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DYNAMICS OF FINDINGS OF NON-SPECIFIC RESISTANCE IN THE MOUTH CAVITY IN CHILDREN WITH LESIONS OF THE MUCOUS MEMBRANE EPITHELIUM OF THE MOUTH CAVITY AGAINST ACUTE LYMPHOBLASTIC LEUKEMIA IN THE TREATMENT PROCESS

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Ключові слова: *неспецифічна резистентність, лізоцим, α-дефензини, гострий лімфобластний лейкоз, слизова оболонка порожнини рота*
Ключевые слова: *неспецифическая резистентность, лизоцим, α-дефензины, острый лимфобластный лейкоз, слизистая оболочка полости рта*
Key words: *nonspecific resistance, lisocyme, α-defensins, acute lymphoblastic leukemia, mucous membrane epithelium of the mouth cavity*

Abstract. Dynamics of findings of non-specific resistance in the mouth cavity in children with lesions of the mucous membrane epithelium of the mouth cavity against acute lymphoblastic leukemia in the treatment process. Bunyatyan K.A., Khotimska Yu.V., Kovach I.V., Lavrenyuk Ya.V., Khotimskiy B.L. *There was conducted study of dynamics of findings of non-specific resistance in the mouth cavity in children with lesions of the mucous membrane epithelium of the mouth cavity against acute lymphoblastic leukemia in the treatment process by authors-developed methods. It is known that in children with leukemia immunodeficiency states develop immunological disorders resulted from treatment with cytotoxic drugs. Moreover, not only general, but also the local immunity of the mouth cavity suffers, which is accompanied by development of infectious processes in the tissues that perform the barrier function, which include mucous membrane epithelium of the mouth cavity. A key role in the system of antimicrobial protection of the mouth cavity is performed by mucolytic enzyme lisocyme and α-defensins (HNP 1-3). 76 children with acute lymphoblastic leukemia aged from 2 to 18 years suffering from such dental diseases as generalized chronic catarrhal gingivitis, erosive-ulcerative and candidal stomatitis took part in the clinical study. All children under clinical study were divided into 2 groups - the main and comparison. Standard protocol treatment was used in the comparison group. Developed treatment-and-prophylactic complex was used in the main group. The children of the main group were prescribed developed treatment-and-prophylactic complex depending on the period of the disease: the first version of local treatment was used in the acute period and the relapse of the disease, the second - in the period of remission. The results of research have shown a stimulating effect of therapeutic and prophylactic measures on the natural antimicrobial system of mouth cavity protection, both in children of the main groups under study and in the comparison groups. Such a phenomenon should be considered as a positive process that contributes to the increase of resistance in periodontal tissues and mucous membrane epithelium of the mouth cavity.*

Реферат. Динаміка показників неспецифічної резистентності в порожнині рота у дітей з ураженнями слизової оболонки порожнини рота на тлі гострого лімфобластного лейкозу в процесі лікування. Бунятян Х.А., Хотімська Ю.В., Ковач І.В., Лавренюк Я.В., Хотімський Б.Л. *Проведено дослідження динаміки показників неспецифічної резистентності в порожнині рота в дітей з ураженнями слизової оболонки порожнини рота на тлі гострого лімфобластного лейкозу у процесі лікування розробленими авторами методами. Відомо, що в дітей, хворих на лейкоз, у результаті їх лікування цитостатичними препаратами розвиваються імунодефіцитні стани, зумовлені імунологічними порушеннями. Причому страждає не тільки загальний, а й місцевий імунітет порожнини рота, що супроводжується виникненням інфекційних процесів у тканинах, що виконують бар'єрну функцію, до яких відноситься слизова оболонка порожнини рота. Ключову роль у системі антимікробного захисту ротової порожнини виконують: муколітичний фермент лізоцим і α-дефензини (HNP 1-3). У клінічних дослідженнях взяло участь всього 76 дітей у віці від 2-х до 18-ти років із гострим лімфобластним лейкозом, які мали такі стоматологічні захворювання, як генералізований хронічний катаральний гінгівіт, ерозивно – виразковий і кандидозний стоматит. Усі 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. Дітям основної групи призначали розроблені лікувально-профілактичні комплекси залежно від періоду перебігу захворювання: перший варіант місцевого лікування застосовувався в гострий період і рецидив хвороби, другий – у період ремісії. Отримані результати досліджень показали стимулюючий вплив проведених лікувально-профілактичних заходів на природну антимікробну систему захисту порожнини рота, як у дітей основних груп спостереження, так і в групах порівняння. Подібне явище слід розглядати як позитивний процес, що сприяє підвищенню резистентності в тканинах пародонта та слизовій оболонці порожнини рота.*

One of the findings of resistance of the child's organism to pathological conditions is the level of humoral immunity, as well as some factors of nonspecific protection.

Suppression of local immunity of the mouth cavity in children affects the development of inflammation in the periodontal tissues and mucous membrane epithelium of the mouth cavity (MMEMC). This is especially pronounced on the background of acute lymphoblastic leukemia (ALL). This is due not only to the fact that oncologic-hematological process itself has a significant impact on the immunological status, but modern protocol treatment also exerts influence on it. It is known that children suffering from ALL resulted from treatment with cytotoxic drugs develop immunodeficiency conditions caused by immunological disorders. Moreover, not only the general, but also the local immunity of the mouth cavity suffers, which is accompanied by the development of infectious processes in the tissues that perform the barrier function, which include MMEMC [1, 2, 6].

The key role in the system of antimicrobial protection of the oral cavity is performed by the mucolytic enzyme lisocyme, which lyses the membrane of microorganisms, primarily gram-positive, destroys bacteria and viruses, and also stimulates the phagocytic activity of leukocytes and is involved in the regeneration of biological tissues [2].

Another important finding of nonspecific resistance in the mouth cavity is α-defensins of different classes.

Defensins activate intracellular mechanisms, have a pronounced bactericidal effect on the main bacterial infectious agents that colonize MMEMC - Streptococcus mutans, Streptococcus sanguis, Fusobacterium nucleatum, Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans. Also, α-defensins have pronounced immunomodulatory properties, cause chemotoxic effect on various pro-inflammatory cells, induce apoptosis, promote tissue repair and play a key role in arranging the relationship between nonspecific defense mechanisms and the adaptive immune system of the body [4, 5, 7, 8].

Therefore, the above factors of nonspecific protection in the moth cavity play an important role in providing a reliable barrier to mucous membrane of the mouth and periodontal tissues in children.

Aim is to study the dynamics of findings of nonspecific resistance in the mouth cavity in children with lesions of MMEMC against acute lymphoblastic leukemia in the course of treatment with developed treatment – prophylactic complex (TPC).

MATERIALS AND METHODS OF RESEARCH

76 children with ALL aged from 2 to 18 years suffering from such dental diseases as generalized chronic catarrhal gingivitis (GCCG), erosive-ulcerative and candidal stomatitis took part in the clinical study All children under clinical study were divided into 2 groups – the main and comparison Dental plaque was removed and full mouth debridement was carried. Children of both groups performed oral care (OC) using an alcohol-free anti-inflammatory mouth-wash “Lisomucoid”. In addition to OC children of the main group were prescribed developed TPC depending on the period of the disease. The first version of local treatment was used in the acute period and recurrence of the disease and included application of mucous gels “Vinogradny” (“Grape”) and "Kvertulin" on MMEM alternating twice a day for 2 weeks, the use of probiotic "Biovestin" in the appropriate age dosage (1 month), treatment of affected areas of the oral mucous membrane with an antimycotic solution for the oral cavity “Candid” (20 drops 3 times a day for 10-14 days); rinsing oral mucous membrane with the antimicrobial drug Sangviritrin 3 times a day for 10-14 days at a dilution of 40-50 drops per 200 ml of water. To advance epithelialization process, applications of the antioxidant vitamins and provitamins “Katomas” were used 2 times a day 30 minutes after meals for 14 days, starting from the third week of treatment. The second variant of local treatment included OC, mouthwash “Lisomucoid”, mucosal gel “Vinogradny” (“Grape”), probiotic “Biovestin,” used in the remission period. Children of the comparison group performed OC and rinsing with mouthwash “Lisomucoid”. Treatment options for MMEMC in ALL according to groups of children are presented in table 1.

Table 1

Treatment options for MMEMC in ALL according to groups of children

Groups		Treatment options	Number of patients
Main	**I**	**OC + “Lisomucoid” + mucosal gel “Vinogradny“+ “Kvertulin ” + probiotic “Biovestin” + “Candid ” + “ Sangviritin” + “ Katomas ”**	**41**
	II	**OC + “Lisomucoid” + mucosal gel “Vinogradny“+ “Kvertulin ” + probiotic “Biovestin”**	**20**
Comparison		**OC + rinsing with ”Lisomycoid ”**	**15**
		Total	**76**

Notes: I - acute period + recurrence, II – remission.

To study the nonspecific resistance in the oral cavity, such findings of local immunity as count of lysocyme and the level of α-defensins in the oral fluid were determined.

To determine lisocyme content of the oral fluid, studies were carried out using the photocolorimetric method, which determines the difference in the degree of extinction at a wavelength of 540 nm (green filter) 15 and 180 minutes after. Oral fluid was collected on an empty stomach in the morning, without prior hygienic measures [3].

Determination of the level of α-defensins (HNP 1-3) in the oral fluid was investigated by enzyme immunoassay (“NVT”, Holland). Measurement range: 156-10000 pg/ml. Sensitivity 156 pg/ml [5].

RESULTS AND DISCUSSION

The study of factors of local immunity recorded a low initial level of lisocyme content in the oral fluid

in all children examined, regardless of age, especially those whose main disease was in the first acute period or in the recurrence period, which is obviously due to a disorder of the antimicrobial defense system in the mouth cavity. Thus, in children with ALL in the first acute period and recurrence period, the digital values of the content of lisocyme in the oral fluid were 9.79±0.54 u/l – 9.81±0.51 u/l. At the same time, in children with ALL in the period of remission, the baseline data of the studied finding at the beginning of treatment were slightly higher and made up 13.51±0.68 u/l – 13.53±0.75 u/l.

Local application of lisocyme-containing mouthwash contributed to a slight increase in the content of lisocyme in the oral fluid in all patients of the comparison groups. At the same time, after a month of research, the level of lisocyme in these groups increased by 1.4-1.6 times, both in children in the first acute period and in recurrence period of ALL, and in children with ALL in remission, and after 3 months it began to decrease and by the end of the research, the digital values of the studied finding were close to the baseline level and significantly low in relation to the main observation groups ($p>0.05$).

At the same time, the treatment of inflammatory foci in periodontal tissues and MMEMC in children of the main group in the first acute period and recurrence period of the underlying disease, through the use of authors-developed TPC led to increase in the lisocyme level in the oral fluid and after a month of treatment digital values of this finding increased by 1.8 times (tab. 2). Herewith, the level of lisocyme remained significantly stably high and after 6 months it was 19.18±1.21 u/l. Such changes of the studied finding remained until the end of the study and after a year of observations its digital values were 18.06±1.16 u/l, which is almost 2 times higher than the baseline data.

Table 2

Dynamics of changes of lisocyme content in the oral fluid in children with ALL in the first acute period and recurrence period, M±m

Findings	Groups	before treatment	in 1 month	in 3 months	in 6 months	in 12 months
Lisocyme u/l	main	9.81±0.51 $p_1>0.05$	17.41±1.28 $p<0.05$ $p_1<0.05$	21.02±1.26 $p<0.05$ $p_1<0.05$	19.18±1.21 $p<0.05$ $p_1<0.05$	18.06±1.16 $p<0.05$ $p_1<0.05$
	comparison	9.79±0.54	15.67±0.99 $p<0.05$	15.22±0.87 $p<0.05$	13.44±0.78 $p<0.05$	10.27±0.67 $p>0.05$

Notes: p - index of statistical significance compared with baseline data; P_1 - index of statistical significance compared with the comparison group.

It is noteworthy that the dynamics of lisocyme content in the oral fluid in children of the main and comparison group differed significantly, despite the fact that the underlying disease was in the same developmental period. Thus, in children of the main group, the level of lisocyme reached its maximum value 3 months after the onset of treatment. Therewith, in children of the comparison group a significant increase in its content was only after a month of research, and after 3 months the content of the studied finding already began to decrease.

A similar trend in the level of lisocyme in the oral fluid was found in children with ALL of both study groups in the period of remission.

Thus, in children of the main group with GCCG and ulcerative-candidal stomatitis in the period of remission, in the treatment of which authors-developed TPC was applied, the content of lisocyme after a month of observations increased by 1.6 times. Therewith, after 3 months its content increased even more and already 2 times exceeded the baseline value (tab. 3).

Along with this, in six months the level of lisocyme began to decline in children of the main group and its digital value was 25.28±1.32 u/l. However, despite the decrease in the level of the studied finding it remained significantly higher compared with the baseline data and data of the comparison group ($p<0.05$), and at the end of the study lisocyme content was by 1.8 times higher than the baseline data and by 1.6 times of those in the comparison group.

The use of the developed treatment methods contributed to a significant increase ($p<0.05$) of another finding of nonspecific resistance in the oral cavity — α-defensins of different classes.

Table 3

Dynamics of changes of lisocyme content in the oral fluid in children with ALL in the remission period, M±m

Findings	Groups	before treatment	in 1 month	in 3 months	in 6 months	in 12 months
Lisocyme, u/l	main	13.53±0.75 p_1>0.05	21.62±1.39 p<0.05 p_1<0.05	26.95±1.35 p<0.05 p_1<0.05	25.28±1.32 p<0.05 p_1<0.05	24.31±1.27 p<0.05 p_1<0.05
	comparison	13.51±0.68	18.67±1.12 p<0.05	17.94±1.08 p<0.05	16.32±1.02 p<0.05	15.04±0.96 p<0.05

Notes: p - index of statistical significance compared with the baseline data; p_1 - index of statistical significance compared with the comparison group.

The leading source providing a sufficient concentration of α-defensins in the oral fluid is the submaxillary salivary glands and the deficiency of HNP-1, HNP-2, HNP-3 allows bacterial agents to colonize the surface of the mucous membrane, causing its inflammation.

The analysis of the baseline data demonstrates a reduced level of HNP 1-3 concentration, both in the main and in comparison group (from 1.12±0.059 μg/ml to 1.15±0.061) – table 4. This, in our opinion can be explained by the fact that the dental pathology under study increases the activation of the vital activity of various parodontotropic microorganisms that cause inflammatory periodontal diseases, as well as Candida fungi. At the same time, the concentration of HNP also depends on the severity of the underlying disease of the child and period of its course. However, in the treatment of inflammatory diseases of the oral mucous membrane with the use of the developed TPC in children in the first acute period and in the period of recurrence of ALL, the concentration of the studied finding increased after 6 months of observation by 6.5 times in the main group. A similar trend was established when analyzing the concentration of HNP and in the comparison group – 3.22±0.174 μg/ml.

Table 4

Dynamics of changes in the concentration of α-defensins (HNP 1-3) in the oral fluid in children with ALL in the first acute period and in the period of recurrence, μg / ml (M±m)

Groups	before treatment	in 6 months	in 12 months
main	1.12 ± 0.059	7.35 ± 0.404*	6.29 ± 0.391*
comparison	1.15 ± 0.061	3.22 ± 0.174	2.04 ± 0.113

Note. * - index of statistical significance of differences compared with the comparison group.

At the same time, a year after treatment the concentration of the studied finding slightly decreased in both groups, the main and comparison ones. However, at the end of the observation it was more than 5 times higher than the baseline data at the beginning of the study in the main group and 1.8 by times in the comparison group.

Analyzing the digital values of HNP 1-3 concentration in the oral fluid of children with inflammatory diseases of periodontal tissues and MMEMC against ALL in the remission period, we found a low content of the studied finding at the beginning of the study from 1.93±0.101 μg/ml to 1.195±0.103 μg/ml (tab. 5).

At the same time, the treatment of dental pathology in children of the main group in the period of remission of ALL by applying the developed TPC significantly increased the concentration of α-defensins and after six months it was 8.91±0.45 μg/ml, which almost corresponded to normal values in somatic healthy children (p<0.05). However, despite a slight decrease in the numerical values of the studied finding, at the end of the study in this group, it was almost 5 times higher than its baseline data, indicating a strengthening of local immunity and pronounced antimicrobial protection in the oral cavity of children under study.

Table 5

Dynamics of changes in the concentration of α-defensins (HNP 1-3) in the oral fluid in children with ALL in the period of remission, μg / ml (M±m)

Groups	before treatment	in 6 months	in 12 months
main	1.93 ± 0.101	8.91 ± 0.45*	8.92 ± 0.43*
comparison	1.95 ± 0.103	4.87 ± 0.25	3.66 ± 0.19

Note. * - index of statistical significance of differences compared with the comparison group.

It is noteworthy that the use of only lysocyme-containing mouth-wash in the comparison group for 6 months increased the concentration of α-defensins by 2.5 times and a year after the observations the value of this finding was almost 2 times higher than the baseline data at the beginning of the study.

CONCLUSIONS

1. The study of local immunity factors showed a low initial level of lysozyme in the oral fluid in all examined children, regardless of age, especially those whose underlying disease was in the first acute period or in the relapse period, which is obviously due to a violation of the antimicrobial defense system in the oral cavity. Thus, the results of the research indicate a stimulating effect of the carried out therapeutic and preventive measures on the natural antimicrobial system of protection of the oral cavity, both in children of the main observation and comparison group. Such a phenomenon should be considered as a positive process that contributes to the increase of resistance in periodontal tissues and MMEMC.

2. The initial level of α-defensins (HNP 1-3) in the oral fluid in all examined children also had low digital values in children in the first acute period and in the relapse period. Under the influence of the developed treatment methods, the concentration of α-defensins (HNP 1-3) in the oral fluid significantly increased in all groups of the examined children. However, a more significant and stable increase in the concentration of HNP 1-3 was found in the oral fluid of children of the main group, which may be due to an increase in the secretion of oral fluid and a decrease in the microflora content in the oral cavity under the influence of the authors-developed treatment methods.

Conflict of interests. The author declares that there is no conflict of interest.

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