ORIGINAL ARTICLE

# Comparative Assessment of the Activities and Characteristics of Caries Related Salivary Microorganism between Children with Acute Lymphoblastic Leukemia and Healthy Children

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## Abstract

**Purpose:** This study was aimed to evaluate the caries activity in children with acute lymphoblastic leukemia (ALL) undergoing maintenance stage chemotherapy courses. **Materials and Methods:** This is an observational-analytical and case-control study conducted on the 27 children (4-12 years old) with ALL who were in the maintenance phase of chemotherapy in the Ahvaz Shafa Hospital, Iran. The participants of the control group, matched in terms of age, gender, and cultural status with the case group, were selected among the healthy children referred to Ahvaz Razi Hospital, Iran. The children received only a clinical dental examination without radiographs. The number of decayed (D), missing (M) and filled (F), and teeth (T) were recorded based on the WHO based DMFT index and without the use of radiography. Then, after radiographic assessment, the stimulated saliva samples were collected from the subjects to assess the salivary *Streptococcus mutans* counts, salivary *Lactobacilli* counts, and salivary buffer capacity. **Results:** The salivary *S. mutans* counts in ALL children were significantly higher than the control group ($P < 0.001$). In both groups, *Lactobacilli* counts and salivary pH and DMFT were similar ($P > 0.05$). Furthermore, the ALL group tended to have lower salivary flow rate than healthy subjects ($P < 0.05$). **Conclusions:** Specific oral prevention regimes should be planned with more cautions for children suffered hematology illness undergoing antineoplastic therapy with respect to children without blood problems.

**Key words:** Acute lymphoblastic leukemia, decayed, missing, and filled teeth, *Streptococcus mutans*, salivary pH, salivary flow rate, *Lactobacilli*

## INTRODUCTION

Leukemia is a virulent of blood textures characterized by unusual leukocytes proliferation of beans nucleus and propagation of these cells into blood circumstance.[1] Leukemia is clinically categorized based on disease period, acute or chronic nature, and the involved cells type (myeloid, lymphocyte, and monocyte).[2] Acute leukemia is the most common virulence disorder among children which contributes to one-third of all childhood virulence; about 80% of them are lymphocytic.[1] The prevalence peak of acute lymphoblastic leukemia (ALL) is for the age range of 2-5 years old and is more common among sons.[3] Childhood leukemia was treated mainly with the use of chemotherapy that has known effects on the oral mucosa.[4-7] Years ago, before chemotherapy, all patients died usually within 2-3 months.[8] Today more than 85% of children diagnosed with ALL survive for at least 5 years.[9] With treatment advances in childhood leukemia, infective complication has emerged as one of the major causes of morbidity and mortality.[10] The antimicrobial defense of the leukemic patient is severely depressed and even communal bacterial can, therefore, become life-threatening.[8]

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Between 25% and 54% of cases of septicemia in neutropenic cancer patients appear to originate from oral colonizing bacteria[11] the dental health of these patients during and after treatment is, therefore, of importance.[12] Accordingly, early diagnosis and treatment are very important to prevent any oral infection from becoming systemic.[8]

Caries is an infection disease with multifactorial etiology.[13] The process of caries development is already unknown, but it can be measured by a dynamic balance between pathologic factors (acidogenic bacteria, salivary function depletion) and maintenance factors (proteins, fluoride, calcium, and phosphate).[14] This disease needs a host (tooth in mouth area), food substrata, and aciduric bacteria. Important agents that adjust progress or regress of disease are outflow, dilution, neutralization, and salivary remineralization capacity. If mouth circumstance not be favorable (high and frequent acid production), reduce tooth can be damaged or reformed by sufficient salivary flow, dilution, and neutralization.

Oral infection treatment increases tooth structure remineralization by reducing cariogenic microorganisms and suitable environment creation. This process stops caries and treats the disease.[1]

## MATERIALS AND METHODS

This was an observational analytical study conducted on 27 children diagnosed with ALL in Ahvaz Shafa Hospital as case group and 27 healthy children in Ahvaz Razi Hospital as a control group. ALL patients were in maintenance stage chemotherapy or 3 months later and received same drugs. None of the patients were undergoing radiotherapy, taking nucleus bone graft and having systemic disease. Witness group was selected based on age, gender, and cultural and economical conditions for synchronizing the patients. ALL patients were prevented eating fruit, vitamins, tea, and coffee-1 h before sampling due to their effects on salivary pH (after taking testimonial from their parents).

A table containing some information about personal data as age, gender, parent academic degree, and decayed, missed, filled teeth (DMFT) of ALL teeth were designed based on WHO, it has been done for examining the patients by senior dentistry students by centralized light, dental explorer, and mirror.

After that, the salivary index was recorded. In this record, the amount of saliva was measured by accumulating saliva in 1 min after 45 times bland paraffin chewing in sterilized tube[15], and pH number was measured by paper strip.

Finally, ALL patients and parents have been educated about oral hygiene, and the educational package was given to them. Some cases that need treatment were sent to clinical centers.

### Microbiological procedure

The salivary samples were collected in sterile cap tube and transported to the laboratory immediately and processed on the same day. The sample was vortexed 15 s and diluted 1:10, 1:100, and 1:1000 with sterile physiologic saline. One loop ($1/1000^{th}$ ml of sample) was inoculated on the modified mitis salivarius agar "mitis salivarius-bacitracin" agar. This medium prepared by solving mitis salivarius agar (HiMedia, India) according to the manufacturer's recommendation with potassium tellurite, 0.2 µ/ml bacitracin and 20% sucrose for detection *Streptococcus mutans*. The plates were incubated anaerobically for 48 h at 37°C.

For *Lactobacilli* one loop of the diluted sample was cultured on Man-Rogosa-Sharpe agar (Merck, Germany) plates and incubated in candle jar with 5% $CO_2$ for 48 h at 37°C.

Further identification of *mutans* streptococci after culturing on the selective media was Gram-staining, and biochemical test (including ability to ferment mannitol, inulin, sorbitol, raffinose, hydrolysis bile esculin, and arginine dehydrolysis).

After 48 h of incubation, characteristics of colonies were studied and the number of colony forming units of *S. mutans* (CFU/ml) and *Lactobacilli* (CFU/ml) of saliva was determined using a colony counter.

All data recorded on the examination dates and all samples were transferred to microbiology laboratories in sterilized condition to record cariogenic microorganism of saliva and laboratory evaluations. To blinding and preventing disorder in counting samples a code was specified for each form and container before sending salivary samples.

## RESULTS

The main goal of this survey was to determine several caries risk factors in children with ALL undergoing chemotherapy. In our study, under observation children have been divided into two 27-member groups; patient group: 8 daughters and 19 sons with mean age of 7.29 years. Healthy group: 14 daughters and 13 sons with mean age of 7.22 years. All data have been analyzed by SPSS software, $20^{th}$ edition. Normality of all data was checked by one sample Kolmogorov–Smirnov test because all variables were quantitative. Applying descriptive exams were impossible due to $P < 0.05$ and Mann–Whitney model was used in replace of *t*-test.

As Graph 1 shows *S. mutans* counts of the ALL group is significantly higher than the control group ($P = 0.04$). The *S. mutans* was detected in saliva of 11 children (mean: 59) among 27 patients, whereas this number was 6 in control group (mean: 21.85).

*Lactobacilli* counts in patients group were more than the control group, but it is not statistically significant ($P = 0.4$). The level of salivary *Lactobacilli* did not grow in 4 leukemic children, whereas it was observed just in one case of the healthy children [Figure 1].

Based on the obtained results, salivary flow rate in the ALL children was significantly lower than healthy counterparts [Figure 2] ($P = 0.00$).

As Figure 2 shows, the both groups had an equivalent pH value and count be compared in them ($P = 0.71$).

Due to the wide age range of the participants of this study, the relevant data were dividing into two age groups of under 7 years old and above 7 years old groups and then analyzed. Under 7-year-old children had primary dentition and above 7 had mixed dentition systems.

In addition, DMF among the ALL children lower than 7 years old was lower than control group and in above 7 years, it was higher than control group. However, this difference was not statistically significant in both groups [Figure 3].

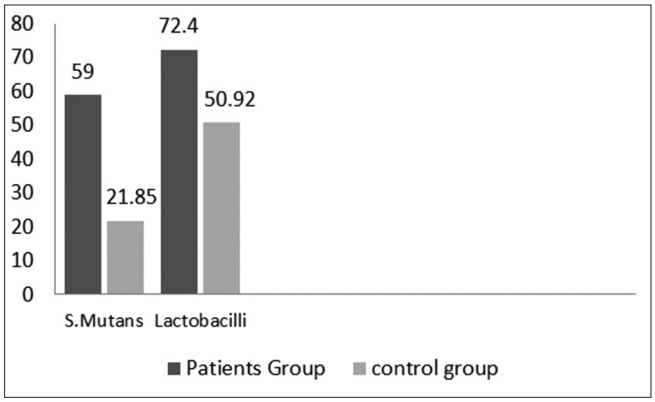


**Figure 1:** Comparison of salivary *Lactobacilli* between healthy and leukemic children

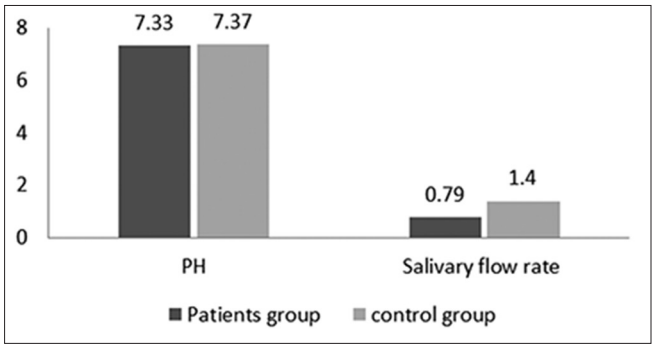


**Figure 2:** Comparison of pH value between the healthy and leukemic children

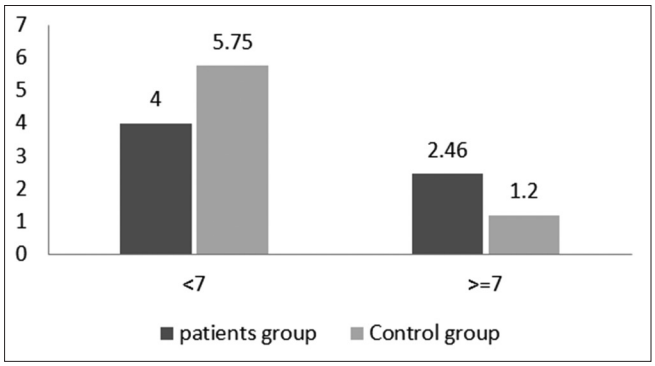


**Figure 3:** Comparison of decayed, missed, filled values in leukemic, and healthy children for the two age groups: Lower than 7 years old and 7 years old or higher children

## DISCUSSION

Regarding the few number of reported studies about comparison of caries microorganism and salivary characteristics in healthy and ALL children, the aim of this study is to do a comprehensive evaluation in field of considering the caries amount in ALL children undergoing maintenance stage chemotherapy courses. Hence, we made a comparison between ALL and healthy children in field of DMFT and some salivary factors as *S. mutans* bacteria, *Lactobacilli*, salivary flow rate, and salivary pH.

In this study, *S. mutans* counts in ALL children were significantly higher than healthy ones. This difference was statistically significant ($P < 0.05$).

In both groups, no significant difference was observed between *Lactobacilli*, Salivary pH, and DMFT ($P > 0.05$). Salivary secretion in ALL children was less than healthy ones, and this difference was statistically significant ($P < 0.05$).

Few previous studies have reported either a similar level or an increased level of decay in children with malignant diseases.[16-19] Most of these studies, however, had used DEFTS/DMFTS values as the only scoring method. Past caries experience is no longer the most powerful predictor for future caries incidence. In addition, patients involved in the previous studies had suffered from different malignant diseases and received different treatment protocols.[12]

This study is an attempt to examine the caries activity in a group of children receiving chemotherapy only. We recruited children suffering ALL under maintenance stage chemotherapy to avoid the differences in anticancer regimens.

Studies have shown that several risk factors should be investigated together to successfully predict the future caries risk.[12] In addition, to the number of decayed teeth, the salivary counts of *S. mutans*, *Lactobacilli,* and buffer capacity were examined in this study.

*S. mutans* are presumed to play a major role in the initiation of carious lesions. Longitudinal studies showed that individuals

with increased *S. mutans* levels in plaque and saliva had significantly higher caries activity.[20-22]

This study shows that *S. mutans* counts of the study group were significantly higher than the normal population. This result is supporting the reported results of Pajari *et al*.[23] They claimed that *S. mutans* amount increases in cancer suffered patients and cured patients. Furthermore, conflicting results have been reported by Ou-Yang *et al*.,[12] O'Sullivan *et al*.[8]

O'Sullivan *et al*.[8] showed that the *S. mutans* level is lower during chemotherapy versus pre-treatment or post-treatment levels; Ou-Yang *et al*.[12] mentioned that *S. mutans* level in children suffering ALL is lower than normal group, they were against our results.

The change of salivary *S. mutans* counts during chemotherapy may be influenced by the reduction of salivary volume, the disturbance of the immunological system[24] or the use of anticancer drugs.[8]

Regarding the fact that pre-treatment and post-treatment levels are comparable, O'Sullivan *et al*.[8] would suggest in his study that the changes in count values are treatment-related rather than disease-related.

O'Sullivan *et al*.[8] mentioned several probable reasons for these findings. First the reference group was smaller than the study group, and second the caries experience was higher in the reference group compared with the study group. Sensitivity testing showed that daunorubicin had the greatest effect on the oral bacteria and *S. mutans* in particular. This drug is used mainly in a combination drug therapy for induction of remission and intensification treatment of acute leukemia, was received by all patients in this study. Daunorubicin is an antibiotic derived drug.

In our study, the average age in both study and reference group was very similar. DMFT was not statistically different. On the one hand, patients did not use daunorubicin drug because of being in maintenance phase or 3 months later. On the other hand, patients use methotrexate that has very low effect on bacteria's.[8]

Ou-Yang *et al*. expressed in his study that the reduction of salivary counts of *S. mutans* could be affected by the prophylactic antibiotics usage in the regimen. ALL children take cotrimoxazole every other day for infection prevention in Ou-Yang *et al*.'s treatment protocol. Cotrimoxazole can inhibit the growth of streptococci and may have accounted for the drop in *S. mutans*, but in our study patients did not use cotrimoxazole.[12]

*Lactobacilli* are believed to have a role in the progression of deep carious lesions. *Lactobacilli* levels also have been used, but they do not seem to be as effective as caries predictors as the *S. mutans*.[25-28]

In this study, salivary *Lactobacilli* weren't statistically different in the study and reference groups that support the Wahlin and Holm[29] and Ou-Yang *et al*. results.[12]

The effects of chemotherapy on human salivary glands and the composition of human saliva are difficult to assess, and available information is relatively sparse and often contradictory.[30] Furthermore, in this study the amount of induced salivate in ALL suffering children was less than control group and this difference was statistically significant ($P < 0.05$).

Wahlin[15] found that at the start of cytotoxic treatment the secretion rate in the patients with leukemia was lower than in healthy persons. The rate fell significantly after 1-3 days and later rose to the level seen in the healthy persons. Main *et al*.[27] found a continuous decrease in the salivary secretion rate in cancer patients after 3 months of treatment with cytotoxic drugs. The rate was lower than in healthy control subjects, which supported our findings.

It can be due to this fact that patients are very anxious when the cytotoxic therapy starts and emotional stress has been shown to reduce the salivary secretion rate.[31] Clinically, patients receiving cytotoxic drugs tend to experience dry mouth with difficulty in mastication.[32]

Nausea and vomiting are frequent side effects during the 1st day of treatment with cytotoxic drugs.[33] To treat nausea and vomiting, antiemetic were used in the patients. This medication coincided with the decrease in salivary secretion rate.[15]

In other studies of cancer patients salivary secretion rates were not affected during medication with cytotoxic drugs, and there is no significant difference between salivary secretion rates in healthy and patients treated with cytotoxic drugs.[34,35] In analyzing the side effects of cytotoxic drugs, it is important to realize that many factors are involved, such as different types of cytotoxic, antiemetic, and antimicrobial drugs; methods of administration, and dosage. Comparisons with other studies are complicated by differences in these factors and in the patients studied.

In this study, salivary pH was not significantly different in both groups. Based on the Sepet *et al*.[36] studies, pH was in normal interval in ALL children, whereas in Pajari *et al*.[23] and Hegde *et al*.[37] studies, pH depletion was observed among ALL children. This similarity can be due to the time of oral examination; examinations of both groups were done before noon that was at least 1 h after their last meal, that is a sufficient time interval for adjusting pH by saliva.[38]

Since a reduced SFR has been reported in children with ALL and that a diminished SFR favors accumulation of dental plaque on tooth surfaces, it may be hypothesized that

children with ALL may be more susceptible to dental caries as compared to medically healthy children.[37]

In this study, no significant difference is observed in DMFT of both groups, which supports the results of Maciel *et al*.[39]/ Kinirons *et al*.[40] studies; it can be due to sanitarian educations and parents' awareness.

Conflicting results have been reported by Hegde *et al*.[37] and Nasim *et al*.[41] Although the negative effects of anticancer therapy on SFR are well-established;[37,41-43] studies have reported that the oral mucosal inflammation induced by chemotherapy, may prevent some patients from performing daily oral hygiene maintenance regimes.[42,44]

Hence, hematology patients need special dental considerations beside antineoplastic treatments. Oral sanitarian in these children should be done with more cautions than children without blood problem.[45] Special oral and dental prevention should be managed in ALL children and sanitarian rules must be educated before starting chemotherapy. Twice brushing daily and gum preservation must be advised by the treatment team. Patients with oral dryness or reduction in salivary buffer capacity background should perform dental sanitary carefully to minimize oral risks. Some method can be applied to increase oral moisture such as more water drinking times, chewing gum, and using artificial saliva. Using adhesive food or sacarose is not advised in their diets. In these children, using local fluorides such as fluoride toothpaste or mouthwash can maintain teeth additionally. Dentists can prescribe centralized local fluoride and mineral agents to prevent caries efficiently.[2]

Caries spoilages should be treated based on chemotherapy phase while neutrophil and placket numbers are approvable. Furthermore, all patients ought to be examined each 3-6 months periodically. It should be mentioned that having a healthy mouth can minimize the side effect of chemotherapy.[46]

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