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## DYNAMICS OF INDICATORS OF ORAL FLUID PROPERTIES IN CHILDREN WITH LESIONS OF THE ORAL MUCOSA AGAINST THE BACKGROUND OF ACUTE LYMPHOBLASTIC LEUKAEMIA DURING TREATMENT

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The work was devoted to the study of the dynamics of indicators of the properties of oral fluid in children with lesions of the oral mucosa against the background of acute lymphoblastic leukemia during treatment with the methods developed by the authors. The clinical trials involved 126 children aged 2 to 18 years who were diagnosed with acute lymphoblastic leukemia. The most common inflammatory diseases of periodontal tissues and oral mucosa in children with acute lymphoblastic leukemia were chronic gingivitis and candidal stomatitis. All children who underwent clinical trials were divided into 2 groups – the main and comparison groups. Children in the comparison group were treated with standard protocol methods. Children in the main group were treated with the developed treatment and prevention complex. The obtained results of the studies showed a stimulating effect of the treatment and prevention measures on the correction of the properties of the oral fluid in both the main study and comparison groups.

**Key words:** acute lymphoblastic leukaemia, chronic gingivitis, candidal stomatitis, oral mucosa, salivation rate, oral fluid viscosity, children.

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## ДИНАМІКА ПОКАЗНИКІВ ВЛАСТИВОСТЕЙ РОТОВОЇ РІДИНИ У ДІТЕЙ З УРАЖЕННЯМИ СЛИЗОВОЇ ОБОЛОНКИ ПОРОЖНИНИ РОТА НА ТЛІ ГОСТРОГО ЛІМФОБЛАСТНОГО ЛЕЙКОЗУ В ПРОЦЕСІ ЛІКУВАННЯ

Робота була присвячена дослідженню динаміки показників властивостей ротової рідини у дітей з ураженнями слизової оболонки порожнини рота на тлі гострого лімфобластного лейкозу в процесі лікування розробленими авторами методами. У клінічних дослідженнях взяло участь 126 дітей у віці від 2-х до 18-ти років, яким було діагностовано гострий лімфобластний лейкоз. Частіше за все серед запальних захворювань тканин пародонту та слизової оболонки порожнини рота в дітей на тлі гострого лімфобластного лейкозу діагностували хронічний гінгівіт та кандидозний стоматит. Всі діти, яким проводили клінічні дослідження, були розподілені на 2 групи - основну та порівняння. У дітей групи порівняння використовували стандартні методи протокольного лікування. Дітям основної групи застосовували розроблений лікувально-профілактичний комплекс. Отримані результати досліджень показали стимулюючий вплив проведених лікувально-профілактичних заходів на корегування властивостей ротової рідини як у дітей основних груп спостереження, так і в групі порівняння.

**Ключові слова:** гострий лімфобластний лейкоз, хронічний гінгівіт, кандидозний стоматит, слизова оболонка порожнини рота, швидкість слиновиділення, в'язкість ротової рідини, діти.

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In recent years, the diagnosis of changes encountered in dental patients suffering from systemic pathologies, particularly acute lymphoblastic leukemia (ALL), and who are required to take medications regularly and for extended periods, has gained increasing significance [1, 2, 5, 6, 8, 9, 10–13]. It often remains unclear whether these dental changes are due to the pathological impact of the systemic disease, the adverse effects of medication, or a combination of both factors. Saliva formation with a specific qualitative and quantitative composition likely results from the filtration of blood components in the salivary glands and the selective excretion of some of the filtered compounds back into the blood. Thus, systemic factors, i.e., factors that alter blood composition, can affect salivation. These changes are particularly pronounced in children [3, 4].

The stability of the physical properties of oral fluid in children with ALL, specifically parameters such as salivation rate and viscosity, is essential for the normal functioning of the oral cavity tissues and organs. Timely identification of qualitative changes in oral fluid, especially in children, allows for early correction of these changes, providing an opportunity to find new solutions to stabilize key indicators of oral fluid.

We have developed a therapeutic and preventive complex for children with ALL at different stages of the disease: the first acute period and relapse, and remission, aimed at eliminating and preventing inflammatory processes in periodontal tissues and the oral mucosa (MMOC). The clinical efficacy of the treatment of inflammatory diseases of the periodontal tissues and oral mucosa was evaluated by changes in clinical indicators of salivation rate and oral fluid viscosity.

**The purpose** of the study was to demonstrate the effectiveness of the developed therapeutic and preventive complex in the treatment and prevention of inflammatory diseases of periodontal tissues and oral mucosa in children with acute lymphoblastic leukemia during different stages of the disease, by assessing the stability of the physical properties of oral fluid through changes in clinical indicators such as salivation rate and oral fluid viscosity.

**Materials and methods.** The clinical study involved 126 children aged 2 to 18 years diagnosed with ALL. Patients were recruited for the study on the basis of the Hematology Department of the Municipal Enterprise "Regional Medical Center for Family Health of the Dnipropetrovs'k Regional Council", Dnipro. The most common inflammatory diseases of periodontal tissues and oral mucosa in children with ALL were chronic gingivitis and candidal stomatitis. All children included in the clinical trials were divided into two groups: the main group and the comparison group. Dental plaque was removed, and oral sanitation was performed for all children, along with regular monitoring and control of oral hygiene.

The main group consisted of 91 children. In addition to general therapeutic measures, these children were treated locally with two variants of the developed therapeutic and preventive complex depending on the disease stage. The first variant of local treatment (61 patients) included: oral hygiene, the use of the anti-inflammatory dental elixir "Lizomuroid" ("Biochimtech" LLC, Odesa, Ukraine), mucosal gels "Vynohradnyi" and "Quertulin" ("Biochimtech" LLC, Odesa, Ukraine), the probiotic "Biovestin" (FC "ENZIPHARM" LLC, Ladyzhyn, Ukraine), the oral solution "Kandid" (Glenmark Pharmaceuticals Ltd, Mumbai, India), the antimicrobial drug "Sangvirin" (LLC DKP "Pharmaceutical factory", Zhytomyr, Ukraine), and the antioxidant vitamin and provitamin preparation "Katomas" ("Biochimtech" LLC, Odesa, Ukraine). This variant was applied during the first acute period and relapse of the disease. The second variant of local treatment (35 patients) included: oral hygiene, the use of the anti-inflammatory dental elixir "Lizomuroid" ("Biochimtech" LLC, Odesa, Ukraine), the mucosal gel "Vynohradnyi" ("Biochimtech" LLC, Odesa, Ukraine), and the probiotic "Biovestin" (FC "ENZIPHARM" LLC, Ladyzhyn, Ukraine). This variant was used during the remission period.

The comparison group consisted of 35 children aged 2 to 18 years with ALL and oral mucosa lesions, treated according to standard protocol methods (Table 1). The salivation rate was determined by measuring unstimulated oral fluid collected over 5 minutes in graduated cylinders. The unit of measurement for salivation rate is ml/min. The salivation rate was calculated using the formula:

$$v_c = \frac{V}{t}$$

t, where V is the volume of saliva, and t is the time.

The viscosity of oral fluid was studied using an Ostwald viscometer with a capillary length of 10.0 cm and a diameter of 0.4 mm. The unit of measurement is mPas. For the study, 5.0 ml of freshly collected oral fluid was used, measured three times at intervals of 2–3 hours after meals.

The results were processed by variational statistical methods of analysis using the Microsoft Office Excel 2016 software. Statistical processing of the experimental study results was carried out by the methods of variation analysis using the Student's test. The difference was considered statistically significant at  $p < 0.01$  [7].

**Results of the study and their discussion.** In Table 1, the changes in salivation rate indices in children with inflammation of periodontal tissues and oral mucosa during the first acute period, relapse, and remission periods of acute forms of leukemia are presented.

Table 1

**Dynamics of changes in salivation rate in children with ALL, ml/min (M±m)**

Groups	Terms	First acute period and relapse of ALL		Remission period of ALL	
		Before treatment	After 12 months	Before treatment	After 12 months
Main group		0.27±0.013 $p_1 > 0.05$	0.44±0.025 $p < 0.05$ $p_1 < 0.05$	0.32±0.017 $p_1 > 0.05$	0.59±0.029 $p < 0.05$ $p_1 < 0.05$
Comparison group		0.28±0.014	0.35±0.018 $p < 0.05$	0.34±0.017	0.46±0.023 $p < 0.05$

Note. p – significance of differences compared to baseline data;  $p_1$  – significance of differences compared to the comparison group.

The analysis of the results of the studies presented in Table 1 showed that in children of both main groups with chronic gingivitis and candidal stomatitis, which occurred both in the first acute period, the period of relapse, and in the period of remission of acute lymphoblastic leukemia, the phenomenon of severe hyposalivation was established before the start of treatment. However, when comparing the average values of the baseline data in all the examined children, it was determined that the lowest rate of saliva formation and salivation was found in those children whose dental diseases occurred in the first acute period and the period of relapse of the underlying blood disease. Thus, the initial value of salivary flow rate in the comparison group in children in the first acute period and the period of relapse of ALL averaged  $0.28 \pm 0.014$  ml/min, and in the period of remission –  $0.34 \pm 0.017$  ml/min. At the same time, after the use of lysozyme-containing rinse, the salivation rate significantly increased ( $p < 0.05$ ) and at the end of the study its digital values were  $0.35 \pm 0.018$  ml/min in children in the comparison group in the first acute period and the period of relapse of ALL, which is 25 % higher compared to the baseline data at the beginning of treatment. In children in the comparison group, whose main disease was in remission, a significant increase in salivary flow rate was also found ( $p < 0.05$ ), and after a year of observation, after the courses of treatment and prevention measures, the studied indicator was  $0.46 \pm 0.023$  ml/min, which is 35 % higher than the baseline values and almost equal to the normal value in healthy children.

The use of different treatment methods significantly increased the rate of salivation in both main groups of children ( $p < 0.05$ ).

Thus, the course with the use of the developed therapeutic and preventive measures, which included the application of quercetin-containing mucosal gel, as well as a gel containing a large amount of polyphenols, flavonols, anthocyanins and catechins, a mixture of sanguinarine and chelerythrine alkaloid bisulfate with probiotic and antifungal drugs, significantly increased the rate of salivation and after a year of observation it was 1.6 times higher compared to the baseline data (Fig. 1).

However, the use of the second method of treatment, when a probiotic preparation and lysozyme-containing rinse were used in combination with mucosal gel, increased the digital values of the studied indicator by 1.8 times after one year at the end of the study and did not differ significantly from normal values in healthy children. At the same time, it is noteworthy that the first method of treatment was used in children with dental diseases in the first acute period and in the period of relapse of the main blood disease – acute lymphoblastic leukemia, and the second – in children in remission.

When we studied the viscosity of the oral fluid, the analysis of the obtained digital data shows that the viscosity of the oral fluid is significantly increased in children with both chronic gingivitis and candidal stomatitis, and is presented in Table 2. At the same time, the highest numerical values of this indicator of oral fluid were found in children whose inflammatory diseases occurred in the first acute period and in the period of relapse of ALL. Thus, at the beginning of the study in these children, the average value was  $2.97 \pm 0.15$  in the main group and  $2.98 \pm 0.15$  in the comparison group, and in children with chronic gingivitis and candidal stomatitis in remission of acute lymphoblastic leukemia, it was  $2.74 \pm 0.14$  and  $2.75 \pm 0.14$ , respectively (Table 2).

Table 2

**Dynamics of changes in oral fluid viscosity in children with ALL,  $M \pm m$** 

Groups	Terms	First acute period and relapse of ALL		Remission period of ALL	
		Before treatment	After 12 months	Before treatment	After 12 months
Main group		$2.98 \pm 0.15$	$2.73 \pm 0.14$ $p > 0.05$	$2.75 \pm 0.14$	$2.39 \pm 0.12$ $p > 0.05$
Comparison group		$2.97 \pm 0.15$ $p_1 > 0.05$	$2.46 \pm 0.13$ $p < 0.05$ $p_1 > 0.05$	$2.74 \pm 0.14$ $p_1 > 0.05$	$2.18 \pm 0.11$ $p < 0.05$ $p_1 > 0.05$

Note.  $p$  – significance of differences compared to baseline data;  $p_1$  – significance of differences compared to the comparison group.

At the same time, after oral treatment, which consisted of the use of quercetin-containing gel in the form of applications, as well as a gel rich in polyphenols, flavonols in combination with a mixture of sanguinarine and chelerythrin alkaloid bisulfate, probiotic and antifungal drugs using lysozyme-containing rinse, This indicator in children with chronic gingivitis and candidal stomatitis in the first acute period and the period of ALL relapse at the end of the study was significantly different from the baseline data at the beginning of treatment ( $p < 0.05$ ), but these differences were not significant ( $p > 0.05$ ). Positive dynamics of changes in oral fluid viscosity was established throughout the observation period and at the end of the study, the digital values of oral fluid viscosity in children of the main group were  $2.46 \pm 0.13$ . However, despite the decrease in viscosity in this group, it remained slightly higher than in healthy children (Fig. 2).

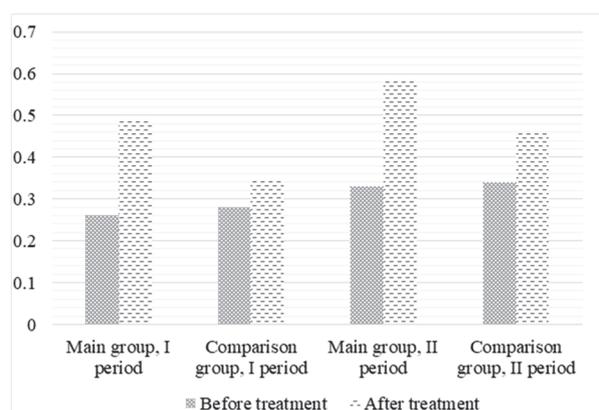


Fig.1. Dynamics of changes in salivation rate in children with acute lymphoblastic leukemia

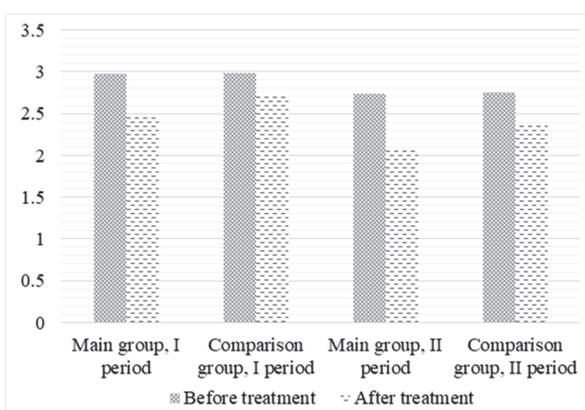


Fig.2. Dynamics of changes in oral fluid viscosity in children with acute lymphoblastic leukemia

Analyzing the digital values of oral fluid viscosity obtained in the study of children with chronic gingivitis and candidal stomatitis, which occurred against the background of remission of the underlying blood disease, it was found that after the use of the developed therapeutic and prophylactic complex, which included a mucosal gel with polyphenols and a probiotic preparation, as well as a lysozyme-containing gel, the studied indicator significantly decreased and at the end of the observation was  $2.18 \pm 0.11$ . At the same time, it is noteworthy that the viscosity of the oral fluid after treatment, although decreased in both main groups, but at the end of the study in the group of children whose blood disease was in remission, the digital value of the studied indicator is 12 % lower compared to the data in children whose acute lymphoblastic leukemia was in the first acute period or in relapse.

The dynamics of oral fluid properties in children with oral mucosa lesions against the backdrop of ALL were comprehensively studied. Our findings align with those of other researchers while highlighting unique aspects of our treatment approach. Previous studies have reported on the altered salivary flow and viscosity in pediatric patients with hematologic disorders, emphasizing the interplay between systemic disease and oral health [1, 2, 6, 8, 9, 11, 13]. Our results demonstrated a significant improvement in salivation rate and reduction in oral fluid viscosity following the application of our developed therapeutic and preventive complex. This is consistent with Kaskova et al. [5], who reported enhanced salivary gland function following targeted oral treatments in children undergoing chemotherapy. Similar improvements were noted by other researchers, indicating that comprehensive oral care can mitigate some adverse effects of ALL treatments on oral health [11, 13]. One of the key differentiators in our study was the specific combination of anti-inflammatory and antimicrobial agents used. Our approach involved the application of a quercetin-containing mucosal gel, polyphenol-rich gels, and probiotic supplements. This multifaceted treatment regimen proved more effective in normalizing salivation rates and viscosity compared to standard protocols. This supports the hypothesis that a multi-targeted approach can better address the complex etiology of oral mucosa lesions in these patients [3, 4]. The stimulating effect of our treatment regimen on salivary flow is particularly noteworthy. While previous studies have documented the benefits of individual components such as lysozyme and probiotics, our integrated treatment protocol appears to provide a synergistic effect, significantly enhancing the functional activity of salivary glands. This could be attributed to the combined anti-inflammatory, antioxidant, and antimicrobial properties of the treatment components, which collectively enhance salivary gland function and reduce mucosal inflammation [12, 13]. Another critical aspect of our study was the focus on different stages of ALL. The observed differential response to treatment during acute and remission phases highlights the need for tailored therapeutic approaches. During acute phases, intensive treatment with quercetin and polyphenol-rich gels showed marked improvements, whereas during remission, a less intensive regimen was sufficient to maintain oral health. This stage-specific treatment strategy ensures that therapeutic interventions are both effective and minimally disruptive to the patient's overall health. In conclusion, our study corroborates the findings of previous research while providing novel insights into the treatment of oral mucosa lesions in children with ALL. The developed therapeutic and preventive complex demonstrates significant efficacy in improving oral fluid properties, thereby enhancing oral health and overall quality of life for these patients. Future studies should explore the long-term benefits and potential side effects of such comprehensive treatment regimens to further refine and optimize care protocols for pediatric patients with hematologic disorders.

### Conclusions

1. It can be assumed that reduced salivation rates in children with inflammatory diseases of the oral cavity, occurring at various stages of acute lymphoblastic leukemia, can significantly impair the protective and cleansing functions of saliva. This can create a pathological situation in the oral cavity and increase the risk of inflammation in both periodontal tissues and the oral mucosa. At the same time, it can be asserted that the course application of the developed treatment methods, which include applications of quercetin-containing mucosal gel and its combination with polyphenols, flavonols, antioxidant vitamins, a mixture of sanguinarine and chelerythrine bisulfate with probiotic and antifungal preparations, and the use of dental elixir as mouth rinses, stimulate the functional activity of the salivary glands. This significantly improves the protective and cleansing functions of oral fluid and ensures the balance of physiological processes in the oral cavity.

2. According to the presented data, it can be stated that in children with chronic gingivitis and candidal stomatitis occurring against the backdrop of the primary blood disease-acute lymphoblastic leukemia-there is a significant change in the composition and properties of oral fluid, with an increase in its viscosity. However, the application of our developed therapeutic and preventive complex, which includes quercetin-containing gel for applications, as well as gel rich in polyphenols, flavonols, an antioxidant vitamin preparation in combination with a mixture of sanguinarine and chelerythrine bisulfate, probiotic and antifungal preparations with the use of lysozyme-containing rinse, stimulates the functional activity of the salivary glands. This significantly enhances the antimicrobial, protective, and cleansing functions of oral fluid, corrects the oral biocenosis, reduces inflammatory phenomena in the MMOC, accelerates wound healing processes in children with acute forms of leukemia, and corrects clinical indicators of oral fluid viscosity.

### References

1. Bulda V, Rodionova I, Dzeman N. Hematologichni zakhvoryuvannya v klinichniy praktytsi. Kyiv: Medknyha, 2023. 196. [in Ukrainian].
2. Hlushko LV, Fedorov SV, Skrypnyk IM, Ostrovskyy MM, Svintsitsky AS, Maslova HS, et al. Vnutrishni khvoroby: u 2 chastynakh. Chastyna 1. Rozdily 1–8: pidruchnyk. 2-e vydannya, 2022. 680. [in Ukrainian].
3. Kaskova LF, Mandziuk TB, Ulasevych LP. Porivnyalna kharakterystyka shvydkosti slynovydilennia u ditei iz riznym stomatologichnym statusom. Visnyk problem biolohiyi i medytsyny. 2018;2(144):363. doi: 10.29254/2077-4214-2018-2-144-363-366. [in Ukrainian].
4. Kaskova LF, Mandziuk TB, Ulasevych LP. Vyazkist rotovoyi ridyny u ditei iz riznym stupenem aktyvnosti kariiesu. Bukovynskiy medychnyi visnyk. 2018;22(3):25–30. doi: 10.24061/2413-0737.XXII.3.87.2018.59. [in Ukrainian].
5. Kaskova LF, Vashchenko IY, Karpenko OO, Amosova LI, Korotych NM. Klinichna efektyvnist likuvannya khvorob tkanyn parodonta v ditei, khvorykh na lymfoblastnyi leikoz, pid chas polikhimioterapiyi. Ukrainskyi stomatologichniy almanakh. 2013;6:74–76 [in Ukrainian].
6. Kuznetsova LP, Bohoslav TV, Reshetilov YI, Dmytriyeva SM, Kravchenko OO. Khvoroby krovi ta krovotvornykh orhaniv. Navchalnyi posibnyk. Zaporizhzhya, 2018. 123. [in Ukrainian].
7. Rohach IM, Keretsman AO, Sitkar AD. Pravylny vybranyy metod statystychnoho analizu – shlyakh do yakisnoyi interpretatsiyi danykh medychnykh doslidzhen. Naukovyy visnyk Uzhhorodskoho universytetu, seriya “Medytsyna”. 2017;2(56):124–128. [in Ukrainian].
8. Senatorova HS, Nikolaeva OV, Makieieva NI, Riha OO, Ishchenko TB. Khvoroby systemy krovi u ditei. Kharkiv: KhNMU, 2012. 132. [in Ukrainian].
9. Svintsitsky AS, Abrahamovych OO, Bodnar PM, Bulda VI, Ostrohlyad AV, Dzeman MI, et al. Vnutrishnya medytsyna: poradnyk likaryu zahalnoyi praktyky. Kyiv: Medytsyna, 2014. 1272. [in Ukrainian].
10. Fish JD, Lipton JM, Lanzkowsky P. Lanzkowsky's Manual of Pediatric Hematology and Oncology. Academic Press; 7th edition. 2021;796. doi: 10.1016/C2019-0-03654-0
11. Hastings CA, Torkildson JC, Agrawal AK. Handbook of Pediatric Hematology and Oncology: Children's Hospital & Research Center Oakland. John Wiley & Sons Ltd. 2021;499. doi:10.1002/9781118358139
12. Ishii E. Hematological Disorders in Children. Pathogenesis and Treatment. Springer Singapore. 2017;X:269. DOI: 10.1007/978-981-10-3886-0
13. Kamat DM, Frei-Jones M. Benign Hematologic Disorders in Children. A Clinical Guide. Springer. 2021;512. doi: 10.1007/978-3-030-49980-8

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