Abstract

Gingivitis, periodontitis and peri-implant infections are inflammatory diseases; yet each is uniquely different. Gingivitis and periodontitis are the result of specific bacterial induced inflammatory responses involving both the innate and adaptive arms of the immune system.\(^1\) While additional factors exists within the surgical model of osseointegrated implants, a significant number of mucositis infections and implant failures also fall within this definition.\(^2\) The clinical application of the more specific parts of this definition suggests that the dentist understand that specific bacteria initiate these inflammatory responses and the severity of the response. Also, it is implies that a current knowledge of the inflammatory process itself be a source of valuable information in patient care. The addition of these “biological characteristics” based on causation and inflammation, refines the individual nature of the definition when applied on a patient to patient basis.

Since both the local and systemic effects of these inflammatory infections are destructive, it is in the understanding and application of the specifics of these diseases that the potential for improved patient care is found.\(^3\) While applicable to all the specialties within oral medicine, the application is implicitly important to the general practitioner due to the myriad of clinical phenotypes that are observed in the early to moderate disease types.\(^2\) As an analogy, it is not necessary to wait until one has a heart attack before determining if the odds of having a heart attack are increased. When the odds are increased, the physician begins a strategy of therapy. The same is true today with these infections. The earlier the clinician includes these biological factors into the diagnose and treatment, the more effective he/she will be in resolving these infections. This is good for both the patient and the profession.

The ability to measure, from the patient, specific bacterial patterns and inflammatory patterns are needed to refine the way periodontal infections and implant diseases are diagnosed and treated.\(^3\) With an understanding of the specific nature of these diseases, there will be a clearer understanding of who is at risk and when proactive periodontal therapy should begin vs. another six month Prophy. This information promises to also provide a clearer understanding of the relationships between these chronic inflammatory diseases and the cumulative effect of inflammation relative to endothelial dysfunction and other systemic inflammatory diseases.\(^4,5,6\)

The aim of this article is to simplify a complex disease process into a clinically applicable model that is based on validated biological information. Saliva contains the hidden uniqueness to all three of these infections and is being used in the day-to-day practice of general and specialized areas of dentistry. The hope is that patient care will be improved by the inclusion of important information that is easily accessible within this important “bio-fluid.”
Over-view

Gingivitis, Periodontitis, and peri-implant infections are similar when measuring clinical signs of inflammation. However, they are often very different even when clinical presentation appears to be similar. Today, the literature encourages a more definitive recognition of biological factors in conjunction with clinical factors as the clinical presentation may be misleading regarding the serious nature of the infection; regardless of the pocket depth. Further, these “apparent similarities” based on pocket depth measurements tend to suggest a “one-size-fits-all” mentality.

Yet, from a biological perspective, individual differences of even early disease are evident and should be detected early. And, not all genetic and epigenetic host responses are the same. Based on specific genetic traits and outside influences, those modifiable and those not, the patient response to the bacterial challenge will trend toward three different predictable patterns: 1.) A response toward chronic gingivitis. 2.) A response chronic periodontitis. 3.) A response toward advanced disease. Thus; periodontal diseases in all of its forms are unique to the individual based on the specific bacteria within biofilm communities, genetic differences, risk factors and inflammatory response.

It behooves the clinician to realize the uniqueness of the individual disease, and of the patient, to best design an appropriate and personal treatment strategy. Both the health of the mouth and the health of the patient may be at a greater risk than when these decisions are based purely on traditional clinical signs of disease and without specific bacterial information.

Saliva as a diagnostic and prognostic “Trend”

Clinical laboratory testing of blood and urine has become an indisputable partner for every practitioner of medicine. Sixty to seventy percent of all clinical decisions in general medicine are based upon the biological information within these body fluids. Saliva is another body fluid that has immediate clinical application for periodontal and peri-implant infections. It is the body fluid of choice that helps to define the biological differences in patients at risk and in patients with disease.

The two general trends in salivary diagnostics are: 1).Information within saliva relative to “oral diseases”. 2).Information within saliva potentially relevant to “systemic diseases”. The need is important for both health categories as both have the potential to affect the patient in a bidirectional manner. This paper will address the present-day trend regarding salivary fluid relevant to oral diseases with particular emphasis on periodontal diseases and peri-implant diseases. Saliva is fast becoming an indisputable partner in oral medicine / dentistry for the same reasons.

“Whole saliva” contains many forms of information for improving the diagnosis for oral diseases including; gingival crevicular fluid, mucosal fluid, and fluid from all of the major and minor salivary glands. It is a storehouse of significant biological information regarding both the individual microbiological nature of periodontal diseases as well as the individual influence of the host response. This additional information can be found and measured from the DNA found within a
simple oral rinse sample. This DNA information includes genetic sequences of oral bacterial species and human cells. DNA of each helps to define the unique differences in patient diseases as well as how they respond to therapy. 18

Current understanding of oral “biofilm infections” has advanced our understanding of how specific infections cause specific host immune responses. The work of microbiologists over the past decade has brought a new understanding of the general term biofilm based on the specific nature of these communities of microorganisms. The current funding from the National Institutes of Health (NIH) for the human microbiome project has brought new attention that the shift in oral microorganisms, as causative to periodontal and peri-implant diseases. These infections based on specific microbiota as opposed to purely clinical signs, are independently associated with risk in arterial diseases. 11,12,19,20 New definitions of disease are now based on “dysbiosis”, or a shift of health related bacteria to disease related microbiota and biofilm communities. 21

The beginning of disease

New molecular based technology, including culture independent methods such as Real Time Polymerase Chain Reaction (rt-DNA-PCR) and Next Generation Sequencing (NGS) is providing new understanding of species interrelationships within the human mouth and how the host responses to these interrelationships. It is more evident that the differences that lead from health to disease are individual: not generalization. 21 In simple language, the host (person) recognizes specific bacterial inter-species communities (the infection) and also the potential threat based on the pathogenic potential of this community. As a result, the host reacts based on the recognition of this pathogenic potential of the species or multiple species. This reaction is highly specialized and better understood today. 1 Genetic influences such as Single Nucleotide Polymorphisms (SNP’s) also influence the particular degree or nature of the host response. The immune response is thus more or less aggressive as observed with the resulting clinical signs such as bleeding and or loss of alveolar bone. Risk factors, such as smoking, DM, obesity, hygiene, and medications are well recognized as influencers that can modify the response.

The “Personal Nature” of these diseases should be emphasized. Each individual tends to have significant variables within biofilm, within genetics and within modifying factors.

Contemporary Science

Our understanding on the internal development and the shift in bacterial biofilm communities is becoming clearer based on recent findings involving shifts from health associated to disease associated microflora. These shifts in species are known as dysbiosis: in the mouth, oral dysbiosis. The impact of dysbiosis is highly specific and dependent upon resident species and the changes in each individual at any given age. When oral biofilms trend toward species with increased pathogenic potential, the “disease risk” increases within the entire biofilm mass. This change in “community” is
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seen in gene expression within the biofilm, in gene expression from the host, and visibly through different patterns of inflammation and phenotype.

Species variables and differences display differences in pathogenic expression. Plus, there is inter-species synergy when species partner with others and their pathogenic potential increases in this partnership. The most validated pathogenic species to date tend that cause periodontal infections, while primarily located in subgingival spaces, are easily detectable in human saliva samples due to GCF flow as well as their location in other intraoral locales. The findings can be reported from a lab to the dentist with extreme accuracy based on presence and thresholds.

The “threshold” point is significantly important. It is not the mere presence of pathogenic species but the ability of species to accumulate to volumes that excite an immune response. Threshold levels of specific bacteria are known to increase risk for alveolar bone loss. And, it is interesting to note that recent discoveries show that some periodontopathogenic species require this “threshold” concept to triggering vascular endothelial cell inflammatory response and “cross talk” with mononuclear cells via Interleukin-6 and Toll-Like receptor 4 activation. While not the topic for this discussion, the importance of this lies not just within the boundaries of periodontal disease inflammatory express, but also in vascular endothelial inflammatory expression.

The core requirements for oral biofilm communities to shift from species to species involve a highly specialized system of virulent molecular patterns, a unique communication system between species within the biofilm, and the entire mass in communication with the host.

It is probable that the ultimate inflammation model for gingivitis or periodontitis revolves around two general trends: First, biofilm shifts become an accumulation of low pathogenic strains of bacteria, with low virulent potential. These biofilms tend to cause bleeding but with little to minimal attachment loss and the result are chronic forms of gingivitis. This scenario is apparent in children with early to mixed dentition prior to either the inoculation of pathogenic strains or when pathogenic strains are at very low levels of concentration. Secondly, many oral biofilm communities shift to highly specific pathogenic species, or combinations of species, with greater virulent potential. These biofilms will ultimately cause loss of clinical attachment and bone loss either slowly or quickly. This scenario is often seen in late teens, early adults and many forms of adult periodontitis and peri-implantitis. The potential for mature pathogenic biofilms tends to increase through-out the adult ages. Both scenarios have been validated in large numbers of laboratory tests that reviewed clinical signs of disease relative to species specific biofilm communities. In summary, the biofilm initiates the host response: the host response does not initiate the biofilm community. And, the response is primarily influenced by the bacterial community of species specific biofilm communities.
Species Unique Infections

Bacterial species in the oral cavity are equipped differently to cause disease based on virulent characteristics, biofilm shifts and the host. Together with volume shifts, species virulent factors help to form synergistic and dysbiotic communities of biofilm. The immune system of the host has the ability to recognize these volume and virulent differences. The biofilm matures toward disease associated microbiota, the response is determined by the perceived threat with the release of inflammatory cascade of cytokines, chemokines and matrix metalloproteinases (MMP’s). In some cases, the response may exceed the demand and magnify the inflammatory cascade of events. Certain species fulfill distinct roles in the convergence from a health related biofilm community to one of disease causing community.

Research initiatives have confirmed and validated the following as pathogens that should be considered as important species that are important elements of these shifts toward disease. And, these particular species have been designated as “targets” of therapy. Based on the current “level of evidence”, these include the following: *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Campylobacter rectus*, *Micromonas micra*, *Eubacterium spp.*, and *Prevotella intermedia*. The addition of more species specific microbes may be included in the future.

The biological Model

For any specific pathogen, an antibody and a cell-mediated response can occur. Both are important for defense against the pathogen. The immune responses are tailored to the pathogen and to where the pathogen resides. Cells of the innate immune system include phagocytic cells (monocyte/macrophages and PMNs), NK cells, basophils, mast cells, eosinophiles and platelets.

The virulent characteristics and invasion potential of specific microorganisms have innate ability to create different immune response patterns. Virulent characteristics include leukotoxins, epithelial toxins, lipopolysaccharides (LPS), fimbriae, host evasion capacity, collagenase, intra- and intercellular invasion: all with pathological potential. All are recognizable by designated cells by highly specific patterns of recognition and patterns of response. It is interesting to note that each microbe has a unique molecular pattern (Pathogen Associated Molecular Pattern or PAMP). This molecular pattern is recognizable by defensive immune cells. The molecular patterns of each microbial species are recognized by specific receptors on the surface of the immune cells: called Pattern Recognition Receptors (PRR’s). The type and strength of the response are determined by receptors within the host cells and the genetic make-up of the individual.

(See illustration one and two).

The host immune response is a “measured response” based on the perceived threat. Recognition receptors are also called Toll Like Receptors or TLR’s. Thus some receptors recognize bacteria, some recognize viruses, and some recognize highly virulent strains that contain lipopolysaccharides (LPS).
The specific response is based upon the interaction between the molecular pattern (PAMP), the pattern receptor (PRR), and genetic profiles. The “pattern to receptor” mechanisms are species specific. These “patterns” and “receptors” resemble “lock-and-key” mechanisms where the unique “key” fits precisely into the unique “receptor”.

Illustration One:

Illustration Two:

A single pathogen represented by the pathogen shape and the PAMP (Pathogen Associated Molecular Pattern). The PRR (Pattern Recognition Receptor) from the host defensive cell is a specialized receptor within the Toll Like Receptor (TLR) apparatus. There are numerous types of TLR’s that attract different molecular patterns of bacteria and viruses. Observe the highly specialized “Lock & Key” apparatus within the circle in Illustration One.

The virulent capacity of the microbial community, the type of response, and length of time of response determines the strength of response and thus the type of injury. The types of inflammatory proteins are released into the surrounding tissue including the interleukin family, TNFα, PGE2, MMP’s, and chemokines. Also, it is important to note that tens of millions of bacteria may be involved in these infections and the host response by releasing these powerful inflammatory molecules intended to kill the invaders has a powerful and potentially detrimental impact on the host. Viruses are also recognized: again at different receptor sites.

Other important cells, not typically defined as defensive cells, have similar capacity to initiate the inflammation cycle. A recent discovery involving Toll Like Receptor 4 (TLR 4) presents another
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window of how the human immune system reacts to activation by specific microbes or virulent potential from microbes. The discovery that microvascular and macrovascular endothelial cells, gingival epithelial cells and the cells included within the gingival attachment apparatus are also highly active in the protective mechanisms. 25

Interestingly, the activation of TLR 4 has significant importance to our understanding of the role of inflammation within the endothelial lining of all blood vessels. When this receptor is activated, multiple inflammatory cytokines are released that contribute to the development of atherosclerosis and arterial plaque instability. TLR 4 plays an important role in the atherosclerotic process when activated by lipopolysaccharide stimulation and stimulates microvascular endothelial cells to express large amounts of inflammatory genes including cytokines, chemokines, growth factors and adhesions molecules. This knowledge supports the role of specific oral microbes that contain LPS as uniquely important to our understanding of the role of oral bacteria in connection to the atherosclerotic process. 25,5 These findings suggest that the dentist understand that specific oral pathogens contain the LPS toxin while others do not. They also support recent discoveries that the specific microbiota of oral biofilms is more relevant to the oral / systemic connection than clinical signs of periodontal disease. 4,5,6,10,11,12

The genetic factors of the host, while not as clearly understood at this time, are also key ingredients of this important host / pathogen response. A single nucleotide polymorphisms (SNP) associated with the interleukin 1 gene pool is thought to be a player as a specific genetic trait that contributes to more severe response thus more tissue and bone damage. A recent meta-analysis concluded that this genetic variation is significantly associated with chronic periodontitis. 26 This genotype is measureable from a saliva sample along with bacterial variations.

Clinical application

Saliva tests are available today for periodontal and peri-implant diseases for the reasons mentioned within this scientific review. * Large clinical studies and laboratory findings have shown that both anatomy and biology of disease are important in the clinician’s ability to detect the specific nature of these diseases. Periodontology, as applied today, has focused primarily on the anatomy. Today, we have important, and measureable, biological factors that help determine risk and also help to design personal treatment plans for each patient. Along with science reviews, it is also important to note that thousands of case studies are continuing to show the improved health benefit for patient care by including these two factors within periodontal and peri-implant diseases.

The information within a “saliva rinse sample”, when sent to a clinical lab on a patient-to-patient basis, is proving to be very useful in providing two key elements in the pathogenesis of periodontal and peri-implant infections and in the clinical application of this new understanding. It is believed by this author that the future of oral medicine, and the future of our understanding of the oral / systemic connection, is being found within the specific nature of oral biofilm diseases and how the
human responds. A saliva sample, with a highly accurate clinical lab report, is the present and future of oral medicine.

Author information

The author has no financial interest in any products mentioned, is not paid by any company, and has no conflict of interest. Today, he is an educator to dental and physician groups and is also an adjunct professor in the area of molecular genetics applicable to oral medicine. As a clinician, and the founder & chief scientific officer in a large clinical laboratory that developed saliva tests, he observed > 40,000 lab reports from saliva samples that included specific microbial patterns, specific genetic traits, medical histories and these relationships to clinical signs of periodontal diseases and implant diseases. Current evidenced-based science clearly validates the role of specific microbial patterns and genetic traits as critical to the diagnosis and treatment strategies in the management of these infections. Dr. Nabors teaches a practical approach to these topics at state and national meetings to dental and medical groups. He can be reached at drtomnabors@gmail.com.

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