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Periodontal Microbiology: The Emergence

Abstract:

There has been an undeniable relationship between microorganisms and the human body, both in terms of health and disease.One such genre is periodontal microbiology and diseases. The aetiology of a disease refers to the causal trigger(s), whereas pathogenesis refers to the mechanism(s) through which the illness advances. Periodontitis has a microbiological aetiology and an inflammatory pathophysiology, although the coordination of the contributing variables for the disease's onset and course may differ from an epidemiological standpoint (1). There has been extensive research on this disease and most of them pointed out the relationship between an unbalanced oral flora and the disease itself. Many newer technologies have helped elaborate the microbiome, from identifying native and novel bacteria to theories explaining how disturbance of oral phylogeny can lead to precipitation of this disease and paradigms based on which different treatments have been formulated. This review of pertinent literature online and offline was conducted, and data and information were then extracted, modified, and arranged under the appropriate headings. The monograph tries to compile the primitive concepts, the eventual shift of paradigms, the latest advances in treatment modalities and futuristic expectations. From a simpler PCR to new generation sequencing, this manuscript covers it all.

Key-words: Oral Microbiome, Landmark Studies, Novel bacteria, Treatment Advances

Introduction:

Extensive Literature based on research in the field of microbiology in periodontics often leads to a herculean task to put it in a nutshell. Hence, this literature accomplishes to abridge the profoundness of periodontal microbiology, right from its inception to its evolution into the recent developments and advancements. It highlights the historical 'eureka' moments in this field in both research and therapeutic evolution. It also delves into novel trends in periodontal microbiology.

Table 1: Historically Important Landmarks

TIME	*SCIENTIST*	*THEORY / SCIENTIFIC CONTRIBUTION*
1000 B.C.E	Sushrut	Classed fifteen ailments affecting tooth roots, with full descriptions of ten (gum) disorders(3)
~500 B.C.E.	Egyptians and Chinese	Periodontal disorders were characterised as inflammatory conditions(2)
18th century.	Hippocrates, Romans & Arabs	the "evil malodor" is caused by "pitius" condition attributed to hard "calculus".(2)
1746	Pierre fauchard	First recommended scaling(2)
1771	John hunter	Coined periodontosis(5)
1882	John Riggs	Coined ""Pyorrhea alveolaris" and lead to introduction of local curettage, debridement etc.(2)
1889	W. D. Miller	first to probe the link between germs and periodontal disease(4)
1911	W. Hunter	"Focal infection"(2)
1966	Harald loe	Demonstrated microbiologic changes in plaque i.e. Gram-positive cocci and rods to a Gram-negative fusobacteria and filaments and lastly spirilla and spirochetes.(7)

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Table 1 : Historically Important Landmarks(contd.)

1973	Walter Loesche	Termed Millers work (1890) as "non-specific"plaque hypothesis
1976	Hubert Schroeder	Demonstrated bacterial plaque as initiator of periodontitis(5)
1979	Walter Loesche.	"specific" plaque hypothesis(5)
1979	Jörgen Slots	Performed anaerobic culture and microscopy on subgingival plaque(5)
1983	Jan lindhe	First time used antimicrobial agent(metronidazole) for treatment(5)
1986	Elise theilade	Gave an updated concept of "non-specific"plaque hypothesis
1994	Philip Marsh	"ecological" plaque hypothesis.(8)
1998	Sigmund Socransky	Plaque flora was categorised in six colour-coded complexes (5)
2012	G. Hajishengallis and R. Lamont	"Polymicrobial synergy and dysbiosis" "Keystone pathogen" hypothesis- focusing on *P.gingivalis* (5)
2016	William Wade	Used siderophore-supplemented culture media to culture fastidious oral bacteria that are challenging to culture (9)
2020	Van Dyke et al.	"Inflammation-Mediated-Polymicrobial-Emergence And Dysbiotic-Exacerbation (IMPEDE)model of periodontitis(5)

3. Progression of Periodontal Microbiology

Periodontal disease has been present since the age of Egyptian mummies, with modern paleopathological investigations revealing the presence of periodontitis and diabetes(6). Early treatments were based on theories with little scientific support, and the isolation of oral microbes was a milestone. As time progressed, researchers realized the difference between basic attributes of medical infections and the complex relationship of oral microflora. The non-linear evolution of periodontal microbiology poses a challenge in identifying factors responsible for the disease and formulating a multidisciplinary approach. Recent research has introduced the term "nosoymbiocity," defying the binary concept of "host" and "commensal."(12) Oral microbiome research continues worldwide, with significant research on new treatments aiming to restore health status while dealing with the multifactorial nature of periodontal diseases. Recent advances have led to newer genetic dysbiosis and dysbiotic exacerbation models, biomarker studies offering promising upgrades in diagnosis and disease progression, and new treatment modalities taking shape.

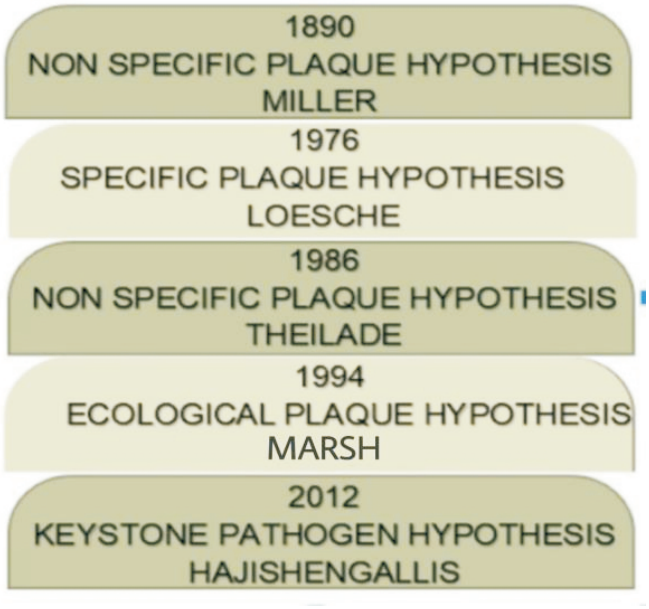


Figure : Various concepts of plaque and biofilms over the years.

4. Advancements in periodontal microbiology

4.1 Concepts of plaque and biofilms:

Periodontal diseases are primarily caused by bacteria, and molecular techniques have explored their role in diseaseetiology. Understanding of plaque biofilms have evolved from understanding virulence quantitatively by non specific plaque hypothesis to qualitatively by specific plaque hypothesis. Bacteria, influenced by pathogens, environment, and host susceptibility, are treated effectively with antibiotics like amoxicillin and metronidazole, forming the basis of periodontitis concepts. Marsh's ecological plaque hypothesis suggests environmental factors increase pathogen competitiveness, but intraspecies genetic diversity in bacteria challenges this hypothesis, raising questions about bacterial species and gene exchange.Further,the keystone pathogen hypothesis explains detrimental presence of bacteria like P.gingivalis placing importance on certain species to turn healthy flora, dysbiotic. Many oral streptococci are naturally transformable, and S. pneumoniae is where transformation was originally identified(20)and more recently, it has been shown that gram-negative periodontal pathobionts *P. gingivalis* and *T. forsythia* undergo natural transformation(21). Open-ended culture independent techniques reveal 347 species and new ones in uncultured segments, potentially linked to periodontal health and disease, paving the way for further studies. Extracellular DNA has recently come to light as being constantly present in the biofilm matrix as it matures and being much mo essential to biofilm stability when an alysed(22). Researchers use primers and next-generation sequencing to overcome biases in periodontal microbiology, while RNAoligonucleotide

quantification uses digoxigenin-labelled sequences to identify uncultured and unnamed taxa in oral biofilms. A 'holistic systems biology' approach is used to study periodontal infections, uncovering new pathways and, genes.

The computational power of computers, advanced analytical methods, and high-throughput technologies provide unprecedented resources for genetic and epigenetic studies, microbiomics, metabolomics, proteomics, and transcriptomics analyses(23). Currently, The proteins found in extracellular vesicles from various gram-negative periodontal pathobionts have been examined using proteomics.(24)

4.2 Oral Microbiome and Novel Pathogens

Table 2: Uncovering oral phylogeny

Year	Scientist	*Contribution*
1912	Klinger	*Described Actinomycetemcomitans (11)*
1921	Oliver and Wherry	Isolated Gram-negative, non-motile rods, *Bacterium melaninogenicum*
1988	Shah and Collins	divided'black-pigmented anaerobic bacteroides' (BPB) to asaccharolytic *Porphyromonas and* moderately saccharolytic *Prevotella (5)*
1994	Flynn *et al.*	Demonstrated presence of *Mitsuokella dentalis* pathogenic microbiota in human periodontitis
1997	Tran *et al.*	Discovered *Porphyromonas endodontalis* in periodontal pockets
1999	Nakazawa et al	Isolated *Cryptobacterium curtum* from diseased periodontium
2002	Ghayoumi et al	Identified *Dialister pneumosintes* as candidate pathogen

Table 2: Uncovering oral phylogeny (contd.)

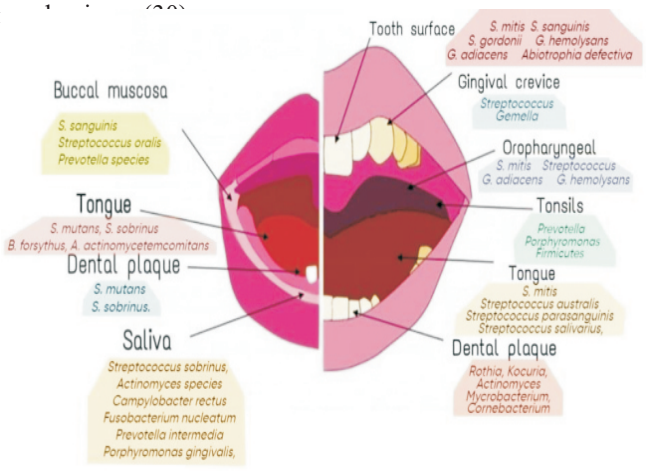
2003	Kazor *et al*	Demonstrated *Solobacterium moorei* as a cause of halitosis
2008	Haffajee *et al*.	Isolated and *Eubacterium nodatum* as a part of red complex
2009	Colombo *et al*	Established the role of *Dialister pneumosintes* in refractory periodontitis
2010	Schlafer et al	Proved presence of strictly anaerobic Gram -positive rod *F. alocis* in subgingival biofilms(10)
2014	Hoglund et al	Demonstrated *Aggregatibacter actinomycetemcomitans* JP2 Genotype as etiological factor of periodontal disease(5)

The introduction of 16s rRNA technology led to discovery of other members present in oral microbiome. The 16srRNA was, in easy terms, able to answer “who” of periodontal microbiome. The further advancements such as OMICS technology was able to tell “nature” of these individual microbiota.(5)The oral microbiome comprises bacteria, fungi, Archaea, viruses, ultra-small bacteria, and protozoa, with bacteriophages influencing bacterial ecology. Fungi are prevalent in the mouth, with Candida albicans and other species being the most studied.(27,25) but finding the communication and regulatory mechanisms remains difficult. *Entamoeba gingivalis* was the first parasite examined and found in the oral cavity, followed by

Trichomonas tenax.(33)

4.3 Site Specificity of Pathogens:

Baas-Becking's quote, "Everything is everywhere but the environment selects," applies to oral cavities, where local factors like bacteria adhesion structure and oxygen availability influence nature of flora .This explains how of two adjacent teeth, one is periodontally compromised, while other is spared. The oral microbial ecosystem is crucial for a symbiotic host-microbiota relationship, with early exposure influencing the immune system. Neonatal microbiomes are homogeneous, with the oral microbiome seeding the gut microbiome. The prevalence of bacteria in subgingival plaque varies by site, and periodontal health status can influence the prevalence of periopathogenic bacteria. Three bacterial species, P. gingivalis, T. denticola, and T. forsythia, are commonly found in biofilms at sites of periodontal disease, associated with progressive periodontitis. The presence of these species in children is not clear, but the periodontal health status of their caregivers may influence their prevalence in childhood. Over time, body sites determine microbial community composition, with saliva serving as a carrier and gastric pH increasing oral commensals(36). Future research is needed to explore mother-foetus microbiota crosstalk



4.4 Pathobionts - an emerging concept:

An emerging concept is the tight relationship between dysbiosis (microbiota imbalance) and disease. Periodontitis is a well-characterized human disease associated with dysbiosis, with the accumulation of multiple bacteria that play individual and critical roles in bone loss around the teeth.

Host immune responses to oral pathobionts act as a doubleedged sword not only by protecting the host against pathobionts, but also by promoting alveolar bone loss.

The concept "pathobiont" includes some opportunistic pathogens that live as commensals in healthy hosts but can cause disease in susceptible hosts (e.g., immunodeficient individuals). Pathobionts could be colonized as one of the resident bacteria (commensals) in human bodies without any obvious symptoms. Alternatively, changes in hosts and bacteria, for instance, by genetic variations and immunological defects, affect the virulence of pathobionts, resulting in disease development. Red complex bacteria possess high levels of protein-degrading activity that is largely mediated by proteases including gingipains (Pg), PrtH (T. forsythia), and dentilisin (T. denticola), and these bacterial proteases appear to be important for virulence (Saito et al., 1997; O'Brien-Simpson et al., 2001; Bamford et al., 2007).

An important event in the ligature model is the marked accumulation (more than 40% of total oral bacteria) of one bacterium identified as a novel Pasteurellaceae species, named NI1060.The finding that NOD1-stimulatory pathobionts can induce alveolar bone loss refines the "keystone-pathogen hypothesis" by suggesting that individual oral pathobionts that accumulate during dysbiosis play a critical and specific role in periodontitis development. One of the major differences between known pathobionts and NOD1-stimulatory pathobionts is the ability of the latter to stimulate host cells without direct bacteria-host cell contact, because the majority of NOD1 ligands are released from bacteria.

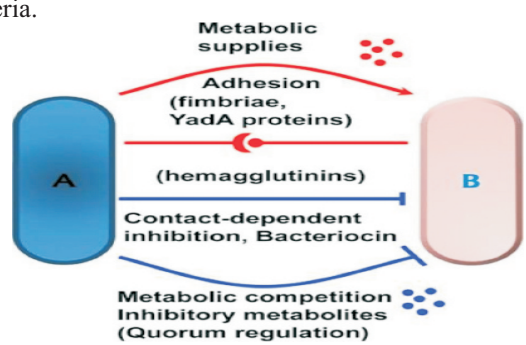


Figure 3: Bacterial-bacterial interactions that regulate dysbiosis. Dysbiosis is largely dependent on cooperative and competitive metabolic and physiological interactions among bacteria.Analysis of microbiota showed that ligature placement induced dysbiosis at damaged gingival sites (Jiao et al., 2013). Reference (37)

4.5 Culture Sequencing Advances:

Microbial culture was crucial for research on pathogenesis, antibiotic resistance, and invasive potential, however, unsatisfactory results remain due to limitations in displaying diversity and resistance to cultivation in oral bacteria. Polymerase chain reaction (PCR) is a rapid, sensitivityspecific, and simple technique used in diagnostic microbiology. However, PCR is not suitable for identifying novel microbes or detecting multiple gene regions simultaneously. Wang et al. developed Viro Chip for virus identification, GreeneChip and MDA for pathogen detection, and Huang et al. developed a high-density microarray platform for vertebrate pathogen discovery. HOMIM, a 16S rRNA-based mid-density array, was used to analyse oral bacteria and understand the relationship between oral microbiota and human health.DNA-DNA hybridization, a method of immobilising single-stranded DNA from cultivated species, most commonly used for studying species in health and disease. However, The recognition of the information content of ribosomal RNA, particularly the 16S ubunit, provided powerful new tools to the microbial ecologist. The Needleman-Wunsch global alignment technique was a bioinformatic approach for sequence similarity, assigning a score based on matches, mismatches, and gaps. In 1981, the Smith Waterman algorithm proposed ocal sequence alignment, considering all lengths between sequences. Local alignment is more reasonable due to sequence starting point and biological variation. The FASTA algorithm, published in 1985, was a popular heuristic-enabled algorithm for DNA-DNA alignment, allowing translated alignments for protein database comparison. In 1990, BLAST, a local alignment tool, revolutionised bioinformatics by focusing on speed and enabling large database searches. In addition, it has inspired a subsequent explosion of heuristic local alignment algorithms, including Sequence Search and Alignment by Hashing Algorithm, miBLAST, BLAT, Bowtie, USEARCH, Bowtie 2, High Speed Basic Local Alignment Search Tool Nucleotide, double index alignment of nextgeneration sequencing data, and Many-against-Many sequence searching. DNA sequencing methodologies enhance our understanding of oral and periodontal microbial ecosystems, identifying unknown species, exploring health contributions, and paving the way for targeted therapeutics(32), with New Generation Sequencing technologies enabling direct investigation of microbial communities.

4.6 OMICS Technologies

The introduction of OMICS has enabled us to understand the role of each bacteria in the biofilm. Exploring the impact of ive omics approaches on expanding our horizons about the periodontal microbiome -metataxonomics (16S ribosomal RNA gene sequencing), metagenomics (whole genome s h o t g u n s e q u e n c i n g o f c ommu n i t y DNA) , metatranscriptomics (sequencing of community RNA), proteomics, and metabolomics. Long-read sequencing technologies like PacBio and Oxford nanopore have revolutionised microbiota studies by providing highthroughput and in-depth information. These platforms can generate reads exceeding 1,500 bp, covering the full 16S rRNA gene(35).Proteomics, coined in 1941, has evolved over the past 25 years, using liquid chromatography coupled to tandem mass spectrometry for large-scale protein identification and quantification. Metaproteomics, defined as large-scale characterization of environmental microbiota, is used for analysing structures based on biomass. Mass spectrometry-based proteomics profiling is used to characterise oral microbiome functions. In 2010, Bostanci et al. identified 154 proteins in gingival crevicular fluid, including Herpes virus protein 2.The study of metaproteomics in dentistry is steadily increasing but is more technically demanding than the study of metagenomics or metatranscriptomics and so lags behind at present.(26)

5. Futuristic Microbiology:

Research in periodontal microbiology has scalloped ahead with a long way to go.Third Generation Sequencing has advantages over New Generation Sequencing for deciphering complex microbial ecosystems and identifying native base modifications. However, its high error rate has been improved, and while Third Generation Sequencing has potential for identifying microorganisms, its main drawback remains.(35).As more pathogens are isolated and discovered, the concept of the quorum is being reshaped. However, mechanical plaque removal procedures are not sufficient for treatment, and globally, therapies are being developed. There are numerous challenges in developing treatment against such a complex microbiome, but significant progress is being made.

5.1 Probiotics:

Probiotics are live microorganisms that offer health benefits when properly administered, possessing desirable characteristics such as non-pathogenicity, safety, genetic stability, and the ability to survive processing and administration conditions. Lactobacillus spp. probiotics have shown improvements in periodontal clinical parameters, reducing periodontitis-associated species, but successful use of other orally present species remains a challenge. Gruner et al.'s meta-analysis of probiotic trials from 1967 to 2015 included periodontal diseases as an outcome(28). Probiotic administration can reduce inflammatory markers in GCF and periodontitis-associated microorganisms, with lactobacilli showing the most positive outcomes in reducing risk factors for periodontal diseases(29).

5.2 Bacterial Replacement Therapy:

Bacterial replacement therapies, including whole microbiome transplantation or ecotherapeutics, use genetically modified bacteria to colonise human tissues, preventing disease associated microorganism growth. The following are some desirable properties of an effector microbial strain:

(I) specifically active against target pathogens without significantly disrupting the existing microbial ecosystem's balance, (ii) indigenous to, and capable of surviving in, the selected habitat and/or ecosystem and not elsewhere, (iii) nonpathogenic (or weakly opportunistic) for the host species, (iv) susceptible to low-risk antibiotics such as penicillin so that the strain can be later eliminated if desired, and (v) easily propagated and readily prepared in (vi) clearly distinguishable among the resident microbiota, (vii) not producing systemic toxicity or immunological sensitization in the host or resulting to the selection of resistant bacteria, and (viii) capable of remaining in host tissues to provide longterm protection. The study suggests that community transplantation could be a promising alternative for treating dysbiotic diseases, particularly by identifying strains with probiotic-like capabilities within the indigenous microbiome and administering them. An alternative method involves identifying indigenous microorganisms that offer resistance to exogenous pathogens post-antibiotic treatment, which can be administered prophylactically to enrich the microbiome. Studies using this approach evaluate genetically modified S. mutans strains for caries prevention and treatment, e c o t h e r a p e u t i c s , a n d p r e d a t o r y b a c t e r I a and bacteriophages(28).However, no whole subgingival microbiome transplantation is available for periodontal ailments currently.

5.3 Predatory Bacteria and Bacteriophages:

Phages, a crucial part of environmental and human microbiomes, impact their development and ecology. However, research on their antimicrobial effects and enzymes is limited. Phages may also hinder genetic material flow(17).Bdellovibrio-and-like-organisms (BALOs) are

predatory bacteria used as antibacterial agents in controlling pathogenic bacteria, particularly in periodontal diseases. B. b acteriovorus HD100reducesviable A. actinomycete mcomitans cells in biofilms. Combining BALOs with an exopolysaccharide hydrolyzing enzyme is more effective. Different strains may be needed to effectively antagonise other Gram-negative species. However, BALOs' predatory activity is completely eliminated under xygenlimiting conditions.(28)Phage therapy lacks clinical investigations, negatively impacting gene transfer.Many new phage genomic sequences have been discovered using metagenomic profiling, but are not fully defined.(18,19) Further research is needed to understand phage contribution to dysbiosis and treatment.

5.4 Quorum Quenching Therapy:

Quorum quenching (QQ), which disrupts microbial communication, is a promising treatment for oral infections due to antibiotic-resistant bacteria and oral biofilms, potentially mitigating undesirable bacterial traits like virulence and biofilm formation. QQ inhibitors like Dgalactose, furanone compounds, and D-ribose reduce b a c t erialinfection and periodontaltissue destruction.(31)Studies using lactonases to disrupt quorum sensing systems have shown profound changes in microbial population structure, affecting surface communities and biofilm formation. These changes are not easily interpretable, as some AHL producers and sensors are not affected. The effects extend beyond AHL-producer and sensor microbes, potentially affecting Gram-positive bacterial composition and abundance. The study suggests that oral delivery of QQ enzymes could facilitate selective QQ and promote healthy microbial composition in the human gut.(34)

5.5 Photodynamic Therapy:

Antimicrobial photodynamic therapy (PDT) is a treatment that employs light to irradiate a photosensitizer, inducing bacterial lipid oxidation and death. In periodontal disease, it reduces gingival index, probing depth, and A. actinomycetemcomitans and P. gingivalis numbers. When PDT is combined with photobiomodulation treatment, healing is accelerated and remission time is reduced. PTD has demonstrated efficacy in a variety of oral diseases, but further research is needed to assess its potential as an alternate mechanical debridement procedure.(31)

Conclusion:

Everlasting quest in chasing the unproven aspects of periodontal microbiology since decades ,have pushed the research into an overdrive .Changing concepts , shifting paradigms , striking research methodologies etc took us this far ,to a point where we could be hitting the " Bullseye "- for a total periodontal control in future. Historically, the use of 16s rRNA gene gave insights into the diversity of oral phylogeny, and with further advances like DNA-DNA hybridization it was elaborated. Advent of OMICS technology gave more insights into the contribution of each species. Treatment modalities have also evolved from fruit juices to mouth washes, plaque removal to sub gingival\ scaling and advances such as use of probiotics, utilisation of predatory bacteria and bacteriophages and treatments like ecotherapeutics. The scope of research, however, remains endless with the ever evolving oral microflora.

References:

1. Lopez R, Hujoel P, Belibasakis GN. On putative periodontal pathogens: an epidemiological perspective. Virulence. 2015;6(3):249-257.
2. Loe H. Periodontal diseases: a brief historical perspective. Periodontology 2000. 1993;2:7-12.
3. K Chandrasekharan Nair et al. Acharya Sushruta - The Patron Saint of Dentistry;Acta Scientific Dental Sciences (ISSN: 2581-4893) Volume 6 Issue 8 August 2022
4. Ring MEWDM. The pioneer who laid the foundation for modern dental research. N Y State Dent J. 2002;68(2):34-37
5. Belibasakis GN, Belstrøm D, Eick S,Gursoy UK, Johansson A, Könönen E. Periodontal microbiology and microbial etiology of periodontal diseases: Historical concepts and contemporary perspectives.Periodontol 2000. 2023;00:1
6. A. Gerloni et al.Dental status of three Egyptian mummies: radiological investigation by multislice computerized tomography;Volume 107, Issue 6, June 2009, Pages e58-e64
7. Theilade, Else, et al. "Experimental gingivitis in man: II. A longitudinal clinical and bacteriological investigation." Journal of periodontal research 1.1 1966): 1-13.
8. Marsh PD. Microbial ecology of dental plaque and its significance in health and disease. Adv Dent Res. 1994;8(2):263-271.
9. Vartoukian SR, Adamowska A, Lawlor M, Moazzez R, Dewhirst FE, Wade WG. In vitro cultivation of 'unculturable' oral bacteria,facilitated by community culture and media supplementation with siderophores. PLoS One. 2016;11(1):e0146926.

10. Schlafer S, Riep B, Griffen AL, et al. Filifactor alocis –involvementin periodontal biofilms. BMC Microbiol. 2010;10:66.
11. Klinger R. Untersuchungen über menschliche Aktinomykose. Zentralbl Bakteriol. 1912;62:191–200.
12. Sufaru, Irina-Georgeta, Maria-Alexandra Martu, and Sorina Mihaela Solomon. "Advances in periodontal pathogens." Microorganisms 10.7 (2022): 1439.
13. Avula H, Chakravarthy Y.Models of periodontal disease pathogenesis: A journey through time. J Indian Soc Periodontol 2022;26:204-12.
14. Arora N, Mishra A, Chugh S. Microbial role in periodontitis: Have we reached the top? Some unsung bacteria other than red complex. J Indian Soc Periodontol 2014;18:9-13.
15. 3Mashburn-Warren L, Stafford GP, Cieplik F. The dental pl aque biof i lm ma t r ix. Pe r iodontol 2000. 2021;86:32–56. https://doi. org/10.1111/prd.12361
16. Tribble GD, Rigney TW, Dao D-H, et al. Natural competence is a major mechanism for horizontal DNA transfer in the oral pathogen Porphyromonas gingivalis. MBio. 2012;3:e00231-11.
17. Paez-Espino D, Eloe-Fadrosh EA, Pavlopoulos GA, et a l . Un c o v e r i n g Ea r t h ' s v i r ome . Na t u r e . 2016;536(7617):425-430.
18. 5Kutter E, De Vos D, Gvasalia G, et al. Phage therapy in clinical practice: treatment of human infections. Curr Pharm Biotechnol. 2010;11(1):69-86. 5.. Dabrowska K, Abedon ST. Pharmacologically aware phage therapy: pharmacodynamic and pharmacokinetic obstacles to phage antibacterial action in animal and human bodies. Microbiol Mol Biol Rev. 2019;83(4):e00012-19
19. Subgingival fungi, Archaea, and viruses under the omics loupe Patricia I. Diaz Department of Oral Biology, School of Dental Medicine, University at Buffalo, Buffalo, NY
20. Jakubovics NS, Yassin SA, Rickard AH. Community interactions of oral streptococci. Adv Appl Microbiol. 2014;87:43-110.
21. Tribble GD, Rigney TW, Dao D-H, et al. Natural competence is a major mechanism for horizontal DNA transfer in the oral pathogen Porphyromonas gingivalis. MBio. 2012;3:e00231-11.
22. Brockson ME, Novotny LA, Mokrzan EM, et al.Evaluation of the kinetics and mechanism of action of anti integration host factor-mediated disruption of bacterial biofilms. Mol Microbiol. 2014;93:1246-1258.
23. Teles, Ricardo, et al. "Lessons learned and unlearned in periodontal microbiology." Periodontology 2000 62.1 (2013): 95-162.
24. Jakubovics NS, Goodman SD, Mashburn-Warren L, Stafford GP, Cieplik F. The dental plaque biofilm matrix. Periodontol 2000. 2021;86:32–56. https://doi. org/10.1111/prd.12361.
25. Hong B-Y, Hoare A, Cardenas A, et al. The salivary mycobiome contains 2 ecologically distinct mycotypes. J Dent Res. 2020;99:730-738.
26. Bostanci, Nagihan, et al. "Metaproteome and metabolome of oral microbial communities." Periodontology 2000 85.1 (2021): 46-81.
27. Kaan AM, Kahharova D, Zaura E. Acquisition and establishment of the oral microbiota. Periodontol 2000. 2021;86:123–141.
28. Hoare A, Marsh PD, Diaz PI. 2017. Ecological therapeutic opportunities for oral diseases. Microbiol Spectrum 5(4):BAD-0006-2016.
29. Staab B, Eick S, Knöfler G, Jentsch H. 2009. The Influence of a probiotic milk drink on the development of gingivitis: a pilot study. J ClinPeriodontol 36:850–856. http://dx.doi.org/10.1111/j.1600-051X.2009.01459.x
30. Kaan, A. M., Dono Kahharova, and Egija Zaura. "Acquisition and establishment of the oral microbiota." Periodontology 2000 86.1 (2021): 123-141.
31. Li, Xinyi, et al. "The oral microbiota: community composition, influencing factors, pathogenesis, and interventions." Frontiers in Microbiology 13 (2022): 895537.
32. Kumar, Purnima S., Shareef M. Dabdoub, and Sukirth M. Ganesan. "Probing periodontal microbial dark matter using metataxonomics and metagenomics." Periodontology 2000 85.1 (2021): 12-27.
33. Abualqomsaan et al., 2010; Ghabanchi et al., 2010; Rashidi Maybodi et al., 2016; Yazar et al., 2016; Fadhil Ali Malaa et al., 2022.
34. Sikdar, Rakesh, and Mikael Elias. "Quorum quenching enzymes and their effects on virulence, biofilm, and microbiomes: a review of recent advances." Expert review of anti-infective therapy 18.12 (2020): 1221-1233.

35. Xiao, Xuan, et al. "Advances in the oral microbiota and rapid detection of oral infectious diseases." Frontiers in Microbiology 14 (2023): 1121737

37. Jiao Y, Hasegawa M, Inohara N. The Role of Oral Pathobionts in Dysbiosis during Periodontitis Development. J Dent Res. 2014 Jun;93(6):539-46. doi: 10.1177/0022034514528212. Epub 2014 Mar 19. PMID: 24646638; PMCID: PMC4023464.

36. Mineoka, Tetsuro, et al. "Site-specific development of periodontal disease is associated with increased levels of Porphyromonas gingivalis, Treponema denticola, and Tannerel la forsythia in subgingival plaque." Journal of periodontology 79.4 (2008): 670-676.