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IMMUNOLOGICAL SHIFT IN CHILDREN FREQUENTLY ILL WITH ACUTE RESPIRATORY DISEASES IN THE ANDIJAN REGION

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Abstract: This article is devoted to the problem of frequently ill children, the analysis of causal factors, in particular, disorders of the immune system, and the principles of including children in the group of frequently ill children. When including a child in the group of frequently ill children, it is necessary to take into account the severity of each acute respiratory infection, the presence of complications, the duration of the intervals between episodes of acute respiratory infections, and the need to use antibiotics in the acute period.

Keywords: frequently ill children, acute respiratory infections, immunity, immunomodulators

Introduction. In recent years, there has been a trend towards an increase in the number of frequent respiratory infections with episodic increases in morbidity, in particular episodes of acute respiratory infections both throughout the year and over a long period of life [1,2,3,4]. Children prone to frequent illnesses and with impaired immune system functioning should be placed in a separate group for dispensary observation [5,6,7]. For children over 3 years of age, an additional criterion was proposed for inclusion in the FAI group: the infection index (II), defined as the ratio of the sum of all cases of acute respiratory infections during the year to the child's age. When including a child in a recurrent acute respiratory disease (ARI) group, it is necessary to consider the severity of each ARI, the presence of complications, the duration of intervals between ARI episodes, and the need for antibiotics during the acute phase. A number of factors contribute to the development of recurrent ARIs: environmental disruption, delayed development of the immune system, disruption of local immunity, sensitization to bacterial allergens and an increase in the incidence of allergic diseases (Korovina N.A. et al., 2001).

In recent years, an important role in the formation of the contingent of FBD has been attributed to immune disorders caused by the activation of Th2 lymphocytes due to the unjustified use of antibiotics and the action of unfavorable environmental factors [7,8,9]. In particular, for such children, immunomodulatory therapy is currently the method of choice, and preference should be given to immunomodulators with multiple mechanisms of action.

The study of immunity confirmed quantitative and functional impairment in T-lymphocyte subpopulations, low interferon production and lysozyme content, and secretory immunoglobulin A (sIgA) levels. Due to these disorders, chronic inflammation develops in the bronchopulmonary system, clinically manifested by frequent recurrent lower respiratory tract diseases, the presence of ENT infections, and promoting the formation of a Th2 immune response. Based on the above-mentioned relevance of the problem, we set ourselves the following goal:

The aim of the study: to study the state of the immune system and the role of immunomodulators in the comprehensive treatment of frequently ill children.

AMERICAN ACADEMIC PUBLISHER

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Material and methods of the study: 40 children aged from 6 months to 14 years with frequent respiratory diseases, who were included in the group of frequent respiratory diseases according to health standards, were examined in the outpatient clinic and pulmonology department of the Children's Regional Medical and Medical Center of Andijan and Markhamat district. All patients underwent clinical, anamnestic, laboratory, instrumental, and immunological testing. A comparative analysis of the study results was conducted taking into account the use of Bronchomunal in the comparison groups. The data obtained were statistically processed.

Results and their discussion. When examining the immune status of children who sought medical care at the above-mentioned healthcare facilities, the results obtained are presented in Table 1. This table and the following tables provide data on both the percentage of lymphocytes and their subpopulations, as well as their absolute number—the content of these cells in 1 liter of blood. This presentation of the material allows for a comprehensive assessment of the presence of a deficiency in a particular subpopulation.

Table 1. Lymphocyte subpopulation composition in frequently ill children (FIC) (M±tm) (depending on age)

Indicators	**6 months - 1 year**	**1-3 years**	**4-7 years**	**8-14 years**
CD20 (%)	17.5±2.5(%)	18±2.5	18±2.56	19.4±2.78
	709±181	523±102	508.6±158.1	558.86+ 191.6
norm	12-15(%)	12-15(%)	12-15(%)	12-15(%)
	406-595	406-595	260-430	260-430
CD3 (%)	54.5±1.5(%)	46.3±4.57	48.4±4.5	47.14±7.8
	2164.5±193.5	1370.7±305.8	1343±455.6	1351.7±697.7
norm	48-61(%)	48-61(%)	48-61(%)	48-61(%)
	1526-2235	1526-2235	1000-1674	1000-1674
CD4	29±1	26±1.43	27.6±1.3	26.43±1.63
norm	29-38(%)	29-38(%)	29-38(%)	29-38(%)
CD8	20.5±2.5	19.1±0.98	19.2±1.52	20±1.43
norm	16-24(%)	16-24(%)	16-24(%)	16-24(%)
CD4/CD8	1.45±0.25	1.2±0.19	1.46±0.1	1.43±0.22
norm	1.6-1.8	1.6-1.8	1.6-1.8	1.6-1.8
CD16	12.5± 2.5	12.3±1.76	11.6±1.52	13.14±1.02

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

norm	8-15(%)	8-15(%)	8-15(%)	8-15(%)
CD25	11.5±1.5	13.14±1.88	15±2.4	12.57±3.06
norm	7-18(%)	7-18(%)	7-18(%)	7-18(%)
CD95	19±5	22±1.86	26±3.6	28.3±7.41
norm	8-18(%)	8-18(%)	18-34(%)	20-37(%)

Table 1 shows that CD20 levels are higher than normal in all age groups, with the increase being more pronounced in children aged 6 months to 1 year. CD20, or B-lymphocyte antigen CD20, is a co-receptor protein located on the surface of B-lymphocytes. A product of the human MS4A1 gene. Although the function of this protein remains unknown, it is believed to be involved in the activation and proliferation of B lymphocytes. In some immunodeficiency conditions, this condition has been associated with recurrent bacterial respiratory infections.

In patients with FBD, a decrease in the percentage and absolute count of lymphocytes, CD3(%) cells, CD4(%) cell count, and a decrease in the CD4(%)/CD8(%) lymphocyte ratio were observed compared to the age-appropriate norm. It should also be noted that the absolute and relative count of CD19(%) cells and the absolute count of CD16(%) cells were reduced. However, this group also included children with normal lymphocyte subpopulations.

A decrease in the absolute number of T lymphocytes (CD3(%) cells) indicates a deficiency in cellular immunity, specifically, a deficiency in the cellular effector component of immunity. It is detected in inflammations of various etiologies, in particular in the patients we observe with recurrent inflammatory diseases of the respiratory organs.

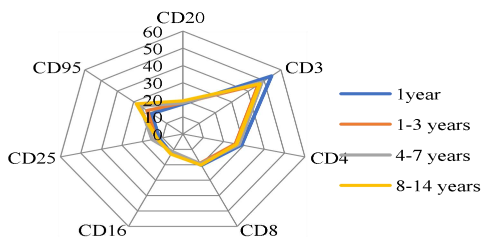

Figure 1. Absolute number of lymphocyte subpopulations in FBD (n=40) as a percentage of the norm (n=20)

Figure 1 shows the results of a study of the number of lymphocyte subpopulations in children with cerebral palsy. These children exhibited some lymphopenia and a significant ($p < 0.05$) decrease in the number (absolute and relative) of almost all major lymphocyte subpopulations compared to age-appropriate norms; only the number of CD8+lymphocytes did not differ significantly.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Based on the data obtained, it seems that frequently ill children have some deficiency in the T-cell component of immunity, and if we take into account the reduced absolute and relative number of CD 19+ cells, then we can also assume some deficiency in the B-cell component of immunity.

Since the objectives of our study included assessing the immune status and sensitivity to immune drugs, the Modus laboratory in Andijan examined the nature of sensitivity to immunomodulators in the observed children, the data for which are presented in Table 2.

Table 2. Sensitivity Of Various Immunomodulators In Frequently Ill Children

Age of patients	sex	Cycloferon	Timalin	Immunomodulin	Immunal	Bronchomunal	Polyoxidonium	amizon	galavit
Up to 1 year	Boy 2	2 100(%)	1 50(%)	1 50(%)	2 100(%)	2 100(%)	2 100(%)	0 0(%)	1 50(%)
	girl 0	0	0	0	0	0	0	0	0
1-3 years	Boy 4	3 75(%)	1 25(%)	2 50 (%)	4 100 (%)	4 100(%)	4 100(%)	4 100(%)	2 50(%)
	girl 3	1 33.3(%)	1 33.3(%)	3 100(%)	2 66.7(%)	2 66.7(%)	3 100(%)	1 33.3(%)	3 100(%)
4-7 years	Boy 0	0	0	0	0	0	0	0	0
	girl -5	2 40(%)	2 40(%)	4 80(%)	3 60(%)	3 60(%)	3 60(%)	2 40(%)	3 60(%)
8-14 years	boy 1	0	0	1 100(%)	0	0	1 100(%)	0	0
	girl 6	3 50(%)	4 66.7(%)	3 50(%)	5 83.3(%)	4 66.7(%)	5 83.3(%)	2 33.3(%)	2 33.3(%)
Summary = 40		11 52.4(%)	9 42.86(	13 61.9(%)	16 76.2(%)	11 71.4(%	17 80.95(	9 42.86(	11 52.4(

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

		%)			)	%)	%)	%)

Table 2 shows that in the group of children under 1 year of age, the highest sensitivity was observed to cycloferon, immunal, bronchomunal, and polyoxidonium. In the other age groups, the highest sensitivity was to immunal, bronchomunal, and polyoxidonium. Since the children had an initially unfavorable background of the immune system, immunocorrective therapy - Polyoxidonium or Bronchomunal - was added to the complex treatment (basic antibacterial, antiviral therapy, rational nutrition, physiotherapy, hardening measures). According to the instructions, these medications can be used in all age groups of pediatric patients. Given the contraindications for prescribing cycloferon to children under 3 years of age, we prescribed Bronchomunal or Polyoxidonium to the study patients.

In order to evaluate the effect of immunomodulators, 21 children were examined before taking the drug and after the course of treatment - three weeks after the initial examination. The patients were divided into 2 groups: 14 children with CHD received bronchomunal at an age-appropriate dose of 3.5 mg or 7 mg once a day, 7 children with CHD were prescribed polyoxidonium in suppositories 6 mg according to the regimen (Table 3).

Table 3. The effect of immunomodulators on the relative and absolute numbers of lymphocyte subpopulations (M±tm, x106/L)

	№	**Polyoxidonium (n=7)**	**Bronchomunal (n=14)**	**norm**
Leukocytes ($x10^6$/л)	1	8584±857	8970±637	7900 ±1000
	2	8632±1055	7894±678*1	
Lymphocytes	1	41±7 3050±457	41±3 2832±236	47+4
	2	38±9 2474+510	34±3* 2857±339	3900 ±600
CD3(%)	1	68±4 1965±261	69+2 1991±183	68±2
	2	63±3 1175±318	66±3 1855±281	2600±400
CD4(%)	1	43±2 1240±171	45±2 1307±115	50±2
	2	38±5 514±281	44±4 1222±230	1950±350
CD8(%)	1	23±2 748±134	26±2 773±76	21±2
	2	23±2 525±193	26±2 779±132	870 ±200

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

CD4(%) CD8(%)	1	2,08±0,19	2,35±0,23	2,4 ±0,15
	2	1,34±0,26	1,91±0,26*1	
CD 19(%)	1	20±2 558±116	23±3 670±90	22±2 900 ±130
	2	16±1 378±96	21±2 662±155	
CD 16(%)	1	20±3 643±107	18±2 505±72	14±2 500 ±150
	2	17±2 306±68	18±2 498±86	

Note: 1 – before treatment; 2 – after treatment

As noted above, the children we examined initially showed a decrease in the numbers of certain blood lymphocyte subpopulations. When various immunomodulators were administered, the following pattern was observed: background therapy had no significant effect on the lymphocyte subpopulation composition—number or percentage.

Bronchomunal treatment resulted in an increase in the relative CD3 lymphocyte count, as well as a decrease in the CD4/CD8 ratio and CD16 lymphocyte count. Polyoxidonium treatment increased the absolute CD3 lymphocyte count, the percentage and absolute CD4 lymphocyte count, and the absolute CD8 cell count. It should be noted that in some cases, under the influence of immunomodulators, a worsening of immunodeficiency was observed, expressed in a decrease in the number of subpopulations, and sometimes an increase in the content of subpopulations was observed, but almost never to the level of the age norm. The effects of immunomodulators on initially normal and initially reduced lymphocyte subpopulations were also analyzed. The results of this analysis are presented in Table 4.

Table 4. The effect of immunomodulators on the initially normal relative (%) and absolute (x106/L) numbers of lymphocyte subpopulations (M±tm)

Indicators	№	Polyoxidonium	Bronchomunal	norm
Leukocytes (x10^6/l)	1	8584±857	8970±637	7900 ±1000
	2	8632±1055	7894±678*1	
Lymphocytes	1	41±7 3050±457	41±3 2832±236	47±4 3900±600
	2	38±9 2474±510	34±3*1 2857±330	
CD3(%)	1	68±4 1965±261	69±2 1991±183	68±2 2600±400
	2	63±3 1175±318*1	66±3 1855±281	
CD4(%)	1	43±2 1240±171	45±2 1307±115	50±2

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

	2	38±5 514±281*1	44±4 1222±230	1950±350
CD8(%)	1	23±2 748±134	26±2 773±76	21±2 870 ±200
	2	23±2 525±193	26±2 779±132	
CD4/ CD8	1	2,08±0,19	2,35±0,23	2,4 ±0,15
	2	1,34±0,26*1	1,91±0,26*1	
CD 19(%)	1	20±2 558±116	23±3 670±99	22±2 900 ±130
	2	16±1* 378±96*1	21±2 662±155	
CD 16(%)	1	20±3 643±107	18±2 505±72	14±2 500 ±150
	2	17±2 306±68*1	18±2 498±86	

*In the columns with data on the number of lymphocytes or their subpopulations, the top line is the percentage, and the bottom line is the absolute number of cells. 1 - before treatment, 2 - after treatment, * significant difference from the baseline level (p < 0.05).*

With initially normal lymphocyte subpopulation numbers, baseline treatment had virtually no effect on the numbers of the main lymphocyte subpopulations, but a decrease in the absolute number of CD19 cells was observed. The use of immunomodulators caused a more or less pronounced decrease in the number of lymphocyte subpopulations. In the group of children receiving Polyoxidonium, a decrease in the absolute count of CD3, CD4, CD19, and CD16 lymphocytes and the CD4/CD8 ratio was observed. Bronchomunal significantly reduced the leukocyte count and somewhat reduced the CD4/CD8 ratio.

A different picture was observed when immunomodulators were administered to children with initially reduced lymphocyte subpopulation composition. The relative number of CD3 lymphocytes and the absolute number of CD16 cells increased significantly. The use of immunomodulators in combination with spa treatment generally had a beneficial effect and a greater impact.

Table 5. Effect of immunomodulators on the initially reduced relative (%) and absolute (x106/L) numbers of lymphocyte subpopulations (M±tm)

Indicators	**№**	**Polyoxidonium**	**Bronchomunal (n=14)**	**norm**
Leukocytes ($x10^6$/л)	1	4300±1511	4785±275	7900±1000
	2	9000±2674*8	7196±814*1	
Lymphocytes	1	22±2(%) 1356±132	21±2(%) 1441±131	47±4(%) 3900±600
	2	29±3(%)*1 2393±372*1	34±4(%) * 2282±375*1	

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

CD3 (%)	1	52±5(%) 925±130	51±3(%) 988±91	68±2(%)
	2	59±4(%) 1360±213*1	61±4(%) 1546±242*1 *	2600±400
CD4(%)	1	30±2(%) 565±75	30±2(%) 626±61	50±2(%)
	2	32+2(%) 686±95*1	38±2(%) 971±126*1 *	1950±350
CD8(%)	1	16±1(%) 311±46	14±1(%) 322±30	21±2(%)
	2	23±7(%)*1 538±87*1	20±3(%) 567±127*1 *	870 ±200
CD4/CD8	1	1,36±0,12	1,21±0,09	2,4 ±0,15
	2	1,31±0,14	1,63±0,21*1	
CD 19(%)	1	10±2(%) 211±51	11±2(%) 284±38	22±2(%)
	2	15±3,2 [illegible]	19±12 420±94*1	900 ±130
CD 16(%)	1	9±1(%) 142±23	9±1(%) 240±32	14±2(%)
	2	13±4,1(%) 281±96*1	11±3(%) 390±141*1	500 ±150

In the columns with data on the number of lymphocytes or their subpopulations, the top row is the

percentage, and the bottom row is the absolute cell count. 1 - before treatment, 2 - after treatment,

*significant difference from baseline ($p < 0.05$)

Polyoxidonium administration increased the number of key lymphocyte subpopulations. Increased white blood cell (leukocyte) counts, lymphocyte counts, and CD3, CD4, CD8, CD19, and CD16 cell counts were observed. Bronchomunal administration also increased white blood cell (leukocyte) counts and lymphocyte counts, as well as increases in CD3, CD4, CD8, CD19, and CD16 cell counts and the CD4/CD8 ratio.

Taking into account the obtained data (Table 4 and Table 5), it can be said that the use of immunomodulators in children with an initially normal number of lymphocyte subpopulations has an adverse effect on the immune system. On the contrary, the use of immunomodulators in children with an initially reduced number of lymphocyte subpopulations leads to an increase in the number of the main lymphocyte subpopulations and thus has a positive effect on the state of the immune system.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Our study also examined serum immunoglobulin levels in frequently ill children, as well as their levels during treatment with immunomodulators. The data obtained are presented in Tables 6 and 7.

Table 6. Immunoglobulin concentrations in serum of frequently ill children (M±tm, mg/ml)

Immunoglobulin	Originally	Norm
IgG	10,4±1,3*	12,3±1,8
IgM	1,4±0,3	1,6±0,2
IgA	1,0±0,2	1,1±0,4

* significant difference from baseline, p < 0.05

Table 7. Immunoglobulin levels in frequently ill children before and after treatment (M±tm, mg/ml)

Type of treatment	IgG		IgM		IgA	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Basic standard therapy	13,7±2,9	14,8±2,9	1,0±0,4	1,0±0,4	1,2±0,3	1,3±0,3
Polyoxidonium	8,9±0,8	9,6±1,0	1,5±0,3	1,9±0,4	0,6±0,3	0,7±0,3
Bronchomunal	8,0±1,2	8,6±1,7	1,3±0,2	1,5±0,2	1,9±0,3	2,2±0,3
Norm	12,3±1,8		1,6±0,2		1,1±0,4	

It seems that the treatment we conducted did not significantly affect the concentration of IgG, IgM, or IgA. Only a tendency toward an increase in the concentration of immunoglobulins after treatment was noted (Table 7). However, an analysis of the effect of immunomodulators on the serum immunoglobulin level in FBD after treatment with Polyoxidonium or Bronchomunal showed that the immunoglobulin The serum composition changed relatively, in particular, polyoxidonium increased the concentration of IgM (probably due to the child's immune response to infection). Bronchomunal led to an increase in the concentration of IgA, which may have contributed to protection against infections due to the secretory fraction.

CONCLUSIONS

1. The immune status of healthy children of the same age differs from that of frequently ill children. These differences include a decrease in the number of certain lymphocyte subpopulations in children with frequent leukemia.

2. The use of immunomodulators (Polyoxidonium, Bronchomunal) affects the number of lymphocyte subpopulations, with their effect being most pronounced in children with frequent leukemia with reduced immune status.

3. When comparing different immunomodulatory therapy regimens in children with frequent leukemia, Bronchomunal was found to be the most effective in correcting the identified changes,

as it normalized the number of lymphocyte subpopulations and increased immunoglobulin A production.

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