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ABSTRACT

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DIAGNOSTIC AND PROGNOSTICS ASPECTS OF LUNG FUNCTION IN CHILDREN WITH ACUTE LEUKEMIA

Introduction. The aim of the study was to assess lung function in children with acute leukemia at different periods and determine a tolerance to physical activity in acute leukemia survivors.

Methods. Spirometry was conducted in 46 children aged 6–17 years with acute leukemia at the beginning of chemotherapy protocols (Group 1) and acute leukemia survivors, who had completed chemotherapy course, with remission for at least 2 years (Group 2). In acute leukemia survivors with a confirmed absence of respiratory diseases, a test with physical activity was performed (Group 2A). Spirometry was conducted with the help of the "SpiroCom", "KHAI-Medyka" spinographic complex Kharkiv, Ukraine. STATISTICA 8 (Tulsa, OK) and MedCalc 17.2 were used for statistical data analysis.

Results. Despite the normal values of medians of lung function parameters in children at the beginning of treatment, obstructive disorders were detected in 28.6% of children and restrictive disorders were detected in 9.5% of children. In acute leukemia subjects, obstructive disorders were detected in 12.0% of children and restrictive disorders were found in 12.0% of children. A decrease in tolerance to physical activity in acute leukemia survivors was detected. The study confirmed diagnostic and prognostic value of spirometry in pediatric acute leukemia patients. A decrease in mean expiratory flow at 75% of forced vital capacity by less than 76.4% at the beginning of chemotherapy increases the risk of developing wheezing in children by 12.5 times during the treatment of acute leukemia (RR 12.5 (95 CI% 1.8–85.9)). Acute leukemia survivors with restrictive changes on spirometry revealed the formation of lung fibrosis, while those with obstructive changes – showed the signs of asthma.

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Conclusions. Spirometry is a proper instrument for lung function monitoring and management of pulmonary complications in children with acute leukemia.

Keywords: acute leukemia, children, lung function, spirometry.

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ДІАГНОСТИЧНІ ТА ПРОГНОСТИЧНІ АСПЕКТИ ФУНКЦІЇ ЗОВНІШНЬОГО ДИХАННЯ У ДІТЕЙ, ХВОРИХ НА ГОСТРУ ЛЕЙКЕМІЮ

Вступ. Метою дослідження було оцінити функцію зовнішнього дихання у дітей з гострою лейкемією у різні періоди захворювання, а також визначити толерантність до фізичного навантаження у дітей в періоді тривалої ремісії гострої лейкемії.

Методи. Спірографію проводили 46 дітей віком 6–17 років з гострою лейкемією на початку протоколів хіміотерапії (1 група) та після завершенням протоколів лікування та ремісією не менше ніж 2 роки (2 група). При підтвердженій ремісії гострої лейкемії та за відсутності респіраторних скарг у цієї групи дітей проводилося дослідження, яке включало пробу з фізичним навантаженням (група 2А). Спірографічне дослідження проводилося за допомогою спінографічного комплексу «СпіроКом», «ХАІ-Медика», Харків, Україна. STATISTICA 8 (Tulsa, OK) і MedCalc 17.2 використовувалися для статистичної обробки даних.

Результати. Незважаючи на нормальні значення медіан показників функції легень у дітей на початку лікування гострої лейкемії обструктивні зміні функції зовнішнього дихання виявлені у 28,6 % дітей, рестриктивні – у 9,5 % дітей. У періоді тривалої ремісії обструктивні зміни виявлені у 12,0 % дітей, рестриктивні – у 12,0 % дітей. Було виявлено зниження толерантності до фізичного навантаження у дітей в тривалій ремісії гострої лейкемії. Дослідження підтвердило діагностичну та прогностичну цінність спірометрії у дітей з гострою лейкемією. Зниження показника миттєвої об'ємної швидкості видиху в моменті 75 % від форсованої миттєвої ємкості легень менше ніж 76,4 % на початку хіміотерапії підвищує ризик розвитку бронхообструктивного синдрому у дітей у 12,5 разів під час лікування гострої лейкемії (RR 12,5 (95 ДІ% 1,8–85,9)). У хворих дітей на гостру лейкемію за наявності рестриктивних змін на спірометрії виявлено формування фіброзу легень, за наявності обструктивних змін – ознаки задухи.

Висновки. Спірометрія є важливим інструментом для моніторингу функціонального стану легень і лікування легеневих ускладнень у дітей, хворих на гостру лейкемію.

Ключові слова: гостра лейкемія, діти, функція зовнішнього дихання, спірометрія.

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ABBREVIATIONS

VC – vital capacity
FVC – forced vital capacity
FEV1 – one-second forced expiratory volume
PEF – peak expiratory flow
MEF25, MEF50, MEF75 – mean expiratory flow at 25%, 50%, and 75% of FVC
MEF25-75 – mid-expiratory flow between 25% and 75% of FVC
MW – Mann–Whitney test
W – Wilcoxon test
Me – median
Lq – lower quartile
Uq – upper quartile

INTRODUCTION

According to the National Cancer Registry [1] and international databases [2], acute leukemia is the most common cancer in the pediatric population. Despite certain achievements in the treatment of acute leukemia [3, 4], the presence of various complications influences the prognosis of acute leukemia in children [5, 6, 7].

Pulmonary complications are an important aspect related to the course of acute leukemia and the therapy provided [8]. Among the documented cases of infection, the respiratory system is one of the most common loci [9, 10].

What is more, long-term pulmonary complications and pulmonary function disorders may remain even in acute leukemia survivors [11, 12, 13], which requires additional screening programs for diagnosis and development of treatment or rehabilitation measures in acute leukemia survivors [14, 15].

The latest literary data indicate a growing interest in the problem of impaired lung function in patients with oncological diseases, including acute leukemia. American researchers Armenian SH, Landier W et al. (2015) studied lung function and biochemical markers of lung damage in patients with childhood cancer in anamnesis. The study found that, as a result of toxic therapy, restrictive changes in the spirogram and impaired diffusion capacity of the lungs (DLCO) were significantly more common in studied patients compared to healthy individuals [16]. A study by Oslo University Hospital (2018) of childhood acute lymphoblastic leukemia survivors found that lung function and general fitness in this group were generally lower than expected, even after a median of 23 years after successful chemotherapy treatment [17]. According to the results of a cohort study at the Sydney Children's Hospital (2019), lung abnormalities and/or significant long-term respiratory symptoms were found in almost one-third of acute lymphoblastic leukemia survivors. According to the study results, 26% of the participants experienced a decrease in at least one of the spinographic parameters [18]. Researchers Tantawy AA, Elbarbary N, et al. (2011) noted that despite the absence of respiratory symptoms in children who had lymphoma or leukemia in the past, a significant proportion of obstructive (14.3%), restrictive (5.7%), and mixed (20%) disorders on the spirogram. It was also declared that children who received a combination of chemotherapy drugs and radiation had probably more frequent pulmonary complications than those who received only chemotherapy treatment [19]. A study by de Macêdo TM, Campos TF (2014) studied pulmonary function during maintenance therapy in children with acute leukemia, which did not show changes in spirometry values. However, researchers noted that in this group of patients, there was a decrease in muscle strength during inhalation [20].

In addition, the predicting possibility of lung function parameters for pulmonary complications in patients with an oncological profile is considered. A randomized controlled study by Møller T, Moser C et al. testified to the importance of the FEV1 indicator as a tool for early prediction and prevention of pneumonia during critical phases of neutropenia in patients with acute myeloblastic leukemia and proved the necessity for constant monitoring of this indicator [21].

Taking into account the importance of long-term complications in children who had cancer, the Children's Oncology Group, USA, has developed special long-term follow-up guidelines for survivors of childhood, adolescent, and youth cancer (Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers), which, among other things, indicated the need to check the lung function and clinical symptoms after pulmonary toxic therapy [11, 15]. Swiss researchers Kasteler R, Kam LMH et al. (2018) also declared the importance of lung function monitoring in cancer survivors and lung-toxic treatment with bleomycin, busulfan, nitrosoureas, and chest radiation therapy [14].

Early diagnosis, monitoring, and treatment of pulmonary complications in children with acute leukemia are critical for the improvement of their

prognosis [22, 23] and quality of life [24, 25, 26]. Despite the growing attention to the study of pulmonary function disorders in children with acute lymphoblastic and myeloid leukemia and a great number of conducted studies, the problem remains insufficiently studied and systematized.

The purpose of our study is to determine the frequency of lung function disorders in children with acute leukemia using spirometry at different stages of the disease, as well as to assess the presence of latent disorders and tolerance to physical activity in acute leukemia survivors by conducting physical exercise tests.

MATERIALS AND METHODS.

The study involved 46 children aged 6 to 17 with acute leukemia (40 with acute lymphoblastic and 6 with myeloid leukemia), who were treated in the hematology department of Municipal Non-Profit Enterprise «City Clinical Children's Hospital № 16» of Kharkiv City Council. Inclusion criteria included a verified diagnosis of acute leukemia, age of patients from 6 to 17 years, and signed consent of parents and/or patients. Exclusion criteria for the study included the age of patients under 6 years, the refusal of parents and/or patients to sign consent, the presence of diagnosed chronic lung diseases or disorders of endothelial function before the manifestation of acute leukemia, hereditary diseases affecting the structure and function of the respiratory system, including cystic fibrosis, confirmed primary immunodeficiencies. The examined children were divided into two groups. Group 1 included children at the beginning of protocols of treatment for acute leukemia (n=21). The 2nd group includes children with acute leukemia after complete completion of chemotherapy treatment and remission for at least 2 years (n=25).

The diagnosis and treatment of acute leukemia were according to the orders of the Ministry of Health of Ukraine No. 364 dated 20.07.2005 "Pediatric Hematology", No. 617 dated 23.07.2010 "About changes to Ministry of Health of Ukraine order dated 20.07.2005 No. 364" On approval of protocols for providing medical care to children in the specialty "Pediatric hematology" [13, 14] that were based on international protocols “Acute Lymphoblastic Leukaemia Intensive Chemotherapy Berlin Frankfurt Munich 2009” (ALL IC BFM 2009) and “Acute myeloid leukemia-Berlin–Frankfurt–Munster (AML-BFM) 2004”.

Lung function assessment. To assess the lung function, we used spirometry with the help of the spinographic complex "SpiroCom АИНЦ. 941311.005И", manufactured by the National Aerospace University "KHAI", National Center of Radioelectronic Medical Devices and Technologies "KHAI-Medyka", Kharkiv, Ukraine (TU In 33.1-02066769-005-2002). The study was conducted according to the standard method of conducting spirometry. The results were evaluated according to the instructions for the spirograph complex [27].

Before the study of lung function, a child with acute leukemia was recommended to be at rest for at least 30 minutes and not to take bronchodilators later than 12 hours before the study.

For children of group 2, who are in remission of acute leukemia (confirmed by the results of clinical blood tests and a myelogram) and had no respiratory complaints, an additional physical exercise test (group 2A) was conducted. Physical exercise tests included a 10-minute treadmill test with a speed of 5-7 km/hour (fast walk) under the control of the general condition, heart, and respiratory rate. After physical exertion, during the lung function study, such parameters as forced vital capacity (FVC), one-second forced expiratory volume (FEV1), FEV1/FVC, peak expiratory flow (PEF), mean expiratory flows at 25% of FVC (MEF25), mean expiratory flows at 50% FVC (MEF50), mean expiratory flows at 75% of FVC (MEF75), mid-expiratory flow between 25% and 75% of FVC (MEF25-75) were re-evaluated.

Statistical analysis. STATISTICA 8 (Tulsa, OK) and MedCalc 17.2 have been used for statistical data analyses. The Shapiro-Wilk test has been used to verify the distribution according to the Gauss law. Considering that the samples had a non-normal distribution, the median (Me) and interquartile range [Lq – lower quartile; Uq – upper quartile] were determined for the statistical analysis. A non-parametric Mann-Whitney (MW) U-test was used to compare two independent samples. The non-parametric Wilcoxon T-test (W) was used to perform a comparative analysis of two dependent samples. The difference in the parameters has been considered significant at $p < 0.05$.

Ethics approval and consent to participate. Each study participant and his /her parents were informed about the nature of the study. Informed consent for participation in the study was obtained from the parents of all patients and patients aged 14-18. The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University, Ukraine (Protocol No. 8 of 5th October 2016) and was conducted according to the Helsinki Declaration (1975).

RESULTS

Table 1 provides an overview of the general characteristics of the acute leukemia patients included in the study. Children with acute lymphoblastic leukemia were significantly more frequent among the examined children ($p < 0.05$). The gender distribution of children showed that there was a significant predominance of boys ($p < 0.05$).

Table 1 – General characteristics of studied patients with acute leukemia

Parameter	Total (n=46)	Group 1 (n=21)	Group 2 (n=25)
Age, Me (Uq; Lq) years	9 (7; 14)	7 (6; 15)	9,5 (7; 13)
Gender, n male/female	29 /17	15 / 6	16 / 9
Type of leukemia, n ALL, AML	39 7	17 4	22 3
Risk group, n Standard High	37 9	15 6	22 3

Pulmonary complications that were registered in examined patients are presented in Table 2. In group 1, all pulmonary complications during treatment protocols were taken into account. We also assessed all persistent pulmonary complications in acute leukemia survivors of group 2.

According to the obtained data (Table 3), all medians of lung function indicators corresponded to normative values. FEV1 levels were statistically significant (p_{1-2}= 0,020584) lower during the acute phase of acute leukemia (group 1) compared to children after the completion of the treatment course (group 2), which may mean the presence of an influence of acute leukemia treatment protocols on the patency of small bronchi and a decrease in the functional capabilities of the respiratory system.

No statistically significant differences were found between other parameters of lung function in children during chemotherapy (group 1) and in acute leukemia survivors (group 2) (all p>0.05).

Only 16/25 (64.0%) acute leukemia survivors managed to finish the physical activity test completely. Other 9/25 (36.0%) acute leukemia survivors stopped the test in 5–9 minutes due to a critical increase in heart rate. In acute leukemia survivors, the following spinographic parameters decreased statistically significantly after the physical activity test: FVC p_{2-2A} <0,001, PEF p_{2-2A} <0,001, MEF25 p_{2-2A} <0,001, MEF50 - p_{2-2A} <0,001, MEF75 p_{2-2A}= 0,036258. This may be a sign of lower tolerance to physical activity in pediatric acute leukemia survivors compared to healthy children.

Table 2 – Pulmonary complications in children with acute leukemia

Complications	Group 1	Group 2
	During chemotherapy	In remission for at least 2 years
Acute bronchitis	12/21	-
Recurrent episodes of acute bronchitis	6/21	1/25
Wheezing	6/21	3/25
Bronchial asthma	-	2/25
Pneumonia	9/21	1/25
Pneumothorax	1/21	
Pulmonary fibrosis	-	3/25
Total	18/21	7/25

Despite the fact that the medians of lung function parameters of children with acute leukemia correspond to the normative ones, in 14/46 children (30.4%), we found pathological changes on spirometry.

Mild obstructive disorders were diagnosed in 6/21 children (28.6%) with acute leukemia at the beginning of chemotherapy (group 1), as well as in 3/25 (12.0%) children in the period of long-term remission of acute leukemia (group 2). In acute leukemia survivors (group 2), in the presence of obstructive changes in lung function, clinical manifestations were noted in all children (3/3 children, 100%); namely, bronchial asthma was diagnosed in 2 children, and a single obstructive episode in 1 child. Among children with acute leukemia at the beginning of chemotherapy (group 1) and the presence of obstructive changes in lung function, clinical manifestations of bronchial obstruction developed in 4/6 children (66.7%) in the form of wheezing episodes during protocol treatment. Retrospectively, it was found that among children with obstructive changes at the beginning of chemotherapy, 1/6 of the children (16.7%) developed bronchial asthma. In other children of this group, no episodes of obstruction were recorded in dynamics after completion of the protocol treatment.

Table 3 – Statistical characteristics of the main spinographic parameters in children with acute leukemia at various stages of treatment, Me (Uq; Lq)

Parameter	GROUP 1 (n=21)	GROUP 2 (n=25)	GROUP 2A (n=25)
VC, %	88.0 (83.0; 95.0)	92.0 (88.0; 95.0)	-
MW U-test p_{1-2}= 0,360094			
FVC, %	88.0 (81.0; 90.5)	90.0 (85.0; 94.0)	86.0 (81.0; 90.0)
MW U-test p_{1-2}= 0,256077; W T-test p_{2-2A}= **0,000060***			
FEV1, %	88.0 (81.0; 94.0)	95.0 (90.0; 98.0)	91.0 (88.0; 95.0)
MW U-test p_{1-2}= **0,020584***; W T-test p_{2-2A}= **0,002961***			
Tiffeneau index, % (FEV1/VC)	90.4 (83.3; 99.0)	95.0 (88.0; 103.0)	-
MW U-test p_{1-2}= 0,177770			
FEV1/FVC	94.8 (85.1; 98.0)	93.0 (88.0; 100.0)	92.0 (86.0; 98.0)
MW U-test p_{1-2}= 0,567973Ж; W T-test p_{2-2A}= 0,313464			
PEF, %	85.0 (73.0; 90.0)	90.0 (85.0; 96.0)	85.0 (79.0; 92.0)
MW U-test p_{1-2}= 0,065564; W T-test p_{2-2A}= **0,000112***			
MEF25, %	90.0 (76.0; 98.0)	91.0 (89.0; 98.0)	88.0 (82.0; 89.0)
MW U-test p_{1-2}= 0,289815; W T-test p_{2-2A}= **0,000065***			
MEF50, %	88.0 (78.0; 95.0)	91.0 (88.0; 95.0)	83.0 (82.0; 92.0)
MW U-test p_{1-2}= 0.120015; W T-test p_{2-2A}= **0.000748***			
MEF75. %	75,0 (63,0; 89,0)	88,0 (80,0; 99,0)	85.0 (78.0; 90.0)
MW U-test p_{1-2}= 0.148613; W T-test p_{2-2F}= **0.036258***			
MEF25-75. %	88,0 (78,0; 97,0)	90,0 (82,0; 96,0)	86.0 (80.0; 96.0)
MW U-test p_{1-2}= 0.566394; W T-test p_{2-2A}= 0.217318			

*Note: VC – Vital Capacity, FVC – Forced Vital Capacity, FEV1 – one-second forced expiratory volume, PEF – peak expiratory flow, MEF25, MEF50, MEF75 – mean expiratory flows at 25%, 50%, and 75% of FVC, MEF25-75 – mid-expiratory flow between 25% and 75% of FVC; * – the difference between the indicators is statistically significant*

Restrictive disorders were detected in 2/21 children (9.5%) during the acute phase of acute leukemia at the beginning of treatment (group 1A) and in 3/25 (12.0%) children in long-term remission after complete completion of protocol treatment (group 2). In all children in the period of long-term remission of acute leukemia, in whom restrictive disorders were detected during the assessment of lung function (3/3 children, 100%), lung fibrosis was confirmed on computed tomography. At that time, in children with restrictive disorders of lung function during chemotherapy, no changes were detected on X-ray and computer tomography. Retrospectively, it can be noted that when remission was achieved, and the protocol treatment was fully completed, X-ray signs of fibrosis were not detected on computed tomography in these children from the 1st group. Restrictive disorders of lung function during chemotherapy treatment are probably related to the transient effect of cytostatics on the respiratory system. The influence of the general asthenic condition during this period cannot be excluded. The clinical and prognostic significance of restrictive lung function disorders in children with acute leukemia on the background of chemotherapy requires further study.

In addition, borderline values of at least one parameter of lung function were found in 33.3% of

patients in group 1 and in 20.0% of children in group 2, which indicates a decrease in the functional capabilities of the respiratory system in comparison to the general pediatric population. Although these values of lung function cannot be assessed as pathology, this cohort of children requires more attention from clinicians. The study detected that a borderline or decreased value of MEF75 (below 76.4%) in children of group 1 significantly increases the risk of wheezing development by 12.5 times (RR 12.5 (95CI% 1.8–85.9)). The prognostic value of other spirometry parameters in children of group 1 was not found in our study.

DISCUSSION

The frequency of lung function disorders in our study is similar to the data of previous studies. In the article, Lin B, Kennedy B, et al. (2019) noted that pathological results on spirometry were found in 26% of acute leukemia survivors who did not receive protocol chemotherapy for the main disease for at least 6 months [18]. In the studies of Wasilewska E, Kuziemski K et al. (2019) in pediatric acute leukemia survivors, impaired lung function was found, namely: 14% of patients had restrictive, and 7% of patients had obstructive types [12]. In both mentioned studies, the Median values of lung function parameters corresponded to normative values, as well as according to our data.

Correspondence of the median values of lung function in examined children with acute leukemia to the normative value can be explained by the compensatory mechanisms of the child's respiratory system. This highlights that even in the presence of pulmonary complications and high levels of markers of lung damage, lung function can be preserved. American researchers Armenian SH, Landier W et al. (2015) found that, as a result of pulmonary toxic therapy, restrictive changes in the spirometry and disorders of the diffusion capacity of the lungs (DLCO) are significantly more common compared to healthy individuals, but did not find any correlations between parameters of lung function and the biochemical markers of lung damage [16].

Analyzing the results of the study of lung function in children in the period of long-term remission of acute leukemia after the exercise test, we detected a significant decrease in FVC, PEF, MEF25, MEF50, MEF75 (all $p<0.05$) and low tolerance to physical activity. Only 64% of acute leukemia survivors managed to finish the physical activity test completely, which was connected not only with the functional state of the respiratory system but also with the general asthenic condition and functional state of the cardiovascular system. A decrease in tolerance to physical exertion is also mentioned in other studies in patients who had suffered from acute leukemia [17, 28, 29].

A study by Møller T, Moser C, et al. (2016) confirmed the prognostic significance of the FEV1 indicator (FEV1) for the development of pneumonia during critical neutropenia in patients with acute myeloid leukemia [21]. This fact was not confirmed in our study, which is probably due to differences in study design and patient sample sizes. However, it was found that a decrease in MEF75<76.4% at the beginning of chemotherapy increases the risk of developing wheezing by 12.5 times (RR 12.5 (95CI% 1.8-85.9)). In addition, the diagnostic and prognostic value of lung function in children during remission was confirmed. All children in the period of remission of acute leukemia in the presence of restrictive changes according to spirometry revealed the formation of lung fibrosis; in the presence of obstructive changes, there were signs of asthma formation. This makes it expedient to monitor lung function in children during treatment protocols.

It should also be noted that none of the examined children with obstructive changes (9/9 children, 100%) on the spirometry had chronic diseases of the respiratory system and episodes of obstruction before the manifestation of acute leukemia. Therefore, the course and treatment of acute leukemia with the formation of bronchial hypersensitivity and the risk of developing chronic inflammation of the respiratory tract in examined children.

Our study has a limitation connected with a small sample of patients due to the fact that acute leukemia is a comparatively rare disease. Further studies with larger samples, including multi-central research, can be useful for a more in-depth study of the problem.

CONCLUSIONS

According to our results, in children with acute at the beginning of treatment protocols, obstructive disorders were detected in 28.6% of children, and restrictive disorders were detected in 9.5% of children. In acute leukemia survivors, obstructive disorders were detected in 12.0% of children, and restrictive disorders were found in 12.0% of children. A decrease in MEF75<76.4% at the beginning of chemotherapy increases the risk of developing wheezing syndrome by 12.5 times during the protocol treatment of acute leukemia (RR 12.5 (95CI% 1.8–85.9)). According to the study of all children in the remission period of acute leukemia, in the presence of restrictive changes, spirometry revealed the formation of lung fibrosis, and in the presence of obstructive changes, the formation of bronchial asthma was diagnosed. So, spirometry is a proper instrument for the diagnosis and prognosis of lung complications in children with acute leukemia.

PROSPECTS FOR FUTURE RESEARCH

The study of pulmonary function in children with acute leukemia holds promising prospects for developing innovative diagnostic and therapeutic approaches. Assessment of pulmonary function can advance the management of acute leukemia patients, improving patient outcomes and their life quality.

AUTHOR CONTRIBUTIONS

Makieieva N. — research concept and design; critical revision of the article; final approval of the article; Koval V. — collection and assembly of data; data analysis and interpretation; writing the article; Tsymbal V. – conduction of spirometry and its interpretation; data analysis; Biriukova M. –data analysis, clinical examination of children with acute leukemia and suspected respiratory pathology, Diachenko M. – data analysis and interpretation; Kucherenko M. – organization of the study in conditions of CNE "City Clinical Children's Hospital № 16" of Kharkiv City Council, final approval of the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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