



# Microbial Odyssey: Unravelling Transitions in the Oral Microbiome from Birth to Old Age for Enhanced Periodontal Care

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## ABSTRACT:

Understanding how the oral microbiota changes is crucial for periodontal practice because it plays a significant impact in determining oral health from infancy to old life. This extensive analysis covers prenatal impacts, childhood and adolescence, maturity, and aging. It also investigates the dynamic changes in the oral microbiome throughout life stages. Important discoveries show unique microbial changes at each stage, influenced by dietary habits, dental hygiene routines, systemic health, and way of life decisions. The review also explores how these transitions affect periodontal health and the likelihood of developing periodontal disorders. The oral microbial landscape is highly influenced by prenatal factors, food, dental hygiene habits, and periodontal health, while aging is also associated with changes in microbial diversity and abundance. Innovative microbiome restoration techniques, probiotics, and prebiotics are emerging as promising therapeutic interventions for supporting oral health, with individualized therapy planning based on microbiome analyses. Periodontists can customize therapeutic and preventive strategies by incorporating microbiome knowledge into their periodontal practice, improving patient outcomes and fostering lifetime dental health and wellbeing. To fully realize the potential of oral microbiome research and its revolutionary implications for periodontal care, the review ends by noting future perspectives and obstacles and emphasizing the need for longitudinal investigations, cutting-edge technologies, and interdisciplinary collaborations.

## 1. Introduction

### The Oral Microbiome: An Overview

The oral microbiome is a dynamic and intricate microbial community found in the oral cavity. It has been a matter of research with several investigations describing the various characteristics like biochemical, microbiological, and morphologic features in great detail [1–3]. The oral microbiome, which consists of a wide variety of microorganisms like bacteria, fungi, viruses, and archaea, is essential for sustaining mouth health and affecting general systemic health [4]. As experts in oral health, periodontists are aware of the crucial role that oral microbiota plays in the development and treatment of periodontal disorders. Therefore, for successful periodontal care and the prevention of oral illnesses, a

thorough understanding of the makeup, changes, and consequences of the oral microbiome across a person's lifetime is necessary. The colonization process of the oral microbiome starts during fetal development and occurs even before birth. The microbial population gradually diversifies after birth as the mouth cavity is exposed to numerous environmental influences, reaching a stable state in adulthood [5]. The oral microbiome, however, changes during the course of a person's life as a result of intrinsic and external factors like food, hormonal changes, smoking, drugs, and general health. The influence of diet on the oral biome being such that not only does the diet impact the presence or absence of certain microbes but inversely the presence of certain bacteria like Clostridia and Prevotella species, have been shown to impact the taste thresholds, such as bitter, salty,



sweet, and sour, probably indicating towards a mechanism by which the oral microbiota influences dietary preferences to sustain and persist [6,7]. Therefore, it is crucial to comprehend these changes because they have been associated with the onset and progression of dental illnesses, particularly periodontitis.

## Importance of Transitions in Oral Microbiome

Particularly in the context of periodontal health, the oral microbiome's dynamic nature and its changes hold substantial clinical value. Critical life stages, such as infancy, puberty, and ageing, each with distinct microbial community compositions, are associated with changes in the oral microbiome. The creation of the oral microbiome during infancy is influenced by a variety of factors, including mode of delivery, feeding practises, and dental cleanliness, therefore early-life transitions can set the foundation for future oral health outcomes. The oral microbial balance can be upset during adolescence due to hormonal changes and lifestyle decisions, which may result in imbalances that put people at risk for periodontal diseases. Additionally, changes in the oral microbiome brought on by ageing may contribute to age-related oral health problems such as periodontitis and tooth loss. The oral microbiome is the second largest and diverse microbial community in the human body after the gut[8] hence for preventive measures and therapeutic interventions to be tailored to the shifting microbial dynamics at various life phases, it is essential to comprehend these shifts.

## Aim and Scope of the Review

Hormonal changes and lifestyle choices can upset the oral microbial balance during adolescence, which may lead to imbalances that increase the risk of periodontal diseases. Additionally, age-related oral health issues including periodontitis and tooth loss may be impacted by changes in the oral microbiome brought on by ageing. Understanding these alterations is crucial in order to tailor preventive measures and therapeutic therapies to the changing microbial dynamics at different life periods.

The scope of this review encompasses several key areas:

**Prenatal and Postnatal Conditions and Oral Health Outcomes:** Examining factors that affect the colonisation and establishment of the oral microbiome during pregnancy and infancy, with an emphasis on the effects of these conditions on oral health outcomes.

**Childhood and Adolescence:** Examining the microbial shifts that take place throughout these crucial developmental years and their relationships to periodontal disease susceptibility, dental caries risk, and oral health status.

**Adulthood:** Investigating the stability and changes in the oral microbiome as adults, taking into account the impact of underlying illnesses, drugs, lifestyle choices, and periodontal health.

**Ageing and the Oral Microbiome:** Analysing alterations in the oral microbiome brought on by ageing and their effects on oral health in geriatric populations, including connections with age-related illnesses.

**Therapeutic Interventions and Periodontal Management:** Examining current and new approaches, such as probiotics, prebiotics, and tailored methods based on microbiome analysis, for controlling the oral microbiome to support periodontal health.

This review seeks to equip physicians with evidence-based knowledge that can guide their clinical decision-making and improve patient care by giving periodontists a thorough understanding of oral microbiota transitions. Furthermore, we anticipate that this analysis will lay the groundwork for future initiatives in the study of the oral microbiota and its uses in periodontal therapy.

## Early-Life Development of the Oral Microbiome

### Prenatal Factors Influencing Oral Microbiome Establishment

Recent studies suggest that microbial colonisation in utero may have an impact on the early formation of the oral microbiome, contradicting the long-held belief that the human foetus develops in a sterile environment[9]. As maternal transfer of germs to the developing foetus has been shown, maternal oral health and microbiota play a crucial part in this process. Literature also supports that the bacteria constitute the placental microbiome and it is responsible for initiation of the colonization of the foetus [10–12]. Additionally, modifications in the foetal oral microbiota have been linked to intrauterine diseases such as gestational diabetes and maternal stress. A review on relationship between maternal periodontitis leading to pregnancy complications concluded that pregnant patient has 1.6 times greater risk of preterm birth, 1.7 times higher risk of delivering a low-birth-weight infant, 2.2



times greater risk of preeclampsia and 3.4 times higher risk of both preterm delivery and having an infant of low birth weight [13].

**Maternal mouth Microbiota Transmission:** Research has demonstrated that some mouth microbes, particularly those linked to dental caries, including *Streptococcus mutans*, can be vertically passed from mother to foetus during pregnancy [14]. As a result, the infant's growing mouth cavity may receive some of its genetic material from the mother's oral microbiome. Various studies have supported that microbes from phyla Firmicutes, Proteobacteria, Neisseria and Fusobacteria mainly inhabit the oral mucosa [15].

**Oral microbiome and intrauterine environment:** Infants' oral microbiomes have been found to shift as a result of maternal health problems, such as gestational diabetes, predisposing them to dental caries later in life. In addition, stress during pregnancy has been linked to microbial changes in the mouth cavities of both mothers and their unborn children. There is sufficient support to suggest that differences in offspring epigenetic patterns may be responsible for stress associated preterm birth and also may serve as a target for novel interventions in future [16].

#### Colonization of the Oral Cavity in Infants

Infants' colonisation of the oral cavity is a dynamic process that is impacted by a number of elements, such as the delivery method, exposure to the outside environment, and dental hygiene habits. The first microbial colonisation patterns may have a lifelong impact on the person's oral health.

**Mode of Delivery:** Infants born vaginally are initially exposed to the vaginal and faecal microbiota of their mother, whereas those born through caesarean section are predominantly exposed to skin microorganisms. The original makeup of the oral microbiome may be impacted by these variations in early exposure. Evidenced by epidemiology the mode of delivery impacts the early microbiome assembly with particular associations in terms of metabolic and immune pathologies [17].

**Early Environmental Exposures:** Within a few moments post-delivery, the microbial colonies in the neonate become homogeneous among the nasal, oral, gut and skin communities [18–20]. Following birth, the mouth cavity is exposed to several germs from the surrounding

environment, including those from carers, siblings, and pets. The diversity of the baby oral microbiota is influenced by these early encounters. Introducing oral hygiene practises, such as brushing an infant's teeth and gums, can affect the colonisation process and can affect the composition of oral microbiota hence ensuring periodontal health [21]. A balanced and healthy oral microbiota may be created with the aid of good dental hygiene throughout the first few months of life.

#### Breastfeeding vs. Formula Feeding: Impact on Microbial Succession

It has been demonstrated that formula feeding and breastfeeding have different effects on the development of the infant's oral microbiota. Prebiotics and immunoglobulins are just two of the many helpful substances found in breast milk that help the infant's immune system develop and the growth of good bacteria. The oral microbiome has wide diversity during breast feeding. Early nutrition which includes breastfeeding and formula milk have been shown to have long lasting impacts even up to adulthood [22]. Newborns who are breastfed have been found to have a more varied oral microbiota than newborns who are formula-fed. It is believed that this diversity makes the microbial community more resilient and may have protective effects against oral illnesses. Research has shown that formula-fed infants' oral microbiomes include higher concentrations of caries-associated bacteria, such as *S. mutans*. Early exposure to these cariogenic bacteria may put a youngster at higher risk for developing dental caries later in life. The microbiota undergoes changes during complimentary feeding. As babies go from liquid to solid foods, the mouth microbiota adapts to dietary changes. The makeup and operation of the oral microbial population can be affected by the introduction of various dietary kinds.

#### Teething and Its Effect on Oral Microbiome Diversity

The emergence of primary teeth, also known as teething, is an important turning point in a child's early development. It denotes a time when salivary flow and masticatory activity are both elevated, which can have an effect on the oral microbiome. It has been seen that in the predecidate and decidate children, more number of not only *S mutans* but also *P Gingivalis*, *Fusobacterium nucleatum* and *Campylobacter rectus* are found when the early caretakers also harbour the same bacteria [23]. Along the



same lines, the detection of *T. denticola* and *Capnocytophaga gingivalis* have been found to be consistent findings between 3 to 9 year olds children and their mothers[24].

**Salivary Changes:** Saliva plays an important role in the maintenance of oral health[25]. In the teething period, as a result of increased salivary flow brought on by teething, various antibacterial substances are introduced, aiding in the elimination of oral waste. The structure and operation of the oral microbial population may be affected by this increased salivary activity.

**Dietary Changes:** When teething starts, babies frequently switch to a broader diet that includes solid meals. These dietary changes can alter the overall microbial balance and bring new bacteria species into the oral cavity.

**Impact on Oral Health:** Increased inflammation and gingival sensitivity have been linked to teething. These modifications to the oral environment could foster the growth of specific bacteria linked to periodontal disorders.

Periodontists must comprehend how the oral microbiome develops early in life since it paves the way for later microbial changes throughout a person's life. Periodontists can develop tailored measures to enhance dental health and stop the start of periodontal diseases in infancy and beyond by understanding the effects of prenatal factors, delivery method, breastfeeding habits, and teething on the oral flora.

**Childhood and Adolescence: Shaping the Oral Microbial Landscape**

The oral microbiota changes dynamically between childhood and adolescence, affected by a variety of internal and external factors[26]. At around 6 years, there is transition from deciduous to permanent dentition which is identified as the mixed dentition period[27]. It is this interval that brings about various changes related to eruption and the onset of puberty. During these formative years, the interplay between a person's nutrition, dental hygiene routines, biofilm development, and microbial interactions shapes the oral microbiome. Understanding these factors and how they affect the oral microbiome is key for periodontists who specialise on oral health to be able to provide targeted preventive and therapeutic therapies during this critical developmental stage.

## The Role of Diet in Modulating the Oral Microbiome

The makeup and operation of the oral microbiome are greatly influenced by dietary practises, particularly during the formative years of childhood and adolescence when dietary preferences are formed. Ingested food particles can act as substrates for microbial growth and metabolism since the mouth cavity acts as the opening to the digestive system.

**Sugars and Fermentable Carbohydrates' Influence:** Cariogenic bacteria like *Streptococcus mutans* receive enough of nutrition from diets high in sugars and fermentable carbohydrates. These microorganisms convert sugars to acids, which demineralize tooth enamel and promote the growth of dental caries. Restricting the consumption of sugary foods and drinks can reduce the development of cariogenic bacteria and safeguard against dental caries.

**The Effect of Fibre and Prebiotics:** Foods high in fibre and prebiotics have been shown to encourage the development of *Lactobacilli* and *Bifidobacteria*, two types of healthy bacteria. Short-chain fatty acids, which are produced by these bacteria, have the ability to alter the oral environment in favour of oral health. The primary role of consumption of dietary fibre in the oral health has been recognized mainly from a correlative perspective [28–31]. A healthy, diverse oral microbiome may hence be preserved by promoting a diet high in fruits, vegetables, and whole grains.

**Oral Health and Nutritional Deficiencies:** An environment that is favourable to opportunistic pathogens can be created by inadequate nutritional intake, which can also weaken the immune system and oral mucosal integrity. Nutritional deficiencies, particularly those involving the vitamins A, C, and D and minerals like calcium, have been connected to poor periodontal health and an unbalanced oral microbiome.

**Oral Hygiene Practices and Their Long-term Consequences**

Childhood and adolescent oral hygiene habits can have a significant long-term impact on the oral microbiome and periodontal health. Reducing bacterial load, preventing biofilm development, and managing inflammation all depend on good dental hygiene practises.



**Brushing Techniques:** Using effective brushing methods, like the modified Bass method, will help get rid of dental plaque and biofilm from tooth surfaces and gingival margins. Brushing your teeth thoroughly and on a regular basis helps to avoid the buildup of oral bacteria that cause periodontal disorders. The role of oral hygiene measures as well as professional mechanical plaque removal have been proven to prevent periodontitis[32,33].

**Flossing and Interdental Cleaning:** Plaque and debris between teeth, where toothbrush bristles cannot reach, must be removed using flossing or interdental brushes. Encouraging proper interdental cleaning from an early age fosters good oral hygiene habits and contributes to periodontal health throughout life.

**Fluoride Use:** The use of fluoride-containing toothpaste and mouthwash can help strengthen tooth enamel and remineralize early carious lesions. Regular exposure to fluoride can enhance the resilience of the oral microbiome against acid-producing bacteria. The preventive effects of conjoint exposure in the form of usage of a fluoridated dentifrice in a fluoridated area are additive hence the WHO has mandated the percolation of these advantages for maximal benefit from appropriate fluoride usage to prevent caries[34].

## Development of Oral Biofilms and Plaque Accumulation

Oral biofilms, commonly referred to as dental plaque, naturally grow on tooth surfaces and soft tissues in the oral cavity. Diet, dental hygiene, and microbial interactions are a few examples of the elements that might affect the growth and maturation of biofilms.

**The Makeup of Biofilms** A complex microbial population made up of bacteria, fungi, viruses, and elements derived from the host makes up dental plaque. The development of particular bacterial species within biofilms, such as *Streptococcus*, *Actinomyces*, and *Porphyromonas*, is related to physiological or pathological conditions.

**Biofilm maturation and pathogenic shifts:** Dental plaque changes its microbial composition and matures with time, favouring the development of pathogenic microorganisms linked to periodontal disorders. Early biofilm production is dominated by *Streptococcus* spp. and *Actinomyces* spp., whereas mature biofilms linked

to periodontitis are more commonly populated with anaerobic and proteolytic bacteria, such as *Porphyromonas gingivalis*.

## Association between Oral Microbiome and Dental Caries Risk

During childhood and adolescence, a person's vulnerability to dental caries is greatly influenced by the composition and dynamics of the oral microbiome. In order to lower the risk of caries, it can be helpful to understand these relationships and design specific preventative actions.

**Cariogenic Microorganisms:** *Streptococcus mutans* and *Lactobacillus* species, in particular, are known for their ability to produce acid, which is principally responsible for dental caries[35]. In the process of breaking down dietary glucose, these bacteria produce acids that demineralize tooth enamel and start the caries process.

**Salivary Factors:** Saliva protects by absorbing acids and supplying necessary minerals for enamel remineralization[36]. The ecology and acid-neutralizing capacity of the oral microbiome are both impacted by variations in salivary flow rate and composition, which can therefore affect a person's risk of developing caries.

Childhood and adolescence are crucial times for developing oral health practises and influencing the composition of the oral microbiome. During these formative years, the makeup and function of the oral microbiome are greatly influenced by the interactions among nutrition, dental hygiene practises, biofilm development, and microbial interactions. Periodontists are better able to provide patients with tailored preventive interventions and patient education to support optimal oral health from childhood into adulthood because they have a better understanding of the relationships between the oral microbiota and factors including diet, oral hygiene, and dental caries risk.

## Adulthood: Stability and Perturbations in the Oral Microbiome

The oral microbiome often reaches a stable, balanced state during maturity. However, a number of things could upset this equilibrium, changing the makeup and behaviour of the microbes. This section investigates the stability and adaptability of oral microbial communities in adulthood by looking at the effects of underlying



illnesses, drugs, periodontal health, and lifestyle choices on the dynamics of the oral microbiome. For periodontists to provide focused interventions for preserving oral health and preventing periodontal disorders, they must have a thorough understanding of these effects.

## Stability and Resilience of Oral Microbial Communities

In healthy people, the oral microbiome typically demonstrates some stability, with microbial communities lasting throughout time. Oral ecosystems are delicately balanced environments where a wide variety of microbial organisms coexist in harmony with the host. This equilibrium is preserved by a variety of ecological factors, such as rivalry for resources and colonisation sites and host immunological reactions.

**Oral Microbiome Core:** A foundational group of oral bacteria that make up the oral microbial community have been discovered through studies as being consistently present in healthy persons. Due to their widespread distribution, important genera like *Streptococcus*, *Prevotella*, and *Veillonella* are sometimes regarded as being a part of the core oral microbiome[37].

**Microbial Succession:** Although the associations between human microbiota and age are robust and reproducible[38], despite the stability of the core microbiome, there may be slight variations in the microbial makeup as a result of changes in the oral environment or host variables. The microbial community may experience a brief disruption as a result of these changes, but the oral microbiome frequently demonstrates resilience, gradually returning to its initial condition.

## Effects of Systemic Diseases and Medications on the Oral Microbiome

The oral microbiota can be profoundly impacted by systemic illnesses and drugs, potentially causing dysbiosis and periodontal problems [39]. An individual's overall health might have an impact on their oral environment, creating microbial growth niches.

**Diabetes and the Oral Microbiome:** Alterations in the oral microbiome have been linked to diabetes mellitus, a systemic metabolic illness. Diabetes' hyperglycaemic condition can encourage the development of specific

pathogenic bacteria, escalating periodontal inflammation and raising the risk of periodontal illnesses [40].

**Drugs and Oral Microbial Imbalances:** Some drugs, including broad-spectrum antibiotics, immunosuppressants, and antiresorptive drugs used to treat osteoporosis, can upset the ecological balance of the oral microbiome. Antibiotics, while necessary for treating infections, can lead to the overgrowth of opportunistic pathogens and increase the risk of oral candidiasis [41].

Immune disorders have an impact: Immune system dysregulation in diseases like HIV/AIDS [42] can change the makeup of oral microbes and make people more vulnerable to opportunistic infections like oral candidiasis and periodontitis.

## Periodontal Health and the Oral Microbiome Interplay

Due to the fact that periodontal disorders can be exacerbated by microbial dysbiosis, and that periodontal inflammation can have an impact on the oral microbial population, there is a bidirectional association between periodontal health and the oral microbiome.

**Dysbiotic Microbiological Changes** with an increase in periodontal pathogens including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* [43], periodontitis is characterised by changes in the oral microbial community. These microorganisms develop biofilms, which encourage persistent inflammation and tissue deterioration and advance periodontal disease.

**Role of the Host Immune Response:** The oral microbiome is significantly shaped and its composition is modulated by the host immune response. The microbial balance may be affected, and disease pathogenesis may be aided by inflammatory mediators released in response to periodontal pathogens.

## Influence of Lifestyle Factors on Oral Microbiome Dynamics

Smoking, drinking alcohol, and eating are just a few lifestyle choices that can affect the dynamics of the oral microbiota and impact oral health outcomes.

**Smoking and Microbial Dysbiosis** Smoking has been linked to changes in the oral microbiome [44] that promote the growth of harmful bacteria and decrease the



diversity of helpful microorganisms. These alterations may raise the risk of periodontal infections and impede the healing of wounds following periodontal procedures.

**Diet and the Diversity of the Oral Microbiome:** Dietary practises, especially those high in fermentable carbohydrates and sugars, might encourage the formation of cariogenic bacteria, which in turn can cause tooth caries [45]. In contrast, diets high in fibre and prebiotics can encourage the development of good bacteria and support a healthy oral microbiome.

**Effect of Alcohol Consumption:** Chronic alcohol use can upset the normal microbial balance in the mouth and raise the risk of oral illnesses such as oral candidiasis and periodontitis.

The oral microbiome exhibits a remarkable degree of resilience and stability throughout maturity, creating a stable ecology that promotes oral health. But a number of things, including systemic illnesses, drugs, periodontal health, and lifestyle decisions, can disturb this balance and result in microbial dysbiosis. To provide focused interventions for preserving oral health and preventing periodontal disorders, periodontists must be aware of these variables. In order to create efficient treatment plans and individualised preventive measures for the best possible periodontal care, it is essential to comprehend the reciprocal relationship between periodontal health and the oral microbiota.

## Aging and the Oral Microbiome

The oral microbiota changes significantly as people age, which may have an impact on both oral health and general wellbeing [46]. Changes in the oral microbial population are a result of the complex interactions between aging-related physiological changes, oral hygiene habits, and environmental factors. In this part, we examine how the composition of the oral microbiome changes as people age, how oral health affects geriatric populations, and how the oral microbiome and age-associated disorders are related. For periodontists to provide specialised care and preventive measures for preserving dental health in the elderly, they must have a thorough understanding of these dynamics.

## Changes in Oral Microbiome Composition during Aging

Changes in the diversity and composition of the oral microbiome are related to ageing. These changes are a

result of a lifetime's worth of food choices, environmental exposures, and alterations to the oral environment.

**Reduced Microbial Diversity:** Research has demonstrated that the diversity of oral microbes tends to decline with ageing, resulting in a less resilient and complex microbial community. The environment could become more prone to the proliferation of opportunistic infections linked to periodontal disorders as a result of the decrease in microbial diversity.

**Changes in Microbial Abundance:** As people age, the amount of different bacterial species in their oral microbiome may change. There is evidence that elderly people have a higher incidence of potentially harmful bacteria including *Porphyromonas gingivalis* and *Prevotella intermedia*, which may raise their risk of developing periodontal illnesses.

**Dry Mouth and Its Effect:** Xerostomia, often known as dry mouth, is a condition that is frequently associated with ageing and a decrease in salivary flow [47]. The oral environment can be impacted by the decrease in salivary flow, changing the oral microbiota and raising the risk of oral illnesses as dental caries and oral candidiasis.

## Oral Health Implications in Geriatric Populations

Oral health in older people may be significantly impacted by changes in the oral microbiome that occur with ageing. For periodontists to customise treatment regimens and preventive measures for senior patients, it is essential that they understand these implications.

**Increased Susceptibility to Periodontal illnesses:** Aging-related changes in the immune system [48] and oral tissues, along with changes in the oral microbiome, can make geriatric people more susceptible to periodontal illnesses. One of the most common oral health issues affecting the elderly is periodontitis, which has a substantial negative influence on general quality of life.

**Dental Caries Risk:** Aging-related changes in the composition of the oral microbiome and decreased salivary flow can raise the risk of dental caries. With gingival recession and exposed root surfaces, root surface caries, in particular, becomes a serious problem in senior populations.

**Oral Candidiasis:** Oral candidiasis is an opportunistic fungal infection that is more common with age,



especially in people with xerostomia or weakened immune systems [49]. The changed oral microbiota might foster a climate where *Candida* species can flourish.

## Associations between Oral Microbiome and Age-Related Diseases

The oral microbiome has been linked to a number of age-related illnesses outside of dental health, underlining the potential systemic repercussions of changes in the mouth microbiota during ageing.

**Cardiovascular Health:** Research has connected oral infections such as *P. gingivalis* to a higher risk of cardiovascular illnesses [50]. Translocation of the oral microbiota into the blood may be a factor in endothelial dysfunction and systemic inflammation.

**Respiratory Health:** It has been discovered that elderly people who have poor oral health, especially oral microbial imbalances, have a higher chance of developing pneumonia and respiratory infections [51]. Particularly in people with impaired swallowing skills, aspiration of oral infections can cause respiratory issues.

**Cognitive Decline:** Emerging research has explored potential links between the oral microbiome and cognitive decline in aging [52]. The concept of the "oral-brain axis" posits that oral pathogens and inflammation may contribute to neuroinflammation and cognitive impairment.

The oral microbiome experiences dramatic changes as we age, including decreased diversity and changing microbial makeup. These adjustments, along with physiological changes brought on by ageing and environmental variables, can have a big impact on elderly populations' dental health. For senior patients, periodontists must understand the implications of these changes in the oral flora in order to give individualised care and preventive measures. The possible systemic effects of oral health in ageing people may also be shown by comprehending the links between the oral microbiome and age-related systemic disorders. Periodontists can help to maintain overall health and well-being in geriatric populations by addressing the particular oral health issues that older people confront.

## Therapeutic Interventions and Periodontal Management

In order to preserve ideal oral health and prevent periodontal illnesses, effective treatment interventions and periodontal management are essential. Innovative strategies that target microbial imbalances and restore the microbial community's equilibrium have been developed as a result of our growing awareness of the impact of the oral microbiome on periodontal health. We examine the function of probiotics and prebiotics in maintaining dental health, discussing periodontal therapies, microbiome restoration techniques, and discussing the possibilities for individualised periodontal care based on microbiome analysis in this part. For periodontists hoping to improve patient outcomes and offer personalised treatment strategies, these developments have positive ramifications.

## Probiotics and Prebiotics in Oral Health Maintenance

By modifying the oral microbiome, probiotics and prebiotics have gained attention as potential therapeutic approaches to improve oral health. Live bacteria known as probiotics can help the host's health when given in sufficient doses. Contrarily, prebiotics are non-digestible food ingredients that specifically promote the development and activity of advantageous bacteria.

**Balance of the Oral Microbiome and Probiotics:** Probiotic oral supplements and oral care products with probiotics have been studied for their potential to support a healthy oral microbiota. Probiotics might assist in preventing the spread of harmful bacteria [53] and promoting a healthy microbial community by introducing good bacteria like *Lactobacillus* and *Bifidobacterium* strains.

**Prebiotics and Microbial Ecology:** In the oral cavity, probiotic bacteria feed on prebiotics like specific fibres and polyols. Prebiotics can maintain a healthy oral microbial habitat by encouraging the expansion of advantageous species [54], which can lead to better periodontal health.

**Synbiotics' Synergistic Effects :** Synbiotics, or probiotics and prebiotics taken together, have demonstrated promise in modifying the oral microbiome [55]. Synbiotics may increase the probiotic bacteria's ability to survive and function, which could result in more pronounced advantages for dental health.

## Periodontal Treatments and Microbiome Restoration Strategies



The goal of conventional periodontal therapies is to lessen the bacterial load and swelling brought on by periodontal disorders. The development of microbiome restoration strategies as a complement to periodontal care, however, is the result of advances in our understanding of the function of the oral microbiome.

**Targeted Therapy and Antibiotics:** To counteract harmful germs, antibiotics have long been utilised in periodontal treatments. However, the rise of antibiotic-resistant strains and their effects on good bacteria need the employment of more focused antibiotic usage strategies. Periodontists can adapt antibiotic therapy to particular pathogens using microbiome analysis, lowering the likelihood of antibiotic resistance.

**Localised Antimicrobial Delivery:** By delivering antimicrobial agents specifically to periodontal pockets, localised antimicrobial delivery devices, including as gels, films, and nanoparticles, can reduce systemic exposure [56]. These tailored treatments could aid in limiting harmful microorganisms while maintaining the balance of the total oral microbiome.

**Photodynamic Therapy:** Photodynamic therapy targets and kills germs by using a mix of light and photosensitizing chemicals [57]. To lessen bacterial load and inflammation, photodynamic therapy can be used to conventional periodontal therapies.

#### Personalized Approaches to Periodontal Care based on Microbiome Analysis

The development of personalised periodontal care methods has been made possible by improvements in microbial sequencing technologies. Characterising an individual's oral microbial composition through microbiome analysis makes it possible to create personalised treatment strategies that cater to their unique oral health requirements.

**Risk assessment using microbiome profiling:** Analysis of a person's microbiome can reveal information about that person's vulnerability to various chronic illnesses [57] like periodontal diseases. Periodontists can stratify patients based on their chance of developing periodontal diseases by detecting important microbial indicators linked to disease risk. This enables early intervention and preventive treatments.

**Exact Treatment Planning:** Based on the individual's oral microbial composition, microbiome analysis can direct the choice of appropriate treatment approaches. A study done by Caselli et al, gave a comprehensive picture of the oral microbiome determined by WGS analysis hence facilitating the identification and characterization of the dysbiotic conditions that occur during various stages of the disease[58].this paves a way for Individualised probiotic and prebiotic regimens, focused antibiotic therapy, and periodontal therapies catered to the patient's oral microbiota may all be included in precision treatment planning.

**Long-term Monitoring and Management:** Periodontists can use microbiome analysis to track the development of the disease and the effectiveness of treatment over time. Clinicians can optimise periodontal care and modify treatment programmes as needed by monitoring changes in the oral flora over time.

With a better understanding of how the oral microbiota affects oral health and illness, therapeutic approaches and periodontal management have undergone tremendous development. Prebiotics and probiotics provide fresh ways to enhance periodontal health and encourage a balanced oral flora. Combining microbiome restoration techniques with conventional periodontal therapies has the potential to improve treatment results and reduce disease recurrence [59]. Furthermore, personalised methods based on microbiome analysis enable periodontists to deliver specialised, personalised care that is catered to each person's dental health requirements. These cutting-edge methods have the potential to revolutionise periodontal care, improving patient outcomes and fostering lifelong dental health as the area of oral microbiota research develops.

#### Future Perspectives and Challenges

An ever-evolving field, the study of the oral microbiota is revealing complex relationships between oral health and general wellbeing. Understanding oral microbiome transitions, utilising cutting-edge technologies, and incorporating microbiome research into practise are crucial for increasing patient care and resolving new difficulties as periodontists adopt a more holistic approach to oral care. In this part, we examine the prospects for and difficulties with the study of the oral microbiome and its implications for periodontal therapy.



## Unraveling the Complexity of Oral Microbiome Transitions

Even though a lot of progress has been made in our understanding of the dynamics of the oral microbiome, many aspects of its transitions are still a mystery. Understanding the underlying mechanisms that drive microbial transformations during various phases of life and in response to environmental changes depends on unravelling the intricacy of these transitions.

**Long-Term Research:** For the purpose of determining patterns of microbial changes throughout time, extensive, longitudinal studies tracking the oral microbiome from infancy to old age are essential. These research can shed light on the variables causing changes in the oral microbiome and offer understanding of how life events, illnesses, and therapies affect the oral microbial community.

**Multi-Omics methodologies:** Integrating multi-omics methodologies, such as metagenomics, metatranscriptomics, and metabolomics, can improve our comprehension of the functional relationships within the oral microbiome. These thorough analyses will clarify the functions of particular bacteria species and functional pathways in mouth health and illness.

**Microbial Interactions** Understanding the stability and resiliency of the oral microbiome will require research on microbial interactions within the oral ecosystem. A more thorough understanding of the oral microbial community may result from knowing how particular microorganisms affect one another's development and behaviour.

## Innovative Technologies for Studying Oral Microbiome Dynamics

Technology advancements have advanced the study of the oral microbiome, allowing for deeper analyses and creating new research opportunities. By utilising these cutting-edge technologies, we can learn more about the dynamics of the oral microbiota and gain fresh insights on dental health.

**Single-Cell Genomics:** Through the genetic analysis of individual microbial cells, single-cell genomics can shed light on the rare and uncultivated species that make up the oral microbiome [60]. A more thorough understanding of the microbial variety and functions in the mouth cavity may be provided by this technology.

**Microbiome Engineering:** Cutting-edge approaches based on CRISPR hold promise for controlling particular bacteria populations in the oral cavity [61]. These methods could open the door for focused therapies to restore microbial balance and fight periodontal disorders.

**Nanotechnology for Drug Delivery:** Nanotechnology offers innovative drug delivery systems that can enhance the precision and efficacy of antimicrobial treatments [62]. Nanoparticles can be engineered to deliver therapeutic agents directly to periodontal sites, minimizing side effects and promoting targeted microbial control.

## Integrating Microbiome Research into Periodontal Practice

The integration of microbiome research into periodontal practice represents a transformative approach to patient care, enabling personalized treatment strategies and improved outcomes.

**Microbiome Analysis for Risk Assessment:** By include microbiome analysis in routine risk assessments, it is possible to identify patients who are prone to periodontal disorders. A tailored approach to prevention and intervention is made possible by early detection of high-risk people.

**Exact Treatment Planning:** Using the results of microbiome analyses to inform treatment planning enables the development of individualised strategies that take into account the makeup of each person's oral microbiome. Planning your treatment strategy carefully will help you get the most out of your therapy options and reduce your chance of getting sick again.

**Microbiome Monitoring for Long-Term Care:** Regular microbiome monitoring can offer useful insights into the effectiveness of a certain treatment and the course of a disease. Long-term management and real-time treatment plan changes are made possible by incorporating microbiome data into routine checkups.

## Challenges and Considerations

Even while oral microbiome research has a bright future, there are still a number of obstacles to overcome before this area can reach its full potential.

1. **Data standardisation:** To enable comparisons between various studies and ensure trustworthy conclusions,



standardising procedures and data analysis approaches is essential.

2. Ethical Considerations: To safeguard participants' rights as microbiome research develops, ethical issues like data privacy and informed consent must be given top priority.

3. Interdisciplinary Collaboration: It is crucial for the advancement of oral microbiome research and the successful application of findings to clinical practise that periodontists, microbiologists, bioinformaticians, and other professionals collaborate.

Opportunities to understand the intricacies of oral microbiome transitions, take advantage of cutting-edge technologies, and apply microbiome knowledge to periodontal practise abound in the future of oral microbiome research. Periodontists can create individualised treatment plans and preventive measures to improve patient care by comprehending the dynamics of the oral microbiome over time and in response to environmental changes. Improved oral health outcomes will be made possible by teamwork, interdisciplinary methods, and ongoing technological advancements, which will eventually improve patients' overall well-being.

## Conclusion

Our knowledge of oral health and illness has been greatly improved by the research of the oral microbiome, which also sheds light on the dynamic relationship between periodontal health and the oral microbiota. The oral microbiome changes over the course of life, from birth to old age, and these changes are driven by both intrinsic and external influences. These changes have an effect on dental health and raise the possibility of periodontal infections. As periodontists, we have the opportunity to transform patient care and improve treatment outcomes by incorporating this information into clinical practise.

### Key Findings and Implications for Periodontists

The comprehensive review of transitions in the oral microbiome from birth till old age has revealed several key findings with profound implications for periodontal practice:

**Life Stage-Specific Microbial Shifts:** The oral microbiome changes at different phases of life, depending on things like food, oral hygiene habits,

hormonal changes, and overall health. For preventive measures and therapeutic interventions to be tailored to the particular needs of patients at various ages, an understanding of these shifts is essential.

**Effect of Prenatal influences:** During the early stages of development, the oral microbiota is established in large part by prenatal influences. The impact of maternal oral health and its consequences for the dental health of the child are highlighted by the fact that maternal oral health, delivery method, and early exposure to microbes all affect the oral microbial landscape.

**Diet and Oral Microbiome:** Dietary practises have a substantial impact on the composition and functionality of the oral microbiome, with sugars and fermentable carbohydrates encouraging the proliferation of cariogenic bacteria. Supporting a varied and healthy oral microbiota can be accomplished by promoting a balanced diet rich in prebiotics and other nutrients.

**Oral Hygiene Habits:** Establishing good oral hygiene habits from childhood and adolescence has long-term effects on oral health. Fluoridation, flossing, and efficient toothbrushing methods must all be emphasised if periodontal diseases are to be avoided and a healthy oral flora is to be maintained.

**The interaction between periodontal health and the oral microbiome:** The composition of the oral microbiome and periodontal health are closely related. Periodontal diseases can result from dysbiotic changes in microbial populations, and periodontal inflammation can have an impact on the oral microbiome. Targeted periodontal therapies can maintain periodontal health and restore microbial balance.

**Ageing and mouth Microbiome Changes:** As we age, our mouth microbiome changes as well, with less diversity and variations in microbial abundance. These alterations raise the likelihood of periodontal diseases in elderly people, along with age-related variables including dry mouth and immunological decline.

**Therapeutic Interventions and Microbiome Restoration:** Probiotics, prebiotics, and cutting-edge microbiome restoration techniques present exciting new ways to advance dental health. Optimising therapeutic interventions and improving patient outcomes can be accomplished with the use of customised treatments based on microbiome analysis.



Personalised Approaches in Periodontal Care: By incorporating microbiome analysis into periodontal practise, risk assessment and treatment planning may be done on an individual basis. Preventive measures and long-term management can be enhanced with precision care based on a person's unique oral microbiota composition.

## Implications for Periodontal Practice

The findings from this comprehensive review have far-reaching implications for periodontists, shaping the future of periodontal care:

1. Targeted Preventive Measures: Periodontists can put targeted preventive measures into place by being aware of the variables driving oral microbiota transitions. Early interventions can help to support ideal oral health starting in infancy, such as maternal oral health programmes and individualised dietary counselling.

2. Precision Treatment Planning: By incorporating the results of microbiome analyses into treatment planning, each patient can receive precise care that is specifically adapted to their dental health needs. Personalised treatment plans can be developed by periodontists to address microbial imbalances and enhance therapeutic efforts.

3. Lifelong Oral Health Management: The significance of lifelong oral health management is highlighted by the knowledge of how ageing and changes in life stages affect the oral microbiome. For senior populations, periodontists can establish long-term monitoring and individualised care regimens.

4. Advancing Research and Technology: Research and technology advancements can be made by embracing cutting-edge technologies and working in interdisciplinary teams. Participation of periodontists in microbiome research can advance knowledge of the oral microbiome and its effects on periodontal health.

In conclusion, research on changes in the oral microbiome from birth to old age has shown how dynamic the oral microbial community is and the significant influence it has on dental health over the course of a person's life. Periodontists can give targeted care and preventive measures to patients by being aware of these transitions, which range from prenatal impacts through geriatric changes. Microbiome analysis in

periodontal practise offers a personalised and revolutionary approach to periodontal care, encouraging lifelong dental health and wellbeing as the field of oral microbiome research develops.

## References

1. Wilson, Prof. M.; Wilson, P. M. Dental Plaque Revisited: Oral Biofilms in Health and Disease. *J. Periodontal Res.* 1998, 33 (7), 438–438. <https://doi.org/10.1111/j.1600-0765.1998.tb02341.x>.
2. Marsh, P. D. Dental Plaque as a Biofilm and a Microbial Community - Implications for Health and Disease. *BMC Oral Health* 2006, 6 Suppl 1 (Suppl 1), S14. <https://doi.org/10.1186/1472-6831-6-S1-S14>.
3. Marsh, P. D.; Zaura, E. Dental Biofilm: Ecological Interactions in Health and Disease. *J. Clin. Periodontol.* 2017, 44 Suppl 18, S12–S22. <https://doi.org/10.1111/jcpe.12679>.
4. Zhang, Y.; Wang, X.; Li, H.; Ni, C.; Du, Z.; Yan, F. Human Oral Microbiota and Its Modulation for Oral Health. *Biomed. Pharmacother. Biomedecine Pharmacother.* 2018, 99, 883–893. <https://doi.org/10.1016/j.biopha.2018.01.146>.
5. Sedghi, L.; DiMassa, V.; Harrington, A.; Lynch, S. V.; Kapila, Y. L. The Oral Microbiome: Role of Key Organisms and Complex Networks in Oral Health and Disease. *Periodontol.* 2000 2021, 87 (1), 107–131. <https://doi.org/10.1111/prd.12393>.
6. Cattaneo, C.; Gargari, G.; Koirala, R.; Laureati, M.; Riso, P.; Guglielmetti, S.; Pagliarini, E. New Insights into the Relationship between Taste Perception and Oral Microbiota Composition. *Sci. Rep.* 2019, 9 (1), 3549. <https://doi.org/10.1038/s41598-019-40374-3>.
7. Frazelle, M. R.; Munro, C. L. Toothbrush Contamination: A Review of the Literature. *Nurs. Res. Pract.* 2012, 2012, 420630. <https://doi.org/10.1155/2012/420630>.
8. Deo, P. N.; Deshmukh, R. Oral Microbiome: Unveiling the Fundamentals. *J. Oral Maxillofac. Pathol. JOMFP* 2019, 23 (1), 122–128. [https://doi.org/10.4103/jomfp.JOMFP\\_304\\_18](https://doi.org/10.4103/jomfp.JOMFP_304_18).
9. Perez-Muñoz, M. E.; Arrieta, M.-C.; Ramer-Tait, A. E.; Walter, J. A Critical Assessment of the “Sterile Womb” and “in Utero Colonization” Hypotheses: Implications for Research on the Pioneer Infant Microbiome. *Microbiome* 2017, 5 (1), 48. <https://doi.org/10.1186/s40168-017-0268-4>.



10. Jiménez, E.; Marín, M. L.; Martín, R.; Odriozola, J. M.; Olivares, M.; Xaus, J.; Fernández, L.; Rodríguez, J. M. Is Meconium from Healthy Newborns Actually Sterile? *Res. Microbiol.* 2008, 159 (3), 187–193. <https://doi.org/10.1016/j.resmic.2007.12.007>.
11. Aagaard, K.; Ma, J.; Antony, K. M.; Ganu, R.; Petrosino, J.; Versalovic, J. The Placenta Harbors a Unique Microbiome. *Sci. Transl. Med.* 2014, 6 (237), 237ra65. <https://doi.org/10.1126/scitranslmed.3008599>.
12. Collado, M. C.; Rautava, S.; Aakko, J.; Isolauri, E.; Salminen, S. Human Gut Colonisation May Be Initiated in Utero by Distinct Microbial Communities in the Placenta and Amniotic Fluid. *Sci. Rep.* 2016, 6, 23129. <https://doi.org/10.1038/srep23129>.
13. Daalderop, L. A.; Wieland, B. V.; Tomsin, K.; Reyes, L.; Kramer, B. W.; Vanterpool, S. F.; Been, J. V. Periodontal Disease and Pregnancy Outcomes: Overview of Systematic Reviews. *JDR Clin. Transl. Res.* 2018, 3 (1), 10–27. <https://doi.org/10.1177/2380084417731097>.
14. Da Silva Bastos, V. de A.; Freitas-Fernandes, L. B.; Fidalgo, T. K. da S.; Martins, C.; Mattos, C. T.; de Souza, I. P. R.; Maia, L. C. Mother-to-Child Transmission of *Streptococcus Mutans*: A Systematic Review and Meta-Analysis. *J. Dent.* 2015, 43 (2), 181–191. <https://doi.org/10.1016/j.jdent.2014.12.001>.
15. Blaser, M. J.; Atherton, J. C. *Helicobacter Pylori* Persistence: Biology and Disease. *J. Clin. Invest.* 2004, 113 (3), 321–333. <https://doi.org/10.1172/JCI20925>.
16. Nowak, A. L.; Anderson, C. M.; Mackos, A. R.; Neiman, E.; Gillespie, S. L. Stress During Pregnancy and Epigenetic Modifications to Offspring DNA: A Systematic Review of Associations and Implications for Preterm Birth. *J. Perinat. Neonatal Nurs.* 2020, 34 (2), 134–145. <https://doi.org/10.1097/JPN.0000000000000471>.
17. Mueller, N. T.; Bakacs, E.; Combellick, J.; Grigoryan, Z.; Dominguez-Bello, M. G. The Infant Microbiome Development: Mom Matters. *Trends Mol. Med.* 2015, 21 (2), 109–117. <https://doi.org/10.1016/j.molmed.2014.12.002>.
18. Costello, E. K.; Carlisle, E. M.; Bik, E. M.; Morowitz, M. J.; Relman, D. A. Microbiome Assembly across Multiple Body Sites in Low-Birthweight Infants. *mBio* 2013, 4 (6), e00782-13. <https://doi.org/10.1128/mBio.00782-13>.
19. Chu, D. M.; Ma, J.; Prince, A. L.; Antony, K. M.; Seferovic, M. D.; Aagaard, K. M. Maturation of the Infant Microbiome Community Structure and Function Across Multiple Body Sites and in Relation to Mode of Delivery. *Nat. Med.* 2017, 23 (3), 314–326. <https://doi.org/10.1038/nm.4272>.
20. Drell, T.; Štšepetova, J.; Simm, J.; Rull, K.; Aleksejeva, A.; Antson, A.; Tillmann, V.; Metsis, M.; Sepp, E.; Salumets, A.; Mändar, R. The Influence of Different Maternal Microbial Communities on the Development of Infant Gut and Oral Microbiota. *Sci. Rep.* 2017, 7, 9940. <https://doi.org/10.1038/s41598-017-09278-y>.
21. Calderon, S. J.; Chung, S. Y.; Fields, C. J.; Mortimer, N. T. Children Tooth Brushing Behavior and Oral Microbiota: A Pilot Study. *Oral* 2021, 1 (2), 112–121. <https://doi.org/10.3390/oral1020012>.
22. Lemaire, M.; Le Huërou-Luron, I.; Blat, S. Effects of Infant Formula Composition on Long-Term Metabolic Health. *J. Dev. Orig. Health Dis.* 2018, 9 (6), 573–589. <https://doi.org/10.1017/S2040174417000964>.
23. Tanner, A. C. R.; Milgrom, P. M.; Kent, R.; Mokeem, S. A.; Page, R. C.; Liao, S. I. A.; Riedy, C. A.; Bruss, J. B. Similarity of the Oral Microbiota of Pre-School Children with That of Their Caregivers in a Population-Based Study. *Oral Microbiol. Immunol.* 2002, 17 (6), 379–387. <https://doi.org/10.1034/j.1399-302x.2002.170608.x>.
24. Kobayashi, N.; Ishihara, K.; Sugihara, N.; Kusumoto, M.; Yakushiji, M.; Okuda, K. Colonization Pattern of Periodontal Bacteria in Japanese Children and Their Mothers. *J. Periodontol. Res.* 2008, 43 (2), 156–161. <https://doi.org/10.1111/j.1600-0765.2007.01005.x>.
25. Dodds, M.; Roland, S.; Edgar, M.; Thornhill, M. Saliva A Review of Its Role in Maintaining Oral Health and Preventing Dental Disease. *BDJ Team* 2015, 2 (1), 11–13. <https://doi.org/10.1038/bdjteam.2015.123>.
26. Belibasakis, G. N. Microbiological Changes of the Ageing Oral Cavity. *Arch. Oral Biol.* 2018, 96, 230–232. <https://doi.org/10.1016/j.archoralbio.2018.10.001>.
27. Lynch, R. J. M. The Primary and Mixed Dentition, Post-Eruptive Enamel Maturation and Dental Caries:



- A Review. *Int. Dent. J.* 2013, 63 Suppl 2 (Suppl 2), 3–13. <https://doi.org/10.1111/idj.12076>.
28. Crittenden, A. N.; Sorrentino, J.; Moonie, S. A.; Peterson, M.; Mabulla, A.; Ungar, P. S. Oral Health in Transition: The Hadza Foragers of Tanzania. *PLoS One* 2017, 12 (3), e0172197. <https://doi.org/10.1371/journal.pone.0172197>.
29. Borges-Yañez, S. A.; Maupomé, G.; Martínez-Gonzalez, M.; Cervantez-Turrubiante, L.; Gutiérrez-Robledo, L. M. Dietary Fiber Intake and Dental Health Status in Urban-Marginal, and Rural Communities in Central Mexico. *J. Nutr. Health Aging* 2004, 8 (5), 333–339.
30. Schwartz, N.; Kaye, E. K.; Nunn, M. E.; Spiro, A.; Garcia, R. I. High-Fiber Foods Reduce Periodontal Disease Progression in Men Aged 65 and Older: The Veterans Affairs Normative Aging Study/Dental Longitudinal Study. *J. Am. Geriatr. Soc.* 2012, 60 (4), 676–683. <https://doi.org/10.1111/j.1532-5415.2011.03866.x>.
31. Nielsen, S. J.; Trak-Fellermeier, M. A.; Joshipura, K.; Dye, B. A. Dietary Fiber Intake Is Inversely Associated with Periodontal Disease among US Adults. *J. Nutr.* 2016, 146 (12), 2530–2536. <https://doi.org/10.3945/jn.116.237065>.
32. Salhi, L.; De Carvalho, B.; Reners, M. Update on the Roles of Oral Hygiene and Plaque Control on Periodontal Disease. *Adv. Exp. Med. Biol.* 2022, 1373, 329–339. [https://doi.org/10.1007/978-3-030-96881-6\\_17](https://doi.org/10.1007/978-3-030-96881-6_17).
33. Lertpimonchai, A.; Rattanasiri, S.; Arj-Ong Vallibhakara, S.; Attia, J.; Thakkinstian, A. The Association between Oral Hygiene and Periodontitis: A Systematic Review and Meta-Analysis. *Int. Dent. J.* 2017, 67 (6), 332–343. <https://doi.org/10.1111/idj.12317>.
34. Whelton, H. P.; Spencer, A. J.; Do, L. G.; Rugg-Gunn, A. J. Fluoride Revolution and Dental Caries: Evolution of Policies for Global Use. *J. Dent. Res.* 2019, 98 (8), 837–846. <https://doi.org/10.1177/0022034519843495>.
35. Ahmed, A.; Dachang, W.; Lei, Z.; Jianjun, L.; Juanjuan, Q.; Yi, X. Effect of Lactobacillus Species on Streptococcus Mutans Biofilm Formation. *Pak. J. Pharm. Sci.* 2014, 27 (5 Spec no), 1523–1528.
36. Farooq, I.; Bugshan, A. The Role of Salivary Contents and Modern Technologies in the Remineralization of Dental Enamel: A Narrative Review. *F1000Research* 2020, 9, 171. <https://doi.org/10.12688/f1000research.22499.3>.
37. Martino, C.; Dilmore, A. H.; Burcham, Z. M.; Metcalf, J. L.; Jeste, D.; Knight, R. Microbiota Succession throughout Life from the Cradle to the Grave. *Nat. Rev. Microbiol.* 2022, 20 (12), 707–720. <https://doi.org/10.1038/s41579-022-00768-z>.
38. Graves, D. T.; Corrêa, J. D.; Silva, T. A. The Oral Microbiota Is Modified by Systemic Diseases. *J. Dent. Res.* 2019, 98 (2), 148–156. <https://doi.org/10.1177/0022034518805739>.
39. Matsha, T. E.; Prince, Y.; Davids, S.; Chikte, U.; Erasmus, R. T.; Kengne, A. P.; Davison, G. M. Oral Microbiome Signatures in Diabetes Mellitus and Periodontal Disease. *J. Dent. Res.* 2020, 99 (6), 658–665. <https://doi.org/10.1177/0022034520913818>.
40. Verdugo, F.; Laksmana, T.; Uribarri, A. Systemic Antibiotics and the Risk of Superinfection in Peri-Implantitis. *Arch. Oral Biol.* 2016, 64, 39–50. <https://doi.org/10.1016/j.archoralbio.2015.12.007>.
41. Boasso, A.; Shearer, G. M.; Chougnet, C. Immune Dysregulation in Human Immunodeficiency Virus Infection: Know It, Fix It, Prevent It? *J. Intern. Med.* 2009, 265 (1), 78–96. <https://doi.org/10.1111/j.1365-2796.2008.02043.x>.
42. Abdulkareem, A. A.; Al-Taweel, F. B.; Al-Sharqi, A. J. B.; Gul, S. S.; Sha, A.; Chapple, I. L. C. Current Concepts in the Pathogenesis of Periodontitis: From Symbiosis to Dysbiosis. *J. Oral Microbiol.* 2023, 15 (1), 2197779. <https://doi.org/10.1080/20002297.2023.2197779>.
43. Shapiro, H.; Goldenberg, K.; Ratiner, K.; Elinav, E. Smoking-Induced Microbial Dysbiosis in Health and Disease. *Clin. Sci. Lond. Engl.* 1979 2022, 136 (18), 1371–1387. <https://doi.org/10.1042/CS20220175>.
44. Mobley, C. C. Nutrition and Dental Caries. *Dent. Clin. North Am.* 2003, 47 (2), 319–336. [https://doi.org/10.1016/s0011-8532\(02\)00102-7](https://doi.org/10.1016/s0011-8532(02)00102-7).
45. Manicone, P. F.; Tarli, C.; Mirijello, A.; Raffaelli, L.; Vassallo, G. A.; Antonelli, M.; Rando, M. M.; Mosoni, C.; Cossari, A.; Lavorgna, L.; Caputo, F.; D’Addona, A.; Gasbarrini, A.; Addolorato, G. Dental Health in Patients Affected by Alcohol Use Disorders: A Cross-Sectional Study. *Eur. Rev. Med. Pharmacol. Sci.* 2017, 21 (22), 5021–5027. [https://doi.org/10.26355/eurrev\\_201711\\_13811](https://doi.org/10.26355/eurrev_201711_13811).



46. Müller, L.; Di Benedetto, S.; Pawelec, G. The Immune System and Its Dysregulation with Aging. *Subcell. Biochem.* 2019, 91, 21–43. [https://doi.org/10.1007/978-981-13-3681-2\\_2](https://doi.org/10.1007/978-981-13-3681-2_2).
47. T, V.; As, S.; D, M.-J.; Ma, J.-R. Oral Candidiasis: A Disease of Opportunity. *J. Fungi Basel Switz.* 2020, 6 (1). <https://doi.org/10.3390/jof6010015>.
48. Mattila, K. J.; Pussinen, P. J.; Paju, S. Dental Infections and Cardiovascular Diseases: A Review. *J. Periodontol.* 2005, 76 (11 Suppl), 2085–2088. <https://doi.org/10.1902/jop.2005.76.11-S.2085>.
49. Scannapieco, F. A.; Cantos, A. Oral Inflammation and Infection, and Chronic Medical Diseases: Implications for the Elderly. *Periodontol.* 2000 2016, 72 (1), 153–175. <https://doi.org/10.1111/prd.12129>.
50. Maitre, Y.; Micheneau, P.; Delpierre, A.; Mahalli, R.; Guerin, M.; Amador, G.; Denis, F. Did the Brain and Oral Microbiota Talk to Each Other? A Review of the Literature. *J. Clin. Med.* 2020, 9 (12), 3876. <https://doi.org/10.3390/jcm9123876>.
51. How, Y.-H.; Yeo, S.-K. Oral Probiotic and Its Delivery Carriers to Improve Oral Health: A Review. *Microbiol. Read. Engl.* 2021, 167 (8). <https://doi.org/10.1099/mic.0.001076>.
52. Da, D.; Zhao, Q.; Zhang, H.; Wu, W.; Zeng, X.; Liang, X.; Jiang, Y.; Xiao, Z.; Yu, J.; Ding, S.; Zheng, L.; Zhang, Y.; Xu, X.; Ding, D. Oral Microbiome in Older Adults with Mild Cognitive Impairment. *J. Oral Microbiol.* 15 (1), 2173544. <https://doi.org/10.1080/20002297.2023.2173544>.
53. Slomka, V.; Hernandez-Sanabria, E.; Herrero, E. R.; Zaidel, L.; Bernaerts, K.; Boon, N.; Quirynen, M.; Teughels, W. Nutritional Stimulation of Commensal Oral Bacteria Suppresses Pathogens: The Prebiotic Concept. *J. Clin. Periodontol.* 2017, 44 (4), 344–352. <https://doi.org/10.1111/jcpe.12700>.
54. Pandey, K. R.; Naik, S. R.; Vakil, B. V. Probiotics, Prebiotics and Synbiotics- a Review. *J. Food Sci. Technol.* 2015, 52 (12), 7577–7587. <https://doi.org/10.1007/s13197-015-1921-1>.
55. H R, R.; Dhamecha, D.; Jagwani, S.; Rao, M.; Jadhav, K.; Shaikh, S.; Puzhankara, L.; Jalalpure, S. Local Drug Delivery Systems in the Management of Periodontitis: A Scientific Review. *J. Control. Release Off. J. Control. Release Soc.* 2019, 307, 393–409. <https://doi.org/10.1016/j.jconrel.2019.06.038>.
56. Jia, Q.; Song, Q.; Li, P.; Huang, W. Rejuvenated Photodynamic Therapy for Bacterial Infections. *Adv. Healthc. Mater.* 2019, 8 (14), e1900608. <https://doi.org/10.1002/adhm.201900608>.
57. Gilbert, J. A.; Blaser, M. J.; Caporaso, J. G.; Jansson, J. K.; Lynch, S. V.; Knight, R. Current Understanding of the Human Microbiome. *Nat. Med.* 2018, 24 (4), 392–400. <https://doi.org/10.1038/nm.4517>.
58. Caselli, E.; Fabbri, C.; D’Accolti, M.; Soffritti, I.; Bassi, C.; Mazzacane, S.; Franchi, M. Defining the Oral Microbiome by Whole-Genome Sequencing and Resistome Analysis: The Complexity of the Healthy Picture. *BMC Microbiol.* 2020, 20 (1), 120. <https://doi.org/10.1186/s12866-020-01801-y>.
59. Fragkioudakis, I.; Riggio, M. P.; Apatzidou, D. A. Understanding the Microbial Components of Periodontal Diseases and Periodontal Treatment-Induced Microbiological Shifts. *J. Med. Microbiol.* 2021, 70 (1). <https://doi.org/10.1099/jmm.0.001247>.
60. Lloréns-Rico, V.; Simcock, J. A.; Huys, G. R. B.; Raes, J. Single-Cell Approaches in Human Microbiome Research. *Cell* 2022, 185 (15), 2725–2738. <https://doi.org/10.1016/j.cell.2022.06.040>.
61. Lum, A. G.; Ly, M.; Santiago-Rodriguez, T. M.; Naidu, M.; Boehm, T. K.; Pride, D. T. Global Transcription of CRISPR Loci in the Human Oral Cavity. *BMC Genomics* 2015, 16 (1), 401. <https://doi.org/10.1186/s12864-015-1615-0>.
62. Li, Y.; Zhang, H. Nanoparticle-Based Drug Delivery Systems for Enhanced Tumor-Targeting Treatment. *J. Biomed. Nanotechnol.* 2019, 15 (1), 1–27. <https://doi.org/10.1166/jbn.2019.2670>.