RE. Scaling and root planing effectiveness: the effect of root surface access and operator experience. *J Periodontol* 1989; **60**: 67–72.
- 58 Brett PM, Zygogianni P, Griffiths GS, Tomaz M, Parkar M, D’Aiuto F, Tonetti M. Functional gene polymorphisms in aggressive and chronic periodontitis. *J Dent Res* 2005; **84**: 1149–1153.
- 59 Brewer JH, Allgeier DL. A safe self-contained carbon dioxide-hydrogen anaerobic system. *Appl Microbiol* 1966; **14**: 985–988.
- 60 Brill N. Influence of capillary permeability on flow of tissue fluid into gingival pockets. *Acta Odontol Scand* 1959; **17**: 23–33.
- 61 Buchanan SA, Robertson PB. Calculus removal by scaling/root planing with and without surgical access. *J Periodontol* 1987; **58**: 159–163.
- 62 Caffesse RG, Sweeney PL, Smith BA. Scaling and root planing with and without periodontal flap surgery. *J Clin Periodontol* 1986; **13**: 205–210.
- 63 Carranza F. Microbiology. In: Carranza F, Shklar G, editors. *History of Periodontology*. Chicago, IL: Quintessence Publishing Co. Inc., 2003: 80–91.
- 64 Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, Massaro JM, Polson AM, Thomas J, Walker C. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol* 2000; **71**: 521–532.

- 65 Cecil RL, Angevine DM. Clinical and experimental observations on focal infections with an analysis of 200 cases of rheumatoid arthritis. *Ann Intern Med* 1938; **12**: 577–584.
- 66 Centers for Disease Control and Prevention. *National Diabetes Fact Sheet*. Atlanta, GA: Centers for Disease Control and Prevention, 2005.
- 67 Cercek JF, Kiger RD, Garrett S, Egelberg J. Relative effects of plaque control and instrumentation on the clinical parameters of human periodontal disease. *J Clin Periodontol* 1983; **10**: 46–56.
- 68 Chambrone L, Sukekava F, Araujo MG, Pustiglioni FE, Chambrone LA, Lima LA. Root coverage procedures for the treatment of localised recession-type defects. *Cochrane Database Syst Rev* 2009; DOI: [0.1002/4651858.CD007161.pub2](https://doi.org/10.1002/4651858.CD007161.pub2).
- 69 Chapple ILC, Milward MR, Dietrich T. The prevalence of inflammatory periodontitis is negatively associated with serum antioxidant concentrations. *J Nutr* 2006; **137**: 657–664.
- 70 Chapple ILC. Potential mechanisms underpinning the nutritional modulation of periodontal inflammation. *J Am Dent Assoc* 2009; **140**: 178–184.
- 71 Choi BK, Paster BJ, Dewhirst FE, Göbel UB. Diversity of cultivable and uncultivable oral spirochetes from a patient with severe destructive periodontitis. *Infect Immun* 1994; **62**: 1889–1895.
- 72 Christou V, Timmerman MF, van der Velden U, van der Weijden FA. Comparison of different approaches of interdental oral hygiene: interdental brushes versus dental floss. *J Periodontol* 1998; **69**: 759–764.
- 73 Chung WO, Dommisch H, Yin L, Dale BA. Expression of defensins in gingival and their role in periodontal health and disease. *Curr Pharm Des* 2007; **13**: 3073–3083.
- 74 Cianciola LJ, Genco RJ, Patters MR, McKenna J, van Oss CJ. Defective polymorphonuclear leukocyte function in a human periodontal disease. *Nature* 1977; **265**: 445–447.
- 75 Claffey N, Nylund K, Kiger R, Garrett S, Egelberg J. Diagnostic predictability of scores of plaque, bleeding, suppuration and probing depth for probing attachment loss. 3½ years of observation following initial periodontal therapy. *J Clin Periodontol* 1990; **17**: 108–114.
- 76 Claffey N, Egelberg J. Clinical indicators of probing attachment loss following initial periodontal treatment in advanced periodontitis patients. *J Clin Periodontol* 1995; **22**: 690–696.
- 77 Clark RA, Page RC, Wilde G. Defective neutrophil chemotaxis in juvenile periodontitis. *Infect Immun* 1977; **18**: 694–700.
- 78 Clarridge JE III. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. *Clin Microbiol Rev* 2004; **17**: 840–862.
- 79 Clementini M, Vittorini G, Crea A, Gualano MR, Macrì LA, La Torre G. Efficacy of AZM therapy in patients with gingival overgrowth induced by cyclosporine A: a systematic review. *BMC Oral Health* 2008; **8**: 34–40.
- 80 Cobb CM. Lasers in periodontics: a review of the literature. *J Periodontol* 2006; **77**: 545–564.
- 81 Cohen RE, on behalf of the Research, Science and Therapy Committee, American Academy of Periodontology. Position paper: periodontal maintenance. *J Periodontol* 2003; **74**: 1395–1401.
- 82 Collet-Schaub D. The prevalence of acute necrotizing ulcerative gingivitis in Swiss military collectives. *Schweiz Monatsschr Zahnmed* 2000; **110**: 538–541.
- 83 Corbet EF, Zee KY, Lo ECM. Periodontal diseases in Asia and Oceania. *Periodontol 2000* 2002; **29**: 122–152.
- 84 Corey LA, Nance WE, Hofstede P, Schenkein HA. Self-reported periodontal disease in a Virginia twin population. *J Periodontol* 1993; **64**: 1205–1208.
- 85 Cortellini P, Prato GP, Tonetti MS. The modified papilla preservation technique. A new surgical approach for interproximal regenerative procedures. *J Periodontol* 1995; **66**: 261–266.
- 86 Cortellini P, Prato GP, Tonetti MS. The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. *Int J Periodontics Restorative Dent* 1999; **19**: 589–599.

- 87 Cosyn J, Sabzevar MM. A systematic review on the effects of subgingival chlorhexidine gel administration in the treatment of chronic periodontitis. *J Periodontol* 2005; **76**: 1805–1813.
- 88 Cosyn J, Wyn I. A systematic review on the effects of the chlorhexidine chip when used as an adjunct to scaling and root planing in the treatment of chronic periodontitis. *J Periodontol* 2006; **77**: 257–264.
- 89 Crane AB, Kaplan H. The technique and results of surgical pyorrhea treatment. *Dental Digest* 1932; **38**: 3.
- 90 Crespi RP, Capparè P, Toscanelli I, Gherlone E, Romanos GE. Effects of Er:YAG laser compared to ultrasonic scaler in periodontal treatment: a 2-year follow-up split-mouth clinical study. *J Periodontol* 2007; **78**: 1195–1200.
- 91 Czarnetzki A, Jakob T, Pusch CM. Palaeopathological and variant conditions of the *Homo heidelbergensis* type specimen (Mauer, Germany). *J Hum Evol* 2003; **44**: 479–495.
- 92 D’Aiuto F, Parkar M, Tonetti MS. Acute effects of periodontal therapy on bio-markers of vascular health. *J Clin Periodontol* 2007; **34**: 124–129.
- 93 Dale BA, Fredericks LP. Antimicrobial peptides in the oral environment: expression and function in health and disease. *Curr Issues Mol Biol* 2005; **7**: 119–134.
- 94 Darré L, Vergnes JN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycemic control in diabetic patients: a meta-analysis of interventional studies. *Diabetes Metab* 2008; **34**: 497–506.
- 95 Dasanayake AP. Poor periodontal health of the pregnant woman as a risk factor for low birth weight. *Ann Periodontol* 1998; **3**: 206–212.
- 96 Davé S, Van Dyke TE. The link between periodontal disease and cardiovascular disease is probably inflammation. *Oral Dis* 2008; **14**: 95–101.
- 97 de Almeida JM, Theodoro LH, Bosco AF, Nagata MJ, Oshiiwa M, Garcia VG. *In vivo* effect of photodynamic therapy on periodontal bone loss in dental furcations. *J Periodontol* 2008; **79**: 1081–1088.
- 98 De Iudicibus S, Castronovo G, Gigante A, Stocco G, Decorti G, Di Lenarda R, Bartoli F. Role of *MDR1* gene polymorphisms in gingival overgrowth induced by cyclosporine in transplant patients. *J Periodontol Res* 2008; **43**: 665–672.
- 99 De Lissovoy G, Rentz AM, Dukes EM, Eaton CA, Jeffcoat MK, Killoy WJ, Finkelman RD. The cost-effectiveness of a new chlorhexidine delivery system in the treatment of adult periodontitis. *J Am Dent Assoc* 1999; **130**: 855–862.
- 100 Dentino AR, Kassab MM, Renner EJ. Prevention of periodontal diseases. *Dent Clin North Am* 2005; **49**: 573–594.
- 101 DeRouen TA, Hujoel PP, Mancl LA. Concise review: statistical issues in periodontal research. *J Dent Res* 1995; **74**: 1731–1737.
- 102 De Stefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ* 1993; **306**: 688–691.
- 103 DeVore CH, Duckworth JE, Beck FM, Hicks MJ, Brumfield FW, Horton JE. Bone loss following periodontal therapy in subjects without frequent periodontal maintenance. *J Periodontol* 1986; **57**: 354–359.
- 104 Dolan TA, McGorray SP, Grinstead-Skigen CL, Mecklenburg R. Tobacco control activities in U.S. dental practices. *J Am Dent Assoc* 1997; **128**: 1669–1679.
- 105 Donnenfeld OW, Glickman I. A biometric study of the effects of gingivectomy. *J Periodontol* 1966; **37**: 447–452.
- 106 Dragoo MR. A clinical evaluation of hand and ultrasonic instruments on subgingival debridement. 1. With unmodified and modified ultrasonic inserts. *Int J Periodontics Restorative Dent* 1992; **12**: 310–323.

- 107 Drisko CL, Cobb CM, Killoy WJ, Michalowicz BS, Pihlstrom BL, Lowenguth EA, Caton JG, Encarnación M, Knowles M, Goodson JM. Evaluation of periodontal treatments using controlled-release tetracycline fibers: clinical response. *J Periodontol* 1995; **66**: 692–699.
- 108 Egelberg J. Permeability of the dento-gingival blood vessels. I. Application of the vascular labeling method and gingival fluid measurement. *J Periodontol Res* 1966; **1**: 180–191.
- 109 Eickholz P, Kim TS, Bürklin T, Schacher B, Renggli HH, Schaecken MT, Holle R, Kübler A, Ratka-Krüger P. Non-surgical periodontal therapy with adjunctive topical doxycycline: a double-blind randomized controlled multicenter study. *J Clin Periodontol* 2002; **29**: 108–117.
- 110 Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. *J Periodontol* 1991; **62**: 123–131.
- 111 Erley KJ, Swiec GD, Herold R, Bisch FC, Peacock ME. Gingival recession treatment with connective tissue grafts in smokers and non-smokers. *J Periodontol* 2006; **77**: 1148–1155.
- 112 Esposito M, Grusovin MG, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. *Cochrane Database Syst Rev* 2005; DOI: [10.1002/14651858.CD003875.pub3](https://doi.org/10.1002/14651858.CD003875.pub3).
- 113 Fauchard P. *Le Chirurgien Dentiste ou Traité Des Dents*, Pierre-Jean Mariette, Paris, Volume I, 2nd edition, 1746: 105–117.
- 114 Ferreira SB Jr, Trombone AP, Repeke CE, Cardoso CR, Martins W Jr, Santos CF, Trevilatto PC, Avila-Campos MJ, Campanelli AP, Silva JS, Garlet GP. An interleukin-1 β (IL-1 β) single-nucleotide polymorphism at position 3954 and red complex periodontopathogens independently and additively modulate the levels of IL-1 β in diseased periodontal tissues. *Infect Immun* 2008; **76**: 3725–3734.
- 115 Fine DH, Kaplan JB, Kachlany SC, Schreiner HC. How we got attached to *Actinobacillus actinomycetemcomitans*: a model for infectious diseases. *Periodontol 2000* 2006; **42**: 114–157.
- 116 Fleischer HC, Mellonig JT, Brayer WK, Gray JL, Barnett JD. Scaling and root planing efficacy in multirrooted teeth. *J Periodontol* 1989; **60**: 402–409.
- 117 Flemmig TF. Periodontitis. *Ann Periodontol* 1999; **4**: 32–37.
- 118 Fourrier F, Duvivier B, Boutigny H, Roussel-Delvallez M, Chopin C. Colonization of the dental plaque: a source of nosocomial infections in intensive care unit patients. *Crit Care Med* 1998; **26**: 301–308.
- 119 Friedman N. Periodontal osseous surgery: osteoplasty and osteoectomy. *J Periodontol* 1955; **26**: 257–259.
- 120 Galicia JC, Tai H, Komatsu Y, Shimada Y, Ikezawa I, Yoshie H. Interleukin-6 receptor gene polymorphisms and periodontitis in a non-smoking Japanese population. *J Clin Periodontol* 2006; **33**: 704–709.
- 121 Gasche C. Review article: the chemoprevention of colorectal carcinoma. *Aliment Pharmacol Ther* 2004; **20**(Suppl.): 31–35.
- 122 Gaunt F, Devine M, Pennington M, Vernazza C, Gwynnett E, Steen N, Heasman P. The cost-effectiveness of supportive periodontal care for patients with chronic periodontitis. *J Clin Periodontol* 2008; **35**: 67–82.
- 123 Giannobile WV, Finkelman RD, Lynch SE. Comparison of canine and non-human primate animal models for periodontal regenerative therapy: results following a single administration of PDGF/IGF-1. *J Periodontol* 1994; **65**: 1158–1168.
- 124 Giannobile WV. Host-response therapeutics for periodontal diseases. *J Periodontol* 2008; **79**(Suppl.): 1592–1600.
- 125 Glick M, Abel SN, Muzyka BC, DeLorenzo M. Dental complications after treating patients with AIDS. *J Am Dent Assoc* 1994; **125**: 296–301.

- 126 Glickman I. Acute vitamin C deficiency and periodontal disease. I. The periodontal tissues of the guinea pig in acute vitamin C deficiency. *J Dent Res* 1948; **27**: 9–23.
- 127 Gold SI. Periodontics. The past. Part (I). Early sources. *J Clin Periodontol* 1985; **12**: 79–97.
- 128 Gold SI. Periodontics. The past. Part (II). The development of modern periodontics. *J Clin Periodontol* 1985; **12**: 171–189.
- 129 Golub LM, Lee HM, Lehrer G, Nemiroff A, McNamara TF, Kaplan R, Ramamurthy NS. Minocycline reduces gingival collagenolytic activity during diabetes. Preliminary observations and a proposed new mechanism of action. *J Periodontol Res* 1983; **18**: 516–526.
- 130 Gore EA, Sanders JJ, Pandey JP, Palesch Y, Galbraith GM. Interleukin-1 β ⁺³⁹⁵³ allele 2: association with disease status in adult periodontitis. *J Clin Periodontol* 1998; **25**: 781–785.
- 131 Gottlow J, Nyman S, Karring T, Lindhe J. New attachment formation as the result of controlled tissue regeneration. *J Clin Periodontol* 1984; **11**: 494–503.
- 132 Gottlow J, Nyman S, Lindhe J, Karring T, Wennström J. New attachment formation in the human periodontium by guided tissue regeneration. Case reports. *J Clin Periodontol* 1986; **13**: 604–616.
- 133 Greenstein G. Efficacy of subantimicrobial-dose doxycycline in the treatment of periodontal diseases: a critical evaluation. *Int J Periodontics Restorative Dent* 2004; **24**: 528–543.
- 134 Griffiths GS. Formation, collection and significance of gingival crevice fluid. *Periodontol 2000* 2003; **31**: 32–42.
- 135 Grob GN. The rise and decline of tonsillectomy in twentieth-century America. *J Hist Med Allied Sci* 2007; **62**: 383–421.
- 136 Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, Zambon JJ, Hausmann E. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol* 1995; **66**: 23–29.
- 137 Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. *J Periodontol* 1997; **68**: 713–719.
- 138 Grossi SG, Zambon J, Machtei EE, Schifferle R, Andreana S, Genco RJ, Cummins D, Harrap G. Effects of smoking cessation on healing after mechanical periodontal therapy. *J Am Dent Assoc* 1997; **128**: 599–607.
- 139 Guerini V. *A History of Dentistry from the Most Ancient Times until the End of the Eighteenth Century*. Philadelphia/New York: Lea & Febiger, 1929: 19–31.
- 140 Gürsoy M, Pajukanta R, Sorsa T, Könönen E. Clinical changes in periodontium during pregnancy and post-partum. *J Clin Periodontol* 2008; **35**: 576–583.
- 141 Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontal therapy. A systematic review. *Ann Periodontol* 2003; **8**: 115–181.
- 142 Haffajee AD, Torresyap G, Socransky SS. Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results. *J Clin Periodontol* 2007; **34**: 243–253.
- 143 Hamp SE, Nyman S, Lindhe J. Periodontal treatment of multirrooted teeth. Results after 5 years. *J Clin Periodontol* 1975; **2**: 126–135.
- 144 Hanes PJ, Purvis JP. Local anti-infective therapy: pharmacological agents. A systematic review. *Ann Periodontol* 2003; **8**: 79–98.
- 145 Hart TC, Atkinson JC. Mendelian forms of periodontitis. *Periodontol 2000* 2007; **45**: 95–112.
- 146 Haslam DW, James WPT. Obesity. *Lancet* 2005; **366**: 1197–1209.
- 147 Hassell TM, Hefti AF. Drug-induced gingival overgrowth: old problem, new problem. *Crit Rev Oral Biol Med* 1991; **2**: 103–137.
- 148 Hasturk H, Kantarci A, Ohira T, Arita M, Ebrahimi N, Chiang N, Petasis NA, Levy BD, Serhan CN, van Dyke TE. RvE1 protects from local inflammation and osteoclast-mediated bone destruction in periodontitis. *FASEB J* 2006; **20**: 401–403.

- 149 Haubek D, Ennibi OK, Poulsen K, Poulsen S, Benzarti N, Kilian M. Early-onset periodontitis in Morocco is associated with the highly leukotoxic clone of *Actinobacillus actinomycetemcomitans*. *J Dent Res* 2001; **80**: 1580–1583.
- 150 Haubek D, Ennibi OK, Poulsen K, Vaeth M, Poulsen S, Kilian M. Risk of aggressive periodontitis in adolescent carriers of the JP2 clone of *Aggregatibacter (Actinobacillus) actinomycetemcomitans* in Morocco: a prospective longitudinal cohort study. *Lancet* 2008; **371**: 237–242.
- 151 Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *J Am Med Assoc* 2004; **291**: 2847–2850.
- 152 Hefti AF, Eshenaur AE, Hassell TM, Stone C. Gingival overgrowth in cyclosporine A-treated multiple sclerosis patients. *J Periodontol* 1994; **65**: 744–749.
- 153 Heijl L, Heden G, Svärdröm G, Ostgren A. Enamel matrix derivative (Emdogain) in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997; **24**: 705–714.
- 154 Heitz-Mayfield LJ, Trombelli L, Heitz F, Needleman I, Moles D. A systematic review of the effect of surgical debridement vs non-surgical debridement for the treatment of chronic periodontitis. *J Clin Periodontol* 2002; **29**(Suppl.): 92–102.
- 155 Heitz-Mayfield LJ. Disease progression: identification of high-risk groups and individuals for periodontitis. *J Clin Periodontol* 2005; **32**: 196–209.
- 156 Helldén LB, Elliot A, Steffensen B, Steffensen JE. The prognosis of tunnel preparations in treatment of class III furcations. A follow-up study. *J Periodontol* 1989; **60**: 182–187.
- 157 Henderson B, Nair SP, Ward JM, Wilson M. Molecular pathogenicity of the oral opportunistic pathogen *Actinobacillus actinomycetemcomitans*. *Annu Rev Microbiol* 2003; **57**: 29–55.
- 158 Henke CJ, Villa KF, Aichelmann-Reidy ME, Armitage GC, Eber RM, Genco RJ, Killooy WJ, Miller DP, Page RC, Polson AM, Ryder MI, Silva SJ, Somerman MJ, Van Dyke TE, Wolff LF, Evans CJ, Finkelman RD. An economic evaluation of a chlorhexidine chip for treating chronic periodontitis: the CHIP (chlorhexidine in periodontitis) study. *J Am Dent Assoc* 2001; **132**: 1557–1569.
- 159 Hiatt WH, Schallhorn RG. Intraoral transplants of cancellous bone and marrow in periodontal lesions. *J Periodontol* 1973; **44**: 194–208.
- 160 Higashi MK, Veenstra DL, del Aguila M, Hujoel P. The cost-effectiveness of interleukin-1 genetic testing for periodontal disease. *J Periodontol* 2002; **73**: 1474–1484.
- 161 Hinrichs JE, Wolff LF, Pihlstrom BL, Schaffer EM, Liljemark WF, Bandt CL. Effects of scaling and root planing on subgingival microbial proportions standardized in terms of their naturally occurring distribution. *J Periodontol* 1985; **56**: 187–194.
- 162 Hirschfeld L, Wasserman B. A long-term survey of tooth loss in 600 treated periodontal patients. *J Periodontol* 1978; **49**: 225–237.
- 163 Holm G. Smoking as an additional risk for tooth loss. *J Periodontol* 1994; **65**: 996–1001.
- 164 Holman WL. Focal infection and ‘elective localization’. *Arch Pathol Lab Med* 1928; **5**: 68–136.
- 165 Holt SC, Kesavalu L, Walker S, Genco CA. Virulence factors of *Porphyromonas gingivalis*. *Periodontol 2000* 1999; **20**: 168–238.
- 166 Holt SC, Ebersole JL. *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*: the ‘red complex’, a prototype polybacterial pathogenic consortium in periodontitis. *Periodontol 2000* 2005; **38**: 72–122.
- 167 Hornef MW, Wick MJ, Rhen M, Normark S. Bacterial strategies for overcoming host innate and adaptive immune responses. *Nat Immunol* 2002; **3**: 1033–1040.
- 168 Hugoson A. Gingival inflammation and female sex hormones. A clinical investigation of pregnant women and experimental studies in dogs. *J Periodontal Res* 1970; **5**(Suppl.): 1–18.

- 169 Hugoson A, Sjödin B, Norderyd O. Trends over 30 years, 1973–2003, in the prevalence and severity of periodontal disease. *J Clin Periodontol* 2008; **35**: 405–414.
- 170 Hujoel PP, DeRouen TA. Validity issues in split-mouth trials. *J Clin Periodontol* 1992; **19**: 625–627.
- 171 Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *J Am Med Assoc* 2000; **284**: 1406–1410.
- 172 Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Examining the link between coronary heart disease and the elimination of chronic dental infections. *J Am Dent Assoc* 2001; **132**: 883–889.
- 173 Hujoel PP, White BA, Garcia RI, Listgarten MA. The dentogingival epithelial surface area revisited. *J Periodontol Res* 2001; **36**: 48–55.
- 174 Hujoel PP. Does chronic periodontitis cause coronary heart disease? A review of the literature. *J Am Dent Assoc* 2002; **133**: 315–365.
- 175 Hujoel PP, Cunha-Cruz J, Selipsky H, Saver BG. Abnormal pocket depth and gingival recession as distinct phenotypes. *Periodontol 2000* 2005; **39**: 22–29.
- 176 Hunter J. In: *A Practical Treatise on the Diseases of the Teeth; intended as a supplement to the Natural History of Those Parts. Chapter III. Of the Diseases of the Gums, and the Consequences of them*. London: J. Johnson, 1778, 55–58.
- 177 Inagaki S, Onishi S, Kuramitsu H, Sharma A. *Porphyromonas gingivalis* vesicles enhance attachment, and the leucine-rich repeat BspA protein is required for the invasion of epithelial cells by 'Tannerella forsythia'. *Infect Immun* 2006; **74**: 5023–5028.
- 178 Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA. Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. *J Dent Res* 2005; **84**: 1154–1159.
- 179 Jeffcoat MK, Bray KS, Ciancio SG, Dentino AR, Fine DH, Gordon JM, Gunsolley JC, Killoy WJ, Lowenguth RA, Magnusson NI, Offenbacher S, Palcanis KG, Proskin HM, Finkelman RD, Flashner M. Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. *J Periodontol* 1998; **69**: 989–997.
- 180 Jenkins DJ, Axelsen M, Kendall CW, Augustin LS, Vulksan V, Smith U. Dietary fibre, lente carbohydrates and the insulin-resistant diseases. *Br J Nutr* 2000; **83**(Suppl.): 157–163.
- 181 Jepsen S, Eberhard J, Fricke D, Hedderich J, Siebert R, Açil Y. Interleukin-1 gene polymorphisms and experimental gingivitis. *J Clin Periodontol* 2003; **30**: 102–106.
- 182 Jin L, Wong KY, Leung WK, Corbet EF. Comparison of treatment response patterns following scaling and root planing in smokers and non-smokers with untreated adult periodontitis. *J Clin Dent* 2000; **11**: 35–41.
- 183 Johnson RH. Principles in periodontal osseous resection. *Dent Clin North Am* 1976; **20**: 35–59.
- 184 Jori G, Fabris C, Soncin M, Ferro S, Coppellotti O, Dei D, Fantetti L, Chiti G, Roncucci G. Photodynamic therapy in the treatment of microbial infections: basic principles and perspective applications. *Lasers Surg Med* 2006; **38**: 468–481.
- 185 Joss A, Adler R, Lang NP. Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. *J Clin Periodontol* 1994; **21**: 402–408.
- 186 Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP. Responses of four tooth and site groupings to periodontal therapy. *J Periodontol* 1990; **61**: 173–179.
- 187 Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP, Dyer JK. Long-term evaluation of periodontal therapy. I. Response to 4 therapeutic modalities. *J Periodontol* 1996; **67**: 93–102.
- 188 Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP, Dyer JK. Long-term evaluation of periodontal therapy: II. Incidence of sites breaking down. *J Periodontol* 1996; **67**: 103–108.
- 189 Kanzler H, Barrat FJ, Hessel EM, Coffman RL. Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. *Nat Med* 2007; **13**: 552–559.

- 190 Kao RT, Conte G, Nishimine D, Dault S. Tissue engineering for periodontal regeneration. *J Calif Dent Assoc* 2005; **33**: 205–213.
- 191 Karpinia KA, Matt M, Fennell RS 3rd, Hefti AF. Factors affecting cyclosporine-induced gingival overgrowth in pediatric renal transplant recipients. *Pediatr Dent* 1996; **18**: 450–455.
- 192 Kato S, Nakashima K, Inuoe M, Tomioka J, Nonaka K, Nishihar T, Kowashi Y. Human epithelial cell death caused by *Actinobacillus actinomycetemcomitans* infection. *J Med Microbiol* 2000; **49**: 739–745.
- 193 Kawai T, Matsuyama T, Hosokawa Y, Makihira S, Seki M, Karimbux NY, Goncalves RB, Valverde P, Dibart S, Li YP, Miranda LA, Ernst CW, Izumi Y, Taubman MA. B and T lymphocytes are the primary sources of RANKL in the bone resorptive lesion of periodontal disease. *Am J Pathol* 2006; **169**: 987–998.
- 194 Kenney EB, Lekovic V, Han T, Carranza FA Jr, Dimitrijevic B. The use of a porous hydroxylapatite implant in periodontal defects. I. Clinical results after six months. *J Periodontol* 1985; **56**: 82–88.
- 195 Kenney EB, Lekovic V, Sa Ferreira JC, Han T, Dimitrijevic B, Carranza FA Jr. Bone formation within porous hydroxylapatite implants in human periodontal defects. *J Periodontol* 1986; **57**: 76–83.
- 196 Kenney EB, Lekovic V, Carranza FA Jr, Dimitrijevic B, Han T, Takei H. A comparative clinical study of solid and granular porous hydroxylapatite implants in human periodontal osseous defects. *J Biomed Mater Res* 1988; **22**: 1233–1243.
- 197 Kiger RD, Nylund K, Feller RP. A comparison of proximal plaque removal using floss and interdental brushes. *J Clin Periodontol* 1991; **18**: 681–684.
- 198 Kigure T, Saito A, Seida K, Yamada S, Ishihara K, Okuda K. Distribution of *Porphyromonas gingivalis* and *Treponema denticola* in human subgingival plaque at different periodontal depths examined by immunohistochemical methods. *J Periodontol Res* 1995; **30**: 332–341.
- 199 Kilian M, Frandsen EV, Haubek D, Poulsen K. The etiology of periodontal disease revisited by population genetic analysis. *Periodontol 2000* 2006; **42**: 158–179.
- 200 Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. *Odontology* 2006; **94**: 10–21.
- 201 Kinane DF, Shiba H, Hart TC. The genetic basis of periodontitis. *Periodontol 2000* 2005; **39**: 91–117.
- 202 Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. *Periodontol 2000* 2007; **43**: 294–315.
- 203 Kirkwood KL, Li F, Rogers JE, Otremba J, Coatney DD, Kreider JM, D'Silva NJ, Chakravarty S, Dugar S, Higgins LS, Protter AA, Medicherla S. A p38 α selective mitogen-activated protein kinase inhibitor prevents periodontal bone loss. *J Pharmacol Exp Ther* 2007; **320**: 56–63.
- 204 Kitano H, Oda K. Robustness trade-offs and host–microbial symbiosis in the immune system. *Mol Syst Biol* 2006; **3**: 1–10.
- 205 Knöfler GU, Purschwitz RE, Jentsch HF. Clinical evaluation of partial- and full-mouth scaling in the treatment of chronic periodontitis. *J Periodontol* 2007; **78**: 2135–2142.
- 206 Kolenbrander PE, Andersen RN, Kazmerzak K, Wu R, Palmer RJ. Spatial organization of oral bacteria in biofilms. *Methods Enzymol* 1999; **310**: 322–332.
- 207 Kolenbrander PE, Palmer RJ Jr, Rickard AH, Jakubovics NS, Chalmers NI, Diaz PI. Bacterial interactions and successions during plaque development. *Periodontol 2000* 2006; **42**: 47–79.
- 208 Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, Wilson TG Jr, Higginbottom FL, Duff GW. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 1997; **24**: 72–77.
- 209 Kornman KS. Mapping the pathogenesis of periodontitis: a new look. *J Periodontol* 2008; **79**: 1560–1568.
- 210 Kressin NR, Boehmer U, Nunn ME, Spiro A 3rd. Increased preventive practices lead to greater tooth retention. *J Dent Res* 2003; **82**: 223–227.

- 211 Krisanaprakornkrit S, Weinberg A, Perez CN, Dale BA. Expression of the peptide antibiotic human β -defensin 1 in cultured gingival epithelial cells and gingival tissue. *Infect Immun* 1998; **66**: 4222–4228.
- 212 Kroes I, Lepp PW, Relman DA. Bacterial diversity within the human subgingival crevice. *Proc Natl Acad Sci USA* 1999; **96**: 14547–14552.
- 213 Kumar PS, Leys EJ, Bryk JM, Martinez FJ, Moeschberger ML, Griffen AL. Changes in periodontal health status are associated with bacterial community shifts as assessed by quantitative 16S cloning and sequencing. *J Clin Microbiol* 2006; **44**: 3665–3673.
- 214 Kuramitsu HK, He X, Lux R, Anderson MH, Shi W. Interspecies interactions within oral microbial communities. *Microbiol Mol Biol Rev* 2007; **71**: 653–670.
- 215 Kwok V, Caton JG. Commentary: prognosis revisited: a system for assigning periodontal prognosis. *J Periodontol* 2007; **78**: 2063–2071.
- 216 Laine MA. Effect of pregnancy on periodontal and dental health. *Acta Odontol Scand* 2002; **60**: 257–264.
- 217 Lalla E. Periodontal infections and diabetes mellitus: when will the puzzle be complete? *J Clin Periodontol* 2007; **34**: 913–916.
- 218 Lamell CW, Griffen AL, McClellan DL, Leys EJ. Acquisition and colonization stability of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in children. *J Clin Microbiol* 2000; **38**: 1196–1199.
- 219 Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease? *J Clin Periodontol* 1986; **13**: 590–596.
- 220 Lang NP, Adler R, Joss A, Nyman S. Absence of bleeding on probing. An indicator of periodontal stability. *J Clin Periodontol* 1990; **17**: 714–721.
- 221 Lang NP, Bartold PM, Cullinan M, Jeffcoat M, Mombelli A, Murakami S, Page R, Papapanou P, Tonetti M, Van Dyke T. Consensus report. Aggressive periodontitis. *Ann Periodontol* 1999; **4**: 53.
- 222 Lang NP, Schätzle MA, Löe H. Gingivitis as a risk factor in periodontal disease. *J Clin Periodontol* 2009; **36**(Suppl.): 3–8.
- 223 Laskaris G, Potouridou I, Laskaris M, Stratigos J. Gingival lesions of HIV infection in 178 Greek patients. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 168–171.
- 224 Lebel S, Trinkaus E, Faure M, Fernandez Ph, Guérin C, Richter D, Mercier N, Valladas H, Wagner GA. Comparative morphology and paleobiology of Middle Pleistocene human remains from the Bau de l'Aubésier, Vaucluse, France. *Proc Natl Acad Sci USA* 2001; **98**: 11097–11102.
- 225 Lesaffre E, Garcia Zattera MJ, Redmond C, Huber H, Needleman I, on behalf of the ISCB subcommittee on dentistry. Reported methodological quality of split-mouth studies. *J Clin Periodontol* 2007; **34**: 756–761.
- 226 Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino RB Jr, Mayer-Davis EJ. Whole-grain intake and insulin sensitivity: the insulin resistance atherosclerosis study. *Am J Clin Nutr* 2003; **78**: 965–971.
- 227 Linden G, Patterson C, Evans A, Kee F. Obesity and periodontitis in 60–70-year-old men. *J Clin Periodontol* 2007; **34**: 461–466.
- 228 Lindhe J, Westfelt E, Nyman S, Socransky SS, Heijl L, Bratthall G. Healing following surgical/non-surgical treatment of periodontal disease. A clinical study. *J Clin Periodontol* 1982; **9**: 115–128.
- 229 Listgarten MA. Structure of the microbial flora associated with periodontal health and disease in man. A light and electron microscopic study. *J Periodontol* 1976; **47**: 1–18.
- 230 Liu D, Xu JK, Figliomeni L, Huang L, Pavlos NJ, Rogers M, Tan A, Price P, Zheng MH. Expression of RANKL and OPG mRNA in periodontal disease: possible involvement in bone destruction. *Int J Mol Med* 2003; **11**: 17–21.

- 231 Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand* 1963; **21**: 533–551.
- 232 Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. *J Periodontol* 1965; **36**: 177–187.
- 233 Löe H, Theilade E, Jensen SB, Schiøtt CR. Experimental gingivitis in man. 3. Influence of antibiotics on gingival plaque development. *J Periodontol Res* 1967; **2**: 282–289.
- 234 Löe H, Anerud A, Boysen H, Morrison E. Natural history of periodontal disease in man. Rapid, moderate and no loss of attachment in Sri Lankan laborers 14 to 46 years of age. *J Clin Periodontol* 1986; **13**: 431–445.
- 235 Löe H, Brown LJ. Early onset periodontitis in the United States of America. *J Periodontol* 1991; **62**: 608–616.
- 236 Loesche WJ, Schork A, Terpenning MS, Chen YM, Kerr C, Dominguez BL. The relationship between dental disease and cerebral vascular accident in elderly United States veterans. *Ann Periodontol* 1998; **3**: 161–174.
- 237 Loomer PM. Microbiological diagnostic testing in the treatment of periodontal diseases. *Periodontol 2000* 2004; **34**: 49–56.
- 238 Loos B, Claffey N, Crigger M. Effects of oral hygiene measures on clinical and microbiological parameters of periodontal disease. *J Clin Periodontol* 1988; **15**: 211–216.
- 239 Loscalzo J, Kohane I, Barabasi AL. Human disease classification in the postgenomic era: a complex systems approach to human pathobiology. *Mol Syst Biol* 2007; **4**: 1–11.
- 240 Luepke PG, Mellonig JT, Brunsvold MA. A clinical evaluation of a bioresorbable barrier with and without decalcified freeze-dried bone allograft in the treatment of molar furcations. *J Clin Periodontol* 1997; **24**: 440–446.
- 241 Lynch SE, Williams RC, Polson AM, Howell TH, Reddy MS, Zappa UE, Antoniadis HN. A combination of platelet-derived and insulin-like growth factors enhance periodontal regeneration. *J Clin Periodontol* 1989; **16**: 545–548.
- 242 Lynch SE, de Castilla GR, Williams RC, Kiritsy CP, Howell TH, Reddy MS, Antoniadis HN. The effects of short-term application of a combination of platelet-derived and insulin-like growth factors on periodontal wound healing. *J Periodontol* 1991; **62**: 458–467.
- 243 Madianos PN, Bobetsis YA, Kinane DF. Generation of inflammatory stimuli: how bacteria set up inflammatory responses in the gingiva. *J Clin Periodontol* 2005; **32**(Suppl. 6): 57–71.
- 244 Magnusson I, Batich C, Collins BR. New attachment formation following controlled tissue regeneration using biodegradable membranes. *J Periodontol* 1988; **59**: 1–6.
- 245 Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol* 2001; **9**: 34–39.
- 246 Mahanonda R, Pichyangkul S. Toll-like receptors and their role in periodontal health and disease. *Periodontol 2000* 2007; **43**: 41–55.
- 247 Maier AW, Orban B. Gingivitis in pregnancy. *Oral Surg Oral Med Oral Pathol* 1949; **2**: 334–373.
- 248 Manson JD, Lehner T. Clinical features of juvenile periodontitis (periodontosis). *J Periodontol* 1974; **45**: 636–640.
- 249 Marazita ML, Burmeister JA, Gunsolley JC, Koertge TE, Lake K, Schenkein HA. Evidence for autosomal dominant inheritance and race-specific heterogeneity in early-onset periodontitis. *J Periodontol* 1994; **65**: 623–630.
- 250 Mariotti A. Sex steroid hormones and cell dynamics in the periodontium. *Crit Rev Oral Biol Med* 1994; **5**: 27–53.
- 251 Mariotti A. Dental plaque-induced gingival diseases. *Ann Periodontol* 1999; **4**: 7–19.
- 252 Mariotti A. Efficacy of chemical root surface modifiers in the treatment of periodontal disease. A systematic review. *Ann Periodontol* 2003; **8**: 205–226.

- 253 Marsh PD, Percival RS. The oral microflora – friend or foe? Can we decide? *Int Dent J* 2006; **56**(Suppl. 1): 233–239.
- 254 Marshall RI. Gingival defensins: linking the innate and adaptive immune responses to dental plaque. *Periodontol 2000* 2004; **35**: 14–20.
- 255 Martinez-Canut P, Lorca A, Magán R. Smoking and periodontal disease severity. *J Clin Periodontol* 1995; **22**: 743–749.
- 256 Matia JI, Bissada NF, Maybury JE, Ricchetti P. Efficiency of scaling of the molar furcation area with and without surgical access. *Int J Periodontics Restorative Dent* 1986; **6**: 24–35.
- 257 Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, Jungeli PS, Isoluoma M, Hietaniemi K, Jokinen MJ. Association between dental health and acute myocardial infarction. *BMJ* 1989; **298**: 779–781.
- 258 Matuliene G, Pjetursson BE, Salvi GE, Schmidlin K, Brägger U, Zwahlen M, Lang NP. Influence of residual pockets on progression of periodontitis and tooth loss: results after 11 years of maintenance. *J Clin Periodontol* 2008; **35**: 685–695.
- 259 Melcher AH. On the repair potential of periodontal tissues. *J Periodontol* 1976; **47**: 256–260.
- 260 Mellonig JT, Seamons BC, Gray JL, Towle HJ. Clinical evaluation of guided tissue regeneration in the treatment of grade II molar furcation invasions. *Int J Periodontics Restorative Dent* 1994; **14**: 254–271.
- 261 Mendez MV, Scott T, LaMorte W, Vokonas P, Menzoian JO, Garcia R. An association between periodontal disease and peripheral vascular disease. *Am J Surg* 1998; **176**: 153–157.
- 262 Merchant AT, Pitiphat W, Franz M, Joshipura K. Whole-grain and fiber intakes and periodontitis in men. *Am J Clin Nutr* 2006; **83**: 1395–1400.
- 263 Merritt AH. Progressive dentistry and stomatology: 2. Periodontology, with special reference to periodontoclasia. *J Dent Res* 1920; **2**: 77–87.
- 264 Merritt AH. A brief history of periodontology. *J Dent Res* 1921; **3**: cxlix–clxi.
- 265 Meyer DH, Sreenivasan PK, Fives-Taylor PM. Evidence for invasion of a human oral cell line by *Actinobacillus actinomycetemcomitans*. *Infect Immun* 1991; **59**: 2719–2726.
- 266 Michalowicz BS, Aepli D, Virag JG, Klump DG, Hinrichs JE, Segal NL, Bouchard TJ Jr, Pihlstrom BL. Periodontal findings in adult twins. *J Periodontol* 1991; **62**: 293–299.
- 267 Michalowicz BS, Diehl SR, Gunsolley JC, Sparks BS, Brooks CN, Koertge TE, Califano JV, Burmeister JA, Schenkein HA. Evidence of a substantial genetic basis for risk of adult periodontitis. *J Periodontol* 2000; **71**: 1699–1707.
- 268 Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med* 2006; **355**: 1885–1894.
- 269 Miller PD Jr, Allen EP. The development of periodontal plastic surgery. *Periodontol 2000* 1996; **11**: 7–17.
- 270 Miller WD. *The Micro-organisms of the Human Mouth*. Philadelphia, PA: S.S. White Dental Mfg. Co., 1890: 321–334.
- 271 Miller WD. The human mouth as a focus of infection. *Dent Cosmos* 1891; **33**: 689–713.
- 272 Mombelli A, Schmid B, Rutar A, Lang NP. Persistence patterns of *Porphyromonas gingivalis*, *Prevotella intermedia/nigrescens*, and *Actinobacillus actinomycetemcomitans* after mechanical therapy of periodontal disease. *J Periodontol* 2000; **71**: 14–21.
- 273 Mongardini C, van Steenberghe D, Dekeyser C, Quirynen M. One-stage full- versus partial-mouth disinfection in the treatment of chronic adult or generalized early-onset periodontitis. I. Long-term clinical observations. *J Periodontol* 1999; **70**: 632–645.
- 274 Moore WEC, Moore LVH. The bacteria of periodontal diseases. *Periodontol 2000* 1994; **5**: 66–77.

- 275 Mucci LA, Björkman L, Douglas CW, Pedersen NL. Environmental and heritable factors in the etiology of oral diseases – a population based study of Swedish twins. *J Dent Res* 2005; **84**: 800–805.
- 276 Murayama Y, Kurihara H, Nagai A, Dompkowski D, van Dyke TE. Acute necrotizing ulcerative gingivitis risk factors involving host defence mechanisms. *Periodontol 2000* 1994; **6**: 116–124.
- 277 Murphy K, Gunsolley J. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann Periodontol* 2003; **8**: 266–302.
- 278 National Center for Health Statistics. *NHANES III Reference Manual and Reports*. Hyattsville, MD: Centers for Disease Control and Prevention, 1996:
URL <http://www.cdc.gov/nchs/nhanes/nh3rrm.htm>.
- 279 Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database Syst Rev* 2006:
DOI:[10.1002/14651858.CD001724.pub2](https://doi.org/10.1002/14651858.CD001724.pub2).
- 280 Needleman I, Suvan J, Gilthorpe MS, Tucker R, St George G, Giannobile W, Tonetti M, Jarvis M. A randomized-controlled trial of low-dose doxycycline for periodontitis in smokers. *J Clin Periodontol* 2007; **34**: 325–333.
- 281 Nelson KE, Fleischmann RD, DeBoy RT, Paulsen IT, Fouts DE, Eisen JA, Daugherty SC, Dodson RJ, Durkin AS, Gwinn M, Haft DH, Kolonay JF, Nelson WC, Mason T, Tallon L, Gray J, Granger D, Tettelin H, Dong H, Galvin JL, Duncan MJ, Dewhirst FE, Fraser CM. Complete genome sequence of the oral pathogen bacterium *Porphyromonas gingivalis* strain W83. *J Bacteriol* 2003; **185**: 5591–5601.
- 282 Nesse W, Abbas F, van der Ploeg I, Spijkervet FK, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. *J Clin Periodontol* 2008; **35**: 668–673.
- 283 Nicholson JK. Editorial. Global systems biology, personalized medicine and molecular epidemiology. *Mol Syst Biol* 2006; **210**: 1–6.
- 284 Nishida M, Grossi SG, Dunford RG, Ho AW, Trevisan M, Genco RJ. Dietary vitamin C and the risk for periodontal disease. *J Periodontol* 2000; **71**: 1215–1223.
- 285 Nørskov-Lauritsen N, Kilian M. Reclassification of *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus* and *Haemophilus segnis* as *Aggregatibacter actinomycetemcomitans* gen. nov., comb. nov., *Aggregatibacter aphrophilus* comb. nov. and *Aggregatibacter segnis* comb. nov., and emended description of *Aggregatibacter aphrophilus* to include V factor-dependent and V factor-independent isolates. *Int J Syst Evol Microbiol* 2006; **56**: 2135–2146.
- 286 Novak MJ, Johns LP, Miller RC, Bradshaw MH. Adjunctive benefits of subantimicrobial dose doxycycline in the management of severe, generalized, chronic periodontitis. *J Periodontol* 2002; **73**: 762–769.
- 287 Nyman S, Lindhe J, Rosling B. Periodontal surgery in plaque-infected dentitions. *J Clin Periodontol* 1977; **4**: 240–249.
- 288 Ochsenein C. A primer for osseous surgery. *Int J Periodontics Restorative Dent* 1986; **6**: 9–47.
- 289 Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol* 1996; **67**(Suppl.): 1103–1113.
- 290 Offenbacher S, Beck JD, Lief S, Slade G. Role of periodontitis in systemic health: spontaneous preterm birth. *J Dent Educ* 1998; **62**: 852–858.
- 291 Offenbacher S, Barros SP, Singer RE, Moss K, Williams RC, Becker JD. Periodontal disease at the biofilm–gingival interface. *J Periodontol* 2007; **78**: 1911–1925.
- 292 Offenbacher S, Barros SP, Beck JD. Rethinking periodontal inflammation. *J Periodontol* 2008; **79**: 1577–1584.

- 293 Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, Couper DJ, Stewart DD, Falkner KL, Graham SP, Grossi S, Gunsolley JC, Madden T, Maupome G, Trevisan M, Van Dyke TE, Genco RJ. Results from the periodontitis and vascular events (PAVE) study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *J Periodontol* 2009; **80**: 190–201.
- 294 Padbury A Jr, Eber R, Wang HL. Interactions between the gingiva and the margin of restorations. *J Clin Periodontol* 2003; **30**: 379–385.
- 295 Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. *Lab Invest* 1976; **33**: 235–249.
- 296 Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. *Periodontol 2000* 1997; **14**: 9–11.
- 297 Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. *Ann Periodontol* 1998; **3**: 108–120.
- 298 Page RC. Milestones in periodontal research and the remaining critical issues. *J Periodontol Res* 1999; **34**: 331–339.
- 299 Page RC, Krall EA, Martin J, Mancl L, Garcia RI. Validity and accuracy of a risk calculator in predicting periodontal disease. *J Am Dent Assoc* 2002; **133**: 569–576.
- 300 Page RC, Sturdivant EC. Noninflammatory destructive periodontal disease (NDPD). *Periodontol 2000* 2002; **30**: 24–39.
- 301 Page RC, Martin J, Krall EA, Mancl L, Garcia R. Longitudinal validation of a risk calculator for periodontal disease. *J Clin Periodontol* 2003; **30**: 819–827.
- 302 Palmer RJ Jr, Gordon SM, Cisar JO, Kolenbrander PE. Coaggregation-mediated interactions of streptococci and actinomyces detected in initial human dental plaque. *J Bacteriol* 2003; **185**: 3400–3409.
- 303 Paquette DW, Brodala N, Nichols TC. Cardiovascular disease, inflammation, and periodontal infection. *Periodontol 2000* 2007; **44**: 113–126.
- 304 Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, Sahasrabudhe A, Dewhirst FE. Bacterial diversity in human subgingival plaque. *J Bacteriol* 2001; **183**: 3770–3783.
- 305 Paster BJ, Olsen I, Aas JA, Dewhirst FE. The breadth of bacterial diversity in the human periodontal pocket and other oral sites. *Periodontol 2000* 2006; **42**: 80–87.
- 306 Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, Mbuguye TL. Prevalence and classification of HIV-associated oral lesions. *Oral Dis* 2002; **8**(Suppl. 2): 98–109.
- 307 Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. *Bull World Health Organ* 2005; **83**: 661–669.
- 308 Pihlstrom BL, McHugh RB, Oliphant TH, Ortiz-Campos C. Comparison of surgical and nonsurgical treatment of periodontal disease. A review of current studies and additional results after 6½ years. *J Clin Periodontol* 1983; **10**: 524–541.
- 309 Pihlstrom BL, Fine DH. Aggressive periodontitis in adolescents in Morocco. *Lancet* 2008; **371**: 188–189.
- 310 Pischon N, Heng N, Bernimoulin JP, Kleber BM, Willich SN, Pischon T. Obesity, inflammation, and periodontal disease. *J Dent Res* 2007; **86**: 400–409.
- 311 Polimeni G, Xiropaidis AV, Wikesjö UME. Biology and principles of periodontal wound healing/regeneration. *Periodontol 2000* 2006; **41**: 30–47.
- 312 Pontoriero R, Nyman S, Lindhe J, Rosenberg E, Sanavi F. Guided tissue regeneration in the treatment of furcation defects in man. *J Clin Periodontol* 1987; **14**: 618–620.
- 313 Pontoriero R, Lindhe J, Nyman S, Karring T, Rosenberg E, Sanavi F. Guided tissue regeneration in degree II furcation involved mandibular molars. *J Clin Periodontol* 1988; **15**: 247–254.

- 314 Porter SR, Luker J, Scully C, Glover S, Griffiths MJ. Orofacial manifestations of a group of British patients infected with HIV-1. *J Oral Pathol Med* 1989; **18**: 47–48.
- 315 Preber H, Bergström J. Cigarette smoking in patients referred for periodontal treatment. *Scand J Dent Res* 1986; **94**: 102–108.
- 316 Preber H, Bergström J. Effect of cigarette smoking on periodontal healing following surgical therapy. *J Clin Periodontol* 1990; **17**: 324–328.
- 317 Preshaw PM, Hefti AF, Novak MJ, Michalowicz BS, Pihlstrom BL, Schoor R, Trummel CL, Dean J, van Dyke TE, Walker CB, Bradshaw MH. Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: a multicenter trial. *J Periodontol* 2004; **75**: 1068–1076.
- 318 Preshaw PM, Hefti AF, Bradshaw MH. Adjunctive subantimicrobial dose doxycycline in smokers and non-smokers with chronic periodontitis. *J Clin Periodontol* 2005; **32**: 610–616.
- 319 Preshaw PM, Novak MJ, Mellonig J, Magnusson I, Polson A, Giannobile WV, Rowland RW, Thomas J, Walker C, Dawson DR, Sharkey D, Bradshaw MH. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. *J Periodontol* 2008; **79**: 440–452.
- 320 Quirynen M, Bollen CM, Vandekerckhove BN, Dekeyser C, Papaioannou W, Eysen H. Full- versus partial-mouth disinfection in the treatment of periodontal infections: short-term clinical and microbiological observations. *J Dent Res* 1995; **74**: 1459–1467.
- 321 Ramfjord SP, Caffesse RG, Morrison EC, Hill RW, Kerry GJ, Appleberry EA, Nissle RR, Stults DL. Modalities of periodontal treatment compared over 5 years. *J Clin Periodontol* 1987; **14**: 445–452.
- 322 Rams TE, Listgarten MA, Slots J. Utility of radiographic crestal lamina dura for predicting periodontal disease activity. *J Clin Periodontol* 1994; **21**: 571–576.
- 323 Ranney RR. Classification of periodontal diseases. *Periodontol 2000* 1993; **2**: 13–25.
- 324 Reddy J, Africa CW, Parker JR. Darkfield microscopy of subgingival plaque of an urban black population with poor oral hygiene. *J Clin Periodontol* 1986; **13**: 578–582.
- 325 Reddy MS, Geurs NC, Gunsolley JC. Periodontal host modulation with antiproteinases, anti-inflammatory, and bone-sparing agents. A systematic review. *Ann Periodontol* 2003; **8**: 12–37.
- 326 Reimann HA, Havens WP. Focal infection and systemic disease: a critical appraisal. *J Am Med Assoc* 1940; **114**: 1–6.
- 327 Renvert S, Wikström M, Dahlen G, Slots J, Egelberg J. Effect of root debridement on the elimination of *Actinobacillus actinomycetemcomitans* and *Bacteroides gingivalis* from periodontal pockets. *J Clin Periodontol* 1990; **17**: 345–350.
- 328 Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Ann Periodontol* 2003; **8**: 227–265.
- 329 Roberts AP, Mullany P. Genetic basis of horizontal gene transfer among oral bacteria. *Periodontol 2000* 2006; **42**: 36–46.
- 330 Robinson P, Deacon SA, Deery C, Heanue M, Walmsley AD, Worthington HV, Glenny AM, Shaw BC. Manual versus powered toothbrushing for oral health. *Cochrane Database Syst Rev* 2005; DOI:[10.1002/14651858.CD002281.pub2](https://doi.org/10.1002/14651858.CD002281.pub2).
- 331 Rosenow EC. The relation of dental infection to systemic disease. *Dent Cosmos* 1917; **59**: 485–491.
- 332 Ross IF, Thompson RH Jr. A long-term study of root retention in the treatment of maxillary molar with furcation involvement. *J Periodontol* 1978; **49**: 238–244.
- 333 Ross SE, Malamed EH, Amsterdam M. The contiguous autogenous transplant – its rationale, indications and technique. *Periodontics* 1966; **4**: 246–255.

- 334 R thlisberger B, Kuonen P, Salvi GE, Gerber J, Pjetursson BE, Attstr m R, Joss A, Lang NP. Periodontal conditions in Swiss army recruits: a comparative study between the years 1985, 1996, and 2006. *J Clin Periodontol* 2007; **34**: 860–866.
- 335 Sabet M, Lee SW, Nauman RK, Sims T, Um HS. The surface (S-) layer is a virulence factor of *Bacteroides forsythus*. *Microbiology* 2003; **149**: 3617–3627.
- 336 Saito T, Shimazaki Y, Sakamoto M. Obesity and periodontitis. *N Engl J Med* 1998; **339**: 482–483.
- 337 Sanz M, Teughels W, on behalf of Group A of the European Workshop on Periodontology. Innovations in non-surgical periodontal therapy: consensus report of the Sixth European Workshop on Periodontology. *J Clin Periodontol* 2008; **35**(Suppl.): 3–7.
- 338 Sax n L. Juvenile periodontitis. *J Clin Periodontol* 1980; **7**: 1–19.
- 339 Sax n L, Nevanlinna HR. Autosomal recessive inheritance of juvenile periodontitis: test of a hypothesis. *Clin Genet* 1984; **25**: 332–335.
- 340 Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. *Crit Care Med* 1992; **20**: 740–745.
- 341 Scannapieco FA, Mylotte JM. Relationships between periodontal disease and bacterial pneumonia. *J Periodontol* 1996; **67**: 1114–1122.
- 342 Scannapieco FA. Systemic effects of periodontal diseases. *Dent Clin North Am* 2005; **49**: 533–550.
- 343 Schallhorn RG, Hiatt WH, Boyce W. Iliac transplants in periodontal therapy. *J Periodontol* 1970; **41**: 556–580.
- 344 Schallhorn RG, Hiatt WH. Human allografts of iliac cancellous bone and marrow in periodontal osseous defects. II. Clinical observations. *J Periodontol* 1972; **43**: 67–81.
- 345 Schluger S. Osseous resection – a basic principle in periodontal surgery. *Oral Surg Oral Med Oral Pathol* 1949; **2**: 316–325.
- 346 Schmidlin PR, Beuchat M, Busslinger A, Lehmann B, Lutz F. Tooth substance loss resulting from mechanical, sonic and ultrasonic root instrumentation assessed by liquid scintillation. *J Clin Periodontol* 2001; **28**: 1058–1066.
- 347 Schroeder HE. *The Periodontium. Handbook of Microscopic Anatomy*, volume V/5. Berlin: Springer, 1986.
- 348 Schroeder HE, Listgarten MA. The gingival tissues: the architecture of periodontal protection. *Periodontol 2000* 1997; **13**: 91–120.
- 349 Schwarz F, Aoki A, Becker J, Sculean A. Laser application in non-surgical periodontal therapy: a systematic review. *J Clin Periodontol* 2008; **35**(Suppl.): 29–44.
- 350 Sculean A, Reich E, Chiantella GC, Brex M. Treatment of intrabony periodontal defects with an enamel matrix protein derivative (Emdogain): a report of 32 cases. *Int J Periodontics Restorative Dent* 1999; **19**: 157–163.
- 351 Sculean A, Nikolidakis D, Schwarz F. Regeneration of periodontal tissues: combinations of barrier membranes and grafting materials – biological foundation and preclinical evidence: a systematic review. *J Clin Periodontol* 2008; **35**(Suppl.): 106–116.
- 352 Seinost G, Wimmer G, Skerget M, Thaller E, Brodmann M, Gasser R, Bratschko RO, Pilger E. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *Am Heart J* 2005; **149**: 1050–1054.
- 353 Sepe WW, Bowers GM, Lawrence JJ, Friedlaender GE, Koch RW. Clinical evaluations of freeze-dried bone allografts in periodontal osseous defects: part II. *J Periodontol* 1978; **49**: 9–14.
- 354 Serino G, Rosling B, Ramberg P, Socransky SS, Lindhe J. Initial outcome and long-term effect of surgical and non-surgical treatment of advanced periodontal disease. *J Clin Periodontol* 2001; **28**: 910–916.
- 355 Seymour GJ, Gemmell E. Cytokines in periodontal disease: where to from here? *Acta Odontol Scand* 2001; **59**: 167–173.

- 356 Seymour GJ, Taylor JJ. Shouts and whispers: an introduction to immunoregulation in periodontal disease. *Periodontol 2000* 2004; **35**: 9–13.
- 357 Shklar G. Ancient India and China. In: Carranza F, Shklar G, editors. *History of Periodontology*. Chicago, IL: Quintessence Publishing Co. Inc., 2003: 9–11.
- 358 Shklar G. The Renaissance. In: Carranza F, Shklar G, editors. *History of Periodontology*. Chicago, IL: Quintessence Publishing Co. Inc., 2003: 43–48.
- 359 Sicilia A, Arregui I, Gallego M, Cabezas B, Cuesta S. A systematic review of powered vs manual toothbrushes in periodontal cause-related therapy. *J Clin Periodontol* 2002; **29** (Suppl. 3): 39–54; discussion 90–91.
- 360 Silness J, Löe H. Periodontal disease in pregnancy. 3. Response to local treatment. *Acta Odontol Scand* 1966; **24**: 747–759.
- 361 Simonka M, Skaleric U, Hojs D. Condition of teeth and periodontal tissue in patients who had suffered a heart attack. *Zobozdrav Vestn* 1988; **43**: 81–83 [article in Slovenian].
- 362 Skudutyte-Rysstad R, Eriksen HM, Hansen BF. Trends in periodontal health among 35-year-olds in Oslo, 1973–2003. *J Clin Periodontol* 2007; **34**: 867–872.
- 363 Slots J. The predominant cultivable organisms in juvenile periodontitis. *Scand J Dent Res* 1976; **84**: 1–10.
- 364 Socransky SS, Haffajee AD, Goodson JM, Lindhe J. New concepts of destructive periodontal disease. *J Clin Periodontol* 1984; **11**: 21–32.
- 365 Socransky SS, Haffajee AD. Evidence of bacterial etiology: a historical perspective. *Periodontol 2000* 1994; **5**: 7–25.
- 366 Socransky SS, Smith C, Martin L, Paster BJ, Dewhirst FE, Levin AE. ‘Checkerboard’ DNA–DNA hybridization. *BioTechniques* 1994; **17**: 788–792.
- 367 Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol* 1998; **25**: 134–144.
- 368 Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol 2000* 2005; **38**: 135–187.
- 369 Söderholm G, Nobréus N, Attström R, Egelberg J. Teaching plaque control. I. A five-visit versus two-visit program. *J Clin Periodontol* 1982; **9**: 203–213.
- 370 Söderholm G, Egelberg J. Teaching plaque control. II. 30-minute versus 15-minute appointments in a three-visit program. *J Clin Periodontol* 1982; **9**: 214–222.
- 371 Stahl SS, Froum S. Histologic evaluation of human intraosseous healing responses to the placement of tricalcium phosphate ceramic implants. I. Three to eight months in human intrabony defects. *J Periodontol* 1986; **57**: 211–217.
- 372 Stahl SS, Froum S, Tarnow D. Human histologic responses to guided tissue regeneration techniques in intrabony lesions. *J Clin Periodontol* 1990; **17**: 191–198.
- 373 Stahl SS, Froum S. Histologic healing responses in human vertical lesions following the use of osseous allografts and barrier membranes. *J Clin Periodontol* 1991; **18**: 149–152.
- 374 Stambaugh RV, Dragoo M, Smith DM, Carasali L. The limits of subgingival scaling. *Int J Periodontics Restorative Dent* 1981; **1**: 30–41.
- 375 Stamm JW. Epidemiology of gingivitis. *J Clin Periodontol* 1986; **13**: 360–366.
- 376 Stavropoulos A, Mardas N, Herrero F, Karring T. Smoking affects the outcome of guided tissue regeneration with bioresorbable membranes: a retrospective analysis of intrabony defects. *J Clin Periodontol* 2004; **31**: 945–950.
- 377 Stefanac SJ, Nesbitt SP. *Treatment Planning in Dentistry*, 2nd edition. St Louis: Mosby, 2007.
- 378 Summers CJ, Oberman A. Association of oral disease with 12 selected variables: I. periodontal disease. *J Dent Res* 1968; **47**: 457–462.
- 379 Suntharalingam P, Cvitkovitch DG. Quorum sensing in streptococcal biofilm formation. *Trends Microbiol* 2005; **13**: 3–6.

- 380 Suzuki A, Ji G, Numabe Y, Muramatsu M, Gomi K, Kanazashi M, Ogata Y, Shimizu E, Shibukawa Y, Ito A, Ito T, Sugaya A, Arai T, Yamada S, Deguchi S, Kamoi K. Single nucleotide polymorphisms associated with aggressive periodontitis and severe chronic periodontitis in Japanese. *Biochem Biophys Res Commun* 2004; **317**: 887–892.
- 381 Syrjänen J, Peltola J, Valtonen V, Iivanainen M, Kaste M, Huttunen JK. Dental infections in association with cerebral infarction in young and middle-aged men. *J Intern Med* 1989; **225**: 179–184.
- 382 Taichman LS, Eklund StA. Oral contraceptives and periodontal diseases: rethinking the association based upon analysis of National Health and Nutrition Examination Survey data. *J Periodontol* 2005; **76**: 1374–1385.
- 383 Takeuchi-Hatanaka K, Ohyama H, Nishimura F, Kato-Kogoe N, Soga Y, Matsushita S, Nakasho K, Yamanegi K, Yamada N, Terada N, Takashiba S. Polymorphisms in the 5' flanking region of IL12RB2 are associated with susceptibility to periodontal diseases in the Japanese population. *J Clin Periodontol* 2008; **35**: 317–323.
- 384 Tanner A, Maiden MF, Macuch PJ, Murray LL, Kent RL Jr. Microbiota of health, gingivitis, and initial periodontitis. *J Clin Periodontol* 1998; **25**: 85–98.
- 385 Tanner AC, Milgrom PM, Kent R Jr, Mokeem SA, Page RC, Riedy CA, Weinstein P, Bruss J. The microbiota of young children from tooth and tongue samples. *J Dent Res* 2002; **81**: 53–57.
- 386 Tanner ACR, Izard J. *Tannerella forsythia*, a periodontal pathogen entering the genomic era. *Periodontol 2000* 2006; **42**: 88–113.
- 387 Taubman MA, Valverde P, Han X, Kawai T. Immune response: the key to bone resorption in periodontal disease. *J Periodontol* 2005; **76**: 2033–2041.
- 388 Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M. Glycemic control and alveolar bone loss progression in type 2 diabetes. *Ann Periodontol* 1998; **3**: 30–39.
- 389 Tervonen T, Karjalainen K. Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type 1 diabetes. *J Clin Periodontol* 1997; **24**: 505–510.
- 390 Theilade E, Wright WH, Jensen SB, Löe H. Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. *J Periodontol Res* 1966; **1**: 1–13.
- 391 Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol* 2000; **71**: 1472–1483.
- 392 Timmerman MF, van der Weijden GA, van Steenberghe TJ, Mantel MS, de Graaff J, van der Velden U. Evaluation of the long-term efficacy and safety of locally-applied minocycline in adult periodontitis patients. *J Clin Periodontol* 1996; **23**: 707–716.
- 393 Tomasi C, Schander K, Dahlén G, Wennström JL. Short-term clinical and microbiologic effects of pocket debridement with an Er:YAG laser during periodontal maintenance. *J Periodontol* 2006; **77**: 111–118.
- 394 Tonetti MS, Imboden MA, Lang NP. Neutrophil migration into the gingival sulcus is associated with transepithelial gradients of interleukin-8 and ICAM-1. *J Periodontol* 1998; **69**: 1139–1147.
- 395 Tonetti MS, Cortellini P, Suvan JE, Adriaens P, Baldi C, Dubravec D, Fonzar A, Fourmouis I, Magnani C, Muller-Campanile V, Patroni S, Anz M, Vangsted T, Zaalegui I, Oini-Prato G, Lang NP. Generalizability of the added benefits of guided tissue regeneration in the treatment of deep intrabony defects. Evaluation in a multi-center randomized controlled clinical trial. *J Periodontol* 1998; **69**: 1183–1192.
- 396 Tonetti MS. Cigarette smoking and periodontal diseases: etiology and management of disease. *Ann Periodontol* 1998; **3**: 88–101.
- 397 Tonetti MS, Mombelli A. Early-onset periodontitis. *Ann Periodontol* 1999; **4**: 39–53.
- 398 Tonetti MS, Claffey N, on behalf of the European workshop in periodontology group C. Advances in the progress of periodontitis and proposal of definitions of periodontitis case and disease

- progression for use in risk factor research. Group C Consensus report of the 5th European Workshop in Periodontology. *J Clin Periodontol* 2005; **32**(Suppl. 6): 210–213.
- 399 Tonetti MS, D’Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007; **356**: 911–920.
- 400 Trombelli L, Farina R. Clinical outcomes with bioactive agents alone or in combination with grafting or guided tissue regeneration. *J Clin Periodontol* 2008; **35**(Suppl.): 117–135.
- 401 Tuite-McDonnell M, Griffen AL, Moeschberger ML, Dalton RE, Fuerst PA, Leys EJ. Concordance of *Porphyromonas gingivalis* colonization in families. *J Clin Microbiol* 1997; **35**: 455–461.
- 402 Tunkel J, Heinecke A, Flemmig TF. A systematic review of efficacy of machine-driven and manual subgingival debridement in the treatment of chronic periodontitis. *J Clin Periodontol* 2002; **29**(Suppl. 3): 72–81.
- 403 van der Velden U, Varoufaki A, Hutter JW, Xu L, Timmerman MF, van Winkelhoff AJ, Loos BG. Effect of smoking and periodontal treatment on the subgingival microflora. *J Clin Periodontol* 2003; **30**: 603–610.
- 404 van der Velden U. Purpose and problems of periodontal disease classification. *Periodontol 2000* 2005; **39**: 13–21.
- 405 Van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. *J Clin Periodontol* 2005; **32**(Suppl.): 214–228.
- 406 van Dyke TE, Horoszewicz HU, Cianciola LJ, Genco RJ. Neutrophil chemotaxis dysfunction in human periodontitis. *Infect Immun* 1980; **27**: 124–132.
- 407 van Dyke TE. Control of inflammation and periodontitis. *Periodontol 2000* 2007; **45**: 158–166.
- 408 van Dyke TE. The management of inflammation in periodontal disease. *J Periodontol* 2008; **79**(Suppl.): 1601–1608.
- 409 Waerhaug J. The interdental brush and its place in operative and crown and bridge dentistry. *J Oral Rehabil* 1976; **3**: 107–113.
- 410 Waite IM. The present status of the gingivectomy procedure. *J Clin Periodontol* 1975; **2**: 241–249.
- 411 Walker CB. The acquisition of antibiotic resistance in the periodontal microflora. *Periodontol 2000* 1996; **10**: 79–88.
- 412 Walker C, Thomas J, Nangó S, Lennon J, Wetzel J, Powala C. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. *J Periodontol* 2000; **71**: 1465–1471.
- 413 Walker C, Preshaw PM, Novak J, Hefti AF, Bradshaw M, Powala C. Long-term treatment with subantimicrobial dose doxycycline has no antibacterial effect on intestinal flora. *J Clin Periodontol* 2005; **32**: 1163–1169.
- 414 Walmsley AD, Lea SC, Landini G, Moses AJ. Advances in power driven pocket/root instrumentation. *J Clin Periodontol* 2008; **35**(Suppl.): 22–28.
- 415 Wang HL, Greenwell H, Fiorellini J, Giannobile W, Offenbacher S, Salkin L, Townsend C, Sheridan P, Genco RJ, on behalf of the Research, Science and Therapy Committee. Periodontal regeneration. *J Periodontol* 2005; **76**: 1601–1622.
- 416 Westfelt E, Rylander H, Blohmé G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. *J Clin Periodontol* 1996; **23**: 92–100.
- 417 Wiebe CB, Putnins EE. The periodontal disease classification system of the American Academy of Periodontology – an update. *J Can Dent Assoc* 2000; **66**: 594–597.
- 418 Williams RC, Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. *Periodontol 2000* 2000; **23**: 9–12.

- 419 Williams RC, Paquette DW, Offenbacher S, Adams DF, Armitage GC, Bray K, Caton J, Cochran DL, Drisko CH, Fiorellini JP, Giannobile WV, Grossi S, Guerrero DM, Johnson GK, Lamster IB, Magnusson I, Oringer RJ, Persson GR, Van Dyke TE, Wolff LF, Santucci EA, Rodda BE, Lessem J. Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial. *J Periodontol* 2001; **72**: 1535–1544.
- 420 Wilson TG Jr, Glover ME, Malik AK, Schoen JA, Dorsett D. Tooth loss in maintenance patients in a private periodontal practice. *J Periodontol* 1987; **58**: 231–235.
- 421 Wilson AG. Epigenetic regulation of gene expression in the inflammatory response and relevance to common diseases. *J Periodontol* 2008; **79**: 1514–1519.
- 422 Wohlfahrt JC, Wu T, Hodges JS, Hinrichs JE, Michalowicz BS. No association between selected candidate gene polymorphisms and severe chronic periodontitis. *J Periodontol* 2006; **77**: 426–436.
- 423 Yamazaki K, Tabeta K, Nakajima T, Ohsawa Y, Ueki K, Itoh H, Yoshie H. Interleukin-10 gene promoter polymorphism in Japanese patients with adult and early-onset periodontitis. *J Clin Periodontol* 2001; **28**: 828–832.
- 424 Ylöstalo P, Suominen-Taipale L, Reunanen A, Knuutila M. Association between body weight and periodontal infection. *J Clin Periodontol* 2008; **35**: 297–304.
- 425 Yukna RA, Mayer ET, Brite DV. Longitudinal evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects after 3 years. *J Periodontol* 1984; **55**: 633–637.
- 426 Yukna RA, Harrison BG, Caudill RF, Evans GH, Mayer ET, Miller S. Evaluation of durapatite ceramic as an alloplastic implant in periodontal osseous defects. II. Twelve month reentry results. *J Periodontol* 1985; **56**: 540–547.
- 427 Yukna RA, Mayer ET, Amos SM. 5-year evaluation of durapatite ceramic alloplastic implants in periodontal osseous defects. *J Periodontol* 1989; **60**: 544–551.
- 428 Zambon JJ, Slots J, Genco RJ. Serology of oral *Actinobacillus actinomycetemcomitans* and serotype distribution in human periodontal disease. *Infect Immun* 1983; **41**: 19–27.
- 429 Zambon JJ. *Actinobacillus actinomycetemcomitans* in human periodontal disease. *J Clin Periodontol* 1985; **12**: 1–20.