# Early warning role of oral microorganisms in systemic systemic diseases in children

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**Abstract:** *The oral microbiome is highly diverse, with approximately 700 microorganisms, including bacteria, fungi, and viruses, and is one of the five major bacterial reservoirs (intestinal, oral, cutaneous, nasal, and genitourinary tracts), making the oral microbiota of children unique and easily accessible compared to other body sites. Several studies have demonstrated that the oral microbiota of children are closely associated with systemic diseases and can be used as an early warning marker of systemic health. In this article, we review several common systemic diseases in children based on recent research advances.*

**Keywords:** *Oral microbiome, systemic diseases, disease warning*

## 1. Introduction

Microbiology has rapidly evolved in recent years, and future developments are focused on more clinical applications. It has been shown that oral microorganisms interact with many organs of the body (e.g., gut, lungs) in a bidirectional manner before and are closely related to systemic health. For children, non-invasive collection of samples by saliva or mucosal swabs is convenient and efficient for diagnosing and monitoring biomarkers of systemic diseases and holds great promise as an aid in diagnosis. Oral microbes play a crucial relationship in maintaining oral homeostasis and systemic health, and are essential for the management of systemic diseases.

## 2. Colonization, development and factors influencing the oral microbiota during childhood

Within 5 minutes of birth, the microflora of the oral, nasal, skin and intestinal tracts are very similar, and subsequently the infant is exposed to a large number of microorganisms through breathing, feeding, caregivers and the outside world, and within 24 hours of birth, pioneer microorganisms have colonized the oral cavity, most commonly Gram-positive bacteria, followed by Gram-negative anaerobic bacteria, including Wegmococcus, Twins. Granulococcus spp. and others [1]. Later, as the infant grows, the microbial community becomes rich and diverse, and by 5 months of age, the infant already exhibits an oral microbial community different from that of the mother, consisting mainly of the thick-walled phylum, the phylum Aspergillus, the phylum Actinomycetes, the phylum Synechococcus, and the phylum Helicobacter [2]. When the first teeth erupt, the oral flora also changes, with a significant increase in Streptococcus mutans. At 12 months of age, Fibrobacter $CO_2$, Neisseria, Streptococcus, Staphylococcus aureus, and Ciliophora dominated, and at 18 and 24 months, the proportion of abundance of Fibrobacter $CO_2$ spp. continued to decrease, but the abundance of Burkholderia and Maltophilus narrow-feeding monocytogenes tended to increase, especially Enterobacter spp. which became the dominant genus, and despite the differences, Neisseria, Streptococcus, and Ciliophora have been the dominant genera [3], at the age of 2 years, the structure of the oral bacterial community in children begins to stabilize, but it also varies during the mammary, mixed and permanent dentition, and in later growth due to caries, antibiotic use, and the placement of biological materials in the oral cavity regarding the health of the host can affect the composition of the oral microbiota.

Fungal communities, especially Candida, can also colonize the infant's mouth during the first day of life, and the common and abundant fungi in the infant's mouth are Pseudomonas, Candida tropicalis, Saccharomyces cerevisiae, Candida mimicum, Candida albicans, and dental branch moulds [4]. Viruses can also be detected in certain disease states, and common viruses in children are herpes simplex virus, coxsackie A virus, human papilloma virus, and EBV [5].

## 3. Oral microbiology and systemic systemic diseases in children

### 3.1. Oral flora and hand, foot and mouth disease in children

Hand, foot and mouth disease (HFMD) is a highly infectious and globally distributed viral disease and a common childhood illness. It is caused by several enteroviruses, the most common being coxsackievirus A6 (CV-A) and enterovirus 71 [6]. In most cases, HFMD is benign and self-limiting, but severe neurological and respiratory complications, such as encephalitis and pulmonary hemorrhage, often lead to death or permanent paralysis [7], often occur. In addition, enteroviral infections may be asymptomatic, but the main treatment of the disease is currently focused on symptomatic relief, so elucidating the differences in HMDF microflora among children with HFMD may provide new clinical strategies for diagnosis, prevention, and even treatment.

It has been found [8] that intestinal microorganisms and enteroviruses can interact, leading to enrichment of Streptomyces and Clostridium in the gut of children with severe HFMD, a result that suggests that these two flora could be used as novel predictive biomarkers for severe cases of HFMD. Similarly enteroviruses interact with oral microorganisms, Si Xian Ho [9] et al. studied the differences in oral microorganisms between healthy children and asymptomatic and symptomatic children with HFMD and showed that Streptococcus was significantly elevated in children with symptomatic HFMD and positively correlated with gut flora levels, while normal flora was also found to be abundant in healthy children, but some flora were This may be due to the fact that different immune responses occur in the two groups and that the immune response in the asymptomatic group is not sufficient to regulate these flora, while the elevation of Streptococcus in children with symptomatic HFMD also significantly affects the composition of other flora in the oral cavity. It is suggested that the differential characteristics of the oral microbiota may serve as a potential marker for the status and prognosis of the disease.

### 3.2. Oral microorganisms and type I diabetes

Type 1 diabetes (T1D), also known as insulin-dependent diabetes mellitus, is a chronic autoimmune-mediated disease and is the second most common autoimmune disease of childhood. The disease is primarily driven by a combination of genetic susceptibility and environmental factors [10]. There is a bidirectional relationship between diabetes and periodontitis, with a fivefold increase in the prevalence of periodontitis reported in adolescents with T1D compared to the healthy group [11], in addition to a positive correlation between the degree of hyperglycemia in T1D and periodontal disease. In T1D, chronic hyperglycemia leads to the formation of bioactivated glycated proteins and lipids that promote an inflammatory response with elevated inflammatory markers such as C immunoglobulin, tumor necrosis factor alpha, and interleukin-6 (IL-6), which in turn cause periodontal damage and increase periodontal pathogens in the oral microbiota, such as Streptococcus granulosus and Rothschildia. Animal studies [12] have also found that diabetes enhances the expression of IL-17 and by blocking IL-17 also alters the composition of oral microbiota.

Some findings [13-15] found that there is variability between the oral microbiota of children with T1D and healthy children, characterized by an increasing number of genera containing a variety of opportunistic pathogens, among which Streptococcus is the most abundant, while several genera found in the saliva of children with T1D are associated with the gut microbiota of children with T1D according to the T1D gut disease database [16].Yuan X et al. studied characterized the oral microbiota of children with T1D in the acute and chronic phases and found significant differences between the acute phase group with reduced oral hygiene diversity and increased windiness of genera containing opportunistic pathogens compared to healthy controls, whereas in chronic T1D with glycemic control, some of the flora recovered. In addition glycated hemoglobin (HbAIc), fasting blood glucose (FBG) and white blood cell counts (WBCs) were positively correlated with oral enrichment of Streptococcus, Streptococcus granulosus spp., Rothschildia, and Bundle Red cocci in children with T1D. The differential enrichment of oral microbial communities between healthy children and children with T1D and different stages of the disease suggests that oral microorganisms may be non-invasive biomarkers as an adjunct to the assessment of glycemic control in T1D, and because the initial β-cell cell damage to clinical manifestation may last for several years, they may also serve as potential markers for early diagnosis in the latent phase, facilitating early treatment and delaying disease progression.

### 3.3. Oral flora and autism in children

Autism Spectrum Disorder (ASD) is a complex group of neurodevelopmental disorders characterized by difficulties in social interaction and repetitive stereotyped interests or behaviors, and its etiology is mainly genetic and environmental. In neuropathology, oral-microbial-brain is interconnected and oral microbes are associated with various neurological disorders. An animal study [17] transferred oral microbes collected from ASD patients to mice and found a significant increase in the expression of serotonin-related genes, and autistic behavior was associated with changes in the abundance of Porphyromonas, Fosetanella, and G-7 specific oral microbes. It has also been found that autism affects the composition of oral microorganisms, altered dopamine (DA) signaling is associated with ASD, and abnormal release of DA [18] may lead to alterations in oral microorganisms, and a significant decrease in Clostridium perfringens wind was found. ragusa M [19] found that dysregulation of salivary miRNA and microbiome in children with ASD may be associated with cognitive impairment in ASD, and miRNAs were correlated with microorganisms, most significantly miRNA-141-3P and Burkholderia cepacia were negatively correlated. And it has been demonstrated that Burkholderia cepacia can be used as a marker of ASD. It has been found [20,21] that there is a significant difference between the oral microbiota of children with ASD and healthy children controls. The current "gold standard" for ASD diagnosis is the fifth edition of the Diagnostic and Statistical Book of Mental Disorders (DSM-5), but these criteria are based only on clinical symptoms and lack laboratory methods. A correlation between oral microbiology and ASD progression has been demonstrated, and although a causal relationship cannot be distinguished at this time, the differential expression in ASD suggests that new diagnostic methods could be designed based on oral microbiological features to improve future diagnostic strategies.

### 3.4. Oral flora and childhood acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy in children, accounting for approximately 30% of childhood malignancies (0-14 years of age), and originates primarily from B- and T-lineage lymphoid progenitor cells. Wang Y [22] et al. studied 13 newly diagnosed ALL patients with 12 healthy children as controls and showed that ALL patients had reduced oral microbial diversity, decreased abundance, increased abundance of thick-walled phylum and decreased abundance of Clostridium phylum. Further study by [23] of children with ALL 1 year after chemotherapy and healthy children showed differences in abundance from phylum to genus level between the two groups.Hoon et al [24] also found a high incidence of oral mucositis and enrichment of gram-negative bacteria such as Clostridium nucleatum and Prevotella in the oral microbiota in the post-chemotherapy population.

Significant differences in microbiology have been observed at disease onset and during chemotherapy, and the interaction between the oral microbiota and the immune system has serious implications for the development and treatment of ALL, for example, increased abundance of opportunistic pathogens may be an important factor in the increased risk of systemic infections in patients with leukemia. Leukemia may be less feasible to perform microbiological analysis at the time of diagnosis, but in terms of prevention strategies, the study of oral microbiota can help identify oral-associated infections and systemic systemic infections necessary to improve health status during chemotherapy [25].

### 3.5. Oral flora and obstructive sleep breathing syndrome symptoms

Obstructive sleep apnea (OSA) in children is one of the most common forms of sleep breathing disorder, caused by collapse and obstruction of the upper airway during sleep, characterized by recurrent partial or complete upper airway collapse and obstruction during sleep, disturbing normal ventilation and sleep architecture, recurrent hypoxemia, hypercapnia, and sleep disturbances [26], and the reported prevalence of OSA in children ranges from 0.7 to 10.3%, with a peak between 2 and 8 years of age [27].

Children with OSA are often associated with tonsillar and/or adenoid hypertrophy and mouth breathing. The composition of oral microorganisms is altered in children with tonsillar and/or adenoid hyperplasia compared to healthy children, and oral microorganisms may also be altered in children with OSA due to the structural proximity of the oral cavity to the adenoids and tonsils, and mouth breathing may also be altered by reduced salivary flow, poor self-cleaning, and easy plaque accumulation on the dental surfaces, but there are also studies suggest that the oral microbial composition may also be

altered by the intermittent hypoxia associated with associated OSA. Although there are no studies to clarify the causal relationship between oral hygiene changes and OSA, a case-control study in which Xu et al. compared the composition of oral microorganisms in 30 children with OSAS and 30 healthy children using 16SrRNA gene sequencing showed that compared to healthy controls, Weronella, Prevotella, Pseudomonas, Campylobacter, and Vibrio butyric acidophilus were OSAS patients were more abundant, and all five groups were Gram-negative bacteria, of which Campylobacter spp. is one of the core groups closely associated with periodontitis, and Prevotella intermedia in Prevotella spp. is the dominant bacteria in periodontal disease in children, and the increased abundance of periodontitis-causing bacteria may be related to the susceptibility of OSA patients to subgingival plaque accumulation. Oral microbial features may serve as a potential marker for OSA disease.

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