# Oral microbiome pattern in hematological pediatric malignancies: need for investigating

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## Abstract

Several evidence suggest the role of oral microbiota in metabolic, immuno-mediated, oncological diseases. In pediatric population, aberration in oral microbiota were investigated in relation to host and environmental factors, pre, during and post chemotherapy. However, limited information can be obtained on effective microbiota pattern in leukemia pediatric patients and on its role related to local and systemic complications. The aim of our study is to conduct a critical review of the literature on this issue, providing to suggest future researches planning.

**Keywords:**  oral microbiome, acute lymphoblastic leukemia, ALL, hematologic disease, childhood leukemia, oral dysbiosis, microbiota.

## Introduction

The oral microbiota represents the second largest microbial community after the intestinal one, able to undergo rapid compositional and metabolic changes induced by multiple host and environmental factors, including local and systemic diseases (e.g., caries, periodontitis, rheumatoid arthritis, diabetes, cancers), in relation of which, the definition of its possible role represents the challenge of the current scientific-translational research [1].

In hematological malignancies the study of oral microbiome could offer interesting interpretations, regarding the onset and persistence of oral complications, especially in the pediatric population.

In children, acute lymphoblastic leukemia (ALL) is the most frequent form of onco-hematological diseases, accounting for almost 25% of all neoplasia. While recent therapeutic advances have made possibilities to increase the five-year survival rate of young patients to almost 90%, there is still a high incidence of incoming complications associated with high morbidity and mortality [2][3]**.** It has been established that in pediatric patients with neoplastic and/or iatrogenic neutropenia, the 25%–45% of septicemia cases are strongly related to oral dysbiosis. In addition, the high incidence of oral mucositis, by cytotoxic effects of the antiblastic treatments, seems to be strongly related to oral microbial changes during treatment.

To date, despite the significant impact of acute oral complications on the *outcome* of onco-hematological

pediatric patients, it seems exist a disarming epidemiological and experimental uncertainty on the oral microbiota status.

The aim of the present study was therefore to conduct a critical review of the literature on the oral microbiota pattern in leukemia pediatric patients.

## Materials and methods

### Focused questions

How many studies regarding the role of oral microbiota in leukemia pediatric patients report an overall microbiota pattern investigation without relation to any local antimicrobial treatments? And how many studies, among these, investigate the variations of the oral microbiota in relation to the pathological state, before starting any oncological treatments?

### Search criteria

Only the studies related to the focused questions were examined. Moreover, studies omitting a well-defined overall microbiota sample and/or investigating its modification in relation to any oral antimicrobial treatment, were excluded. Studies were identified by an electronic search of scientific articles from different biomedical databases (e.g., PubMed, Ovide/MEDLINE, Web of Knowledge, Embase) and by scanning reference lists of articles. Only studies published in English from until December 2021 were considered eligible. The following search terms, used separately and jointly, were deployed: oral microbiome, ALL, hematologic disease, childhood leukemia, dysbiosis, microbiota. The studies were initially selected by applying the inclusion and exclusion criteria of the title and the abstract. Duplicate papers were removed, and selected articles were scrutinized to assess for eligibility.

## Results

According with the focused questions of our research, only 2 cases-control studies were considered eligible, for a total of 52 patients affected of acute lymphoblastic leukemia (ALL) [4][5]. These studies were performed by the same authors in different time (2014 and 2021) using the same methods of oral microbiome sample and detection. As sampling, they use the supragingival plaque picked up, two hours after breakfast, with a sterile Gracey curette from the mesial surface of teeth in upper right and lower left quadrants or upper left and lower right quadrants. The collected plaque samples were released from the curette by agitation in 700 ml of TE buffer (10 mM Tris-Cl [pH 7.5] and 1 mM EDTA). The processing technique involved the extraction of DNA and the use of the hypervariable sequences V1-V3 of the 16s rRNA with pyrosequencing 454**.**

In the 2014 [4], the oral microbiome in 13 untreated ALL cases was detected and compared with what of 12 healthy controls, with the identification of the following microbial species: Firmicutes phylum (p=0.001), Bacilli class (p=0.001), Lactobacillales order (p=0.001), Carnobacteriaceae (p=0.002), Aerococcaceae families (p=0.001), Abiotrophia genus (p=0.012). In the 2021[5],  a similar investigation was performed in 39 ALL cases treated with CCLG-ALL (Chinese Children's Leukemia Gropu protocol), aged 7-18 years. By

comparison with 39 healthy controls, 6 major phyla were identified, including Firmicutes, Proteobacteria, Fusobacteria, Actinobacteria, Bacterioidetes, and Candidate division TM7. Particularly, notable differences in abundance between ALL patients and healthy controls were found for the two phyla: Firmicutes (p=0:002) and Candidate division TM7 (p=0:006).

### Conclusions

The changes of oral microbiome in leukemia patients are controversial. We identified only 2 studies (by the same research group) on changes in overall oral microbiome, respectively before and during oncological treatment. In ALL patients before treatment, there are lower richness and diversity of the oral constituent strains compared to healthy controls, demonstrating how the immune status is strongly associated with the modeling of the oral microbiome. This oral dysbiosis seems to increase in ALL patients undergoing treatment, which is known to seriously affect, directly and indirectly, the oral health integrity of these patients and, consequently, their clinical outcome. A very strong limitations of two investigated studies are the scarce sample size. Another critical issue regards the choice of the microbiological sample. The supra-gingival plaque, especially in hospitalized pediatric subjects, can show variations in its composition related to the oral health conditions as well as in processing techniques.

With the current state of knowledges, there remain too many unanswered questions concerning oral microbiota modulation in pediatric leukemia diseases. Therefore, it remains a challenge to design specific treatment strategies to manipulate oral microbiome (i.e., by use of prebiotic or probiotic) to improve clinical outcome. Progress in systems biology approaches tailored to oral microbiome research in onco-hematological pediatric diseases, are strongly needed.

## References

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