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Article *in* Virulence · April 2015

DOI: 10.1080/21505594.2015.1025191 · Source: PubMed

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Accepted author version posted online: 01 Apr 2015.

Virulence 6:3, 173–176; April 2015; © 2015 Taylor & Francis Group, LLC

Oral infections: clinical and biological perspectives

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The oral cavity is a specialized ecological niche of the human body and forms a continuum with the digestive and respiratory system. The vastly diverse endogenous microbiota of the oral cavity is collectively referred to as the "oral microbiome." It has been, and continues to be, explored by numerous cultivation or culture-independent methods, yielding more than 600 individual taxa.[1] They show tropism for different microhabitats, but may also show differential associations with oral health or disease. Commensal oral microbiota live in a symbiotic relationship with the host, which is crucial for the maintenance of oral health.[2] Yet, disruption of this tight relationship by various factors will result in dysbiosis, allowing for the survival and establishment of a more virulent pathobiotic polymicrobial community, impairing the efficient immune response.[3,4] Clinically, these events could manifest as an oral infectious diseases.

A common oral disease of polymicrobial etiology is dental caries,[5] whose incidence and progression rate has declined in recent years due to successfully introduced population-based prevention measures.[6,7] Progression of dental caries into the pulp space of the tooth will eventually cause pulpitis, and subsequently infection of the root canal space, leading to tooth necrosis. Expansion of the infection beyond the root canal and around the apex of the tooth may manifest as apical periodontitis, a condition associated with resorption of the periapical bone and formation of cysts and granulomas.[8,9] This can develop unnoticed by the patient for years, or be activated with painful symptoms. Although there is consensus that the interplay between the resident microbiota and the local response of the immune system are modulating the course of disease, we still fail to understand when and why these infections are activated. Zehnder and Belibasakis discuss how recent advances in molecular microbiology have given new directions in our understanding of root canal infections, and highlight the missing links between clinical experience and experimental observations on this topic.[10]

Periodontal diseases comprise a cluster of infectious inflammatory diseases that affect 10–15% of the global population in their severe form.[11] Gingivitis is an early form of periodontal disease, manifesting as inflammation restricted to the superficial gingival tissue. Once this inflammation progresses to destroy the deeper periodontal (tooth-supporting) tissues, it manifests as periodontitis, the major cause of tooth loss in adults. Periodontitis compromises quality of life and its treatment poses a significant financial burden on national health systems.

Etiologically, it is the polymicrobial oral biofilms forming on the tooth surface that initiate inflammation, which may eventually become tissue-destructive. Yet, the dysbiotic host response to the biofims is invariably a crucial determinant of the pathogenesis of periodontitis.[4] A well-studied bacterial species frequently associated with biofilms from periodontitis-affected sites is the Gram-negative anaerobe *Porphyromonas gingivalis*. It can effectively evade the immune responses and displays invasive capacities.[12] Hence, it is featured as a "keystone" pathogen in manipulating the host's immune response and causing dysbiosis.[6,13,14] The several virulence factors by which *P. gingivalis* can subvert the function of leukocytes, enabling it to thrive in an inflammation-rich environment are reviewed by Zenobia and Hajishengallis.[15] Tissue invasion by *P. gingivalis* may also be an important virulence property of this species. To this extent Baek et al. show that the invasive capacity of *P. gingivalis* isolates exhibits strong positive correlations with the clinical severity of periodontitis of the subjects who harbored the isolates.[16]

Among the bacteria highly associated with periodontitis is the Gram-negative *Tannerella forsythia*, a species with less well characterized virulence factors. Megson et al have elucidated TfFuc1, a novel fucosidase expressed on its surface.[17] This potential virulence factor may be linked to specific metabolic requirements of *T. forsythia* and its catalytic interactions with host proteins, potentially favoring its invasion properties. TfFuc1 is the first fucosidase to be identified in *T. forsythia*, and its biological roles await further investigation.

While over the years several bacterial taxa have been identified and classified as "putative" oral pathogens, several recently identified species await further characterization. As such, *Streptococcus tigurinus*, a novel species belonging to the *Streptococcus mitis* group, is discussed by Zbinden et al. on its association with other closely related streptococci, and on whether there is evidence of its role in common oral infections.[18] This is plausible, given the association of *S. tigurinus* with severe medical infections, such as infective endocarditis, spondylodiscitis and meningitis.[19] While there is at present only weak

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Submitted: 02/25/2015; Revised: 02/26/2015; Accepted: 02/26/2015
http://dx.doi.org/10.1080/21505594.2015.1025191

evidence on the involvement of *S. tigurinus* in periodontal diseases,[20] its presence in the oral cavity and its association with invasive infections are of high interest with regards to potential links between oral and systemic infections. At this point it should also be noted that, beyond bacterial infections, viruses may also play a role in oral pathologies. One example is human papillomavirus (HPV) infection, which has been postulated as an etiological cause of head and neck squamous cell carcinoma. Hübbers and Akgül debate on whether HPV plays also a role in the development of squamous cell carcinoma of the oral cavity.[21]

Beyond the microbiological aspects, the immunological host response is a crucial element for the pathogenesis of oral infections. There is increasing evidence that specific genetic polymorphisms, or their combinations, confer increased susceptibility for periodontitis, or determine its progression rate.[22] In a case-control study, Cavalla et al. monitored functional polymorphisms that result in the transcriptional activity of the TBX21 gene, which regulates the Th-1 biased immune response.[23] It was found that one of the polymorphic alleles (T) was more prevalent in chronic periodontitis, compared to gingivitis, but no association was found with presence of specific periodontal pathogens or clinical parameters of disease severity.

While the prevalence of chronic periodontitis increases by age and affects particularly the elderly population, a form of the disease deserving special mention is aggressive periodontitis. This is a rapidly progressive form that occurs in young individuals, who run a high risk of losing their teeth at a young age. A limited number of longitudinal studies point to predictive factors for the onset and progression of the disease being both microbial and host genetic ones. The former is backed-up by the frequent presence of *Aggregatibacter actinomycetemcomitans* JP2 clone, a Gram-negative facultative anaerobe, whereas the latter by the familial or ethnic aggregation of the disease. Hoglund Aberg et al. review the current knowledge on the association of *A. actinomycetemcomitans* with the risk for aggressive periodontitis, and discuss the role of its virulence factor leukotoxin in the pathogenesis of the disease.[24] The role of the host response is further discussed by Nibali, who argues that the risk factors for aggressive periodontitis studied to-date apply only to a fragment of the cases. He reviews the evidence on the concept that genetically-driven dysbiotic changes in the subgingival biofilm microbiota may predispose to the rapid periodontal tissue destruction seen in aggressive periodontitis.[25]

Evidently, a number of questions regarding the etiological and pathogenic mechanisms of the periodontal diseases are not fully elucidated or under question. Mendes et al. review the available case-control studies on the relationship between bacterial invasion of the periodontal tissues and progression periodontitis.[26] Due to the diversity in study protocols and methodological approaches employed, no consistent association between specific periodontal pathogens was found across studies. Hence, it is concluded that there is insufficient evidence to support or exclude the invasion of periodontal pathogens as a crucial process in the etiopathogenesis of the disease. Lopez et al. take an epidemiological perspective to discuss whether there is enough evidence to support our current understanding of specific periodontal pathogens as causes of periodontitis.[27] Once again, given the strong methodological heterogeneity among studies, there are obstacles in gauging the distribution of putative periodontal pathogens across age and ethnic populations or geographic locations, with only a minimal amount of studies supporting an association between specific pathogens and progression of periodontitis. From an epidemiological perspective, it is proposed that periodontitis is better understood as an inflammatory disease resulting from the interaction of many causal components, where microbes may as well be adopted.

A special mention should be made to peri-implant infections. These have emerged following the routine use of osseointegrated dental implants in restorative dentistry. Implants provide the oral cavity with new artificial surfaces prone to the formation of biofilms, which can trigger the inflammatory destruction of the peri-implant tissue, clinically manifesting as peri-implantitis. Periodontitis and peri-implantitis feature qualitative similarities in the immune-pathological events that lead to their development, albeit the latter shows more pronounced inflammatory responses and rapid tissue destruction.[28,29] Charalampakis and Belibasakis review the current knowledge on the microbiology of peri-implant infections gained from various methodological approaches, discussing their benefits and limitations.[30] While there are considerable similarities in microbial profiles between periodontal and peri-implant infections, there are also distinctive differences, which are expected to become more diversified with the increasing application of metagenomics platforms.

Research in the field of periodontal (and potentially peri-implant) infections involves clinical, in vivo or in vitro models, all of which have specific limitations, but may also complement each other. Clinical studies bring along a number of complex biological and ethical considerations, whereas animal models do not fully recapitulate the complex processes that govern human periodontitis. Hajishengallis et al. argue that, despite their limitations, animal models are indispensable tools for the study of the etiopathogenesis of periodontal diseases.[31] They are of particular value in testing the significance of biological mechanisms identified by in vitro studies, for consolidating cause-effect relationships deriving from clinical studies, and for testing novel therapeutic targets. In vitro experimental models tend to be over-simplistic, but on the other hand they allow for the dissection of finite biological mechanisms. In vitro oral biofilm models have attracted plenty of attention in recent years, particularly due to their usefulness in testing the efficacy of various anti-infective treatments,[32,33] prior to their application in pre-clinical models or clinical trials. They are also useful in studying aspects of microbial ecology, particularly by evaluating the role of different bacteria, or their virulence factors in the function and structure of the overall biofilm community.[34-36] Thurnheer and Belibasakis have utilized an in vitro biofilm model of 6 oral species, in order to test if bacteria that are not part of the normal oral microbiota (*Eschericia coli,*

Staphylococcus aureus, Enterococcus faecails) can efficiently colonize and grow within this oral biofilm.[37] Indeed these species were able to grow efficiently and in various structural conformations within this oral biofilm model. A derivative of this biofilm can also be used in more complex tissue-biofilm interaction models, in order to study the host response mechanisms of relevance to periodontal disease.[38-40] Bao et al. established a dynamic oral infection model resembling the periodontal pocket in a perfusion bioreactor system, which recapitulates key biological events of periodontal pathogenesis and may reduce the need for experimental animal models in the future.[41]

The treatment of oral infections can pose important difficulties, as these are primarily biofilm-related diseases. Biofilms are considerably more resistant against common antimicrobial treatments, compared to bacteria in their planktonic state. On the other hand, the routine use of antibiotics in common oral infections, such as periodontitis, is not ideal due to the increase in antibiotic resistance and other adverse effects. Allaker and Douglas discuss on the possibilities of non-conventional targeted approaches against biofilm-associated oral infections.[42] These include targeting a single species in the biofilm or its virulence factors, while maintaining the remaining of the oral microbiota. They may involve photodynamic therapy, enzyme inhibitors, enzymes and detergents, probiotics and prebiotics, as well as antimicrobial peptides and nanoparticles.

In summary, this Special Focus issue on "Oral Infections" aspires to highlight current knowledge on oral infectious diseases, while bringing forward advances in the fields of oral microbiology and immunology. Although over the years we have gathered important scientific information on periapical and periodontal infections, these still constitute important human health issues that pose therapeutic challenges. At the same time, the more aggressive and less well-studied peri-implant infections are emerging as a future challenge for practitioners and researchers, due to the ever-increasing implementation of dental implants in practice. At this point, it is important express the notion that prevention strategies for oral infections will be on long term considerably more efficacious than their treatment. Hence, there is a need for personalized dental healthcare and monitoring, in order to identify healthy individuals albeit at disease risk, reach an early diagnosis prior to clinical disease manifestation, and improve the prognosis of treatment outcomes. Last but not least, we should consider that the oral cavity is inseparably linked to the human body, and that the oral health may well affect the systemic health status, and vice versa.

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