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Research article

Assessment of efficacy of secondary prophylactic complex of bronchial obstruction syndrome in young children with respiratory disorders in neonatal period: analysis of symptoms and serological markers

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Abstract: Diseases of respiratory tract in young children are often accompanied by the development of bronchial obstruction syndrome. Recurrent episodes of bronchial obstruction are a common problem in young children with respiratory disorders in neonatal period. The aim of our work was to test secondary prophylactic measures concerning development and progression of recurrent bronchial obstructive syndrome in young children, who had suffered respiratory disorders in neonatal period. Prophylactic complex included basic therapy (inhalation of glucocorticosteroids—fluticasone propionate or budesonide), administration of immunomodulating drug Ribomunyl and conducting of prophylactic vaccination in specialized inpatient department after prior preparation whith antihistamines. *Objectives*: The feature of disease course was assessed based on the need of using drugs with symptomatic action, frequency of exacerbations, their mean duration and severity in 60 children, who had breathing disorders in neonatal period. Children were randomly divided into two groups. The study of efficacy of secondary prophylactic measures was conducted in 30 children (basic group) and in other 30 patients secondary prophylactic complex was not used (control group). *Methods*: Algorithm of secondary prophylactic complex included basic therapy involving inhalation glucocorticosteroids, administration of immunomodulatory drug Ribomunyl as recommended and conduction of planned prophylactic inoculations with the use of antihistamines. *Conclusions*: In children, who were administered secondary prophylactic complex was a positive dynamics in clinical picture and laboratory data. *Results*: Administration of secondary prophylactic complex enabled, to a

certain extent, to prevent progression of bronchial obstructive syndrome and achieve a reliable increase in γ-INF, IgA, IgM, IgG levels and decrease in IL-4 ($p < 0.01$).

Keywords: secondary prophylactic complex; young children; respiratory disorders; neonatal period; interleukin-4; gamma-interferon; immunoglobulins

Abbreviations: OB: obstructive bronchitis; BA: bronchial asthma; Ig: immunoglobulin; Th-1: T-helpers I; Th-2: T-helpers II; IFN-γ: γ-interferon; IL: interleukin; SPC: secondary prophylactic complex; TMB: tetramethylbenzidine; BOS: bronchial obstruction syndrome; CS: corticosteroids; ARVI: acute respiratory viral infections

1. Introduction

Diseases of the respiratory tract in young children are often accompanied by the development of bronchial obstruction syndrome. Based on investigation data, conducted according to international standardized program ISAAC, in Ukraine recurrent wheezing with prolonged exhalation occurs in 29.2% of children [1]. By literature data, from 30 to 50% of children below three years, at least once had signs of bronchial obstruction, and 54% of them with recurrent episodes [2,3].

The most typical causes of bronchial obstruction in young children is obstructive bronchitis (OB); bronchial asthma (BA); anomalies and congenital failures of respiratory organs; congenital defects of the heart and blood vessels; bronchopulmonary dysplasia; bronchiolitis; foreign body in the bronchi; cystic fibrosis; immotile cilia syndrome; mediastinum tumors [4,5].

Nowadays, the existence of correlation between conduction of continuous respiratory support in neonatal period (artificial ventilation), spontaneous breathing with continuous positive airway pressure, oxygen therapy and further formation of hyperactivity of the airways, which is clinically manifested by recurrent bronchial obstruction, has been proven. Such situation is associated with unfavorable ante- and intranatal factors, perinatal damages to the central nervous system, age-related morphofunctional peculiarities in young children (narrow airways, flexible cartilages, rigid thorax, lower elasticity of lung tissue, abundant vascularization, tendency to edema and exudation) [6,7].

Overall, diagnostic algorithm of bronchial obstruction involves application of clinical, laboratory and instrumental methods [8]. Laboratory investigations can include different serological markers. Frequently, assessment of hemogram and immune condition is included with determination of serum immunoglobulins (Ig)A, IgM, IgG, total IgE, if required—determination of the level of specific immunoglobulins to different groups of allergens [1,9]. Considering predominantly infectious etiology of exacerbations of this pathology in young children, dynamics of immunoglobulins has practical meaning for the assessment of efficacy of therapeutic tactics.

Literature data prove that imbalances of T-helpers I (Th-1) and II (Th-2) play one of the most significant roles in pathogenesis of atopic diseases [10,11]. Th-1 synthesizes predominantly pro-inflammatory cytokines, which include γ-interferon (IFN-γ). Th-2 synthesizes interleukins (IL), which provide humoral reactions, anti-inflammatory cytokine IL-4 being one of them. Thus, determination of INF- γ and IL-4 in dynamics in blood serum of children with bronchial obstruction plays a significant role for the assessment of treatment efficacy [12,13].

Secondary prophylactic complex (SPC) implies measures aimed at prevention of new exacerbations of the disease, considering different causes of the disease—infectious agents, specific (influence of allergen) and nonspecific factors [14,15].

The aim of our research was to test secondary prophylactic measures concerning the development and progress of recurrent bronchial obstruction syndrome in young children, who had suffered respiratory disorders in neonatal period.

2. Materials and methods

Assessment of a child's general condition, type of feeding, physical development, prophylactic vaccinations, signs of atopia in children (detailed description of occurrence and duration of symptoms, provoking factors), incidence and peculiarities of respiratory pathology and extent of treatment, presence of any other health problems was performed.

Peculiarity of the disease course was assessed based on the need in using drugs with symptomatic action, frequency of exacerbations, their mean duration and severity. Patients of the basic group had levels of immunoglobulins IgA, IgM, IgG, IgE and cytokines—IL-4, INF-γ determined in blood serum before administration of secondary prophylactic complex and in 12 months dynamic.

2.1. Study design and population

The study was conducted following the 7th revision of the principles of the Declaration of Helsinki Human Rights (2013), the Council of Europe Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. All patients selected to participate in the study signed (parents of children) an informed consent document approved by the Ethics Committee of Clinical Research of Danylo Halytsky Lviv National Medical University and Nonprofit Communal Enterprise "City Children's Clinical Hospital of Lviv".

The investigation included 60 children with recurrent bronchial obstruction syndrome, who had undergone artificial ventilation in neonatal period. Children were randomly divided into two groups. The study of efficacy of secondary prophylactic measures was conducted in 30 children of the basic group; and in other 30 patients secondary prophylactic complex was not used (control group).

Only patients of the basic group received elaborated prophylactic complex, which included:

(1) Basic therapy, which was administered depending on the degree of severity and individual peculiarities of the disease course, using inhalation glucocorticosteroids (fluticasone propionate or budesonide) from three to six months. As symptomatic treatment, broncholytics were administered, such as cholinolytic (ipratropium bromide).
(2) Administration of immunomodulating drug ribomunyl (bacterial immunomodulator with systemic action of vaccine type) for 6 months. The drug was used by the scheme: 0.75 mg in the morning fasting first days of the week during three weeks and five following months—four first days of the month.
(3) Conduction of scheduled prophylactic inoculations in specialized inpatient department after prior preparation, which included administration of antihistamines.

In case of exacerbation of bronchial obstruction, patients of both groups received similar treatment, in particular, systemic glucocorticosteroids and drugs with symptomatic action were administered as required.

Patients of control group after exacerbation episodically received antihistamines; however, continuous basic therapy was not administered.

Patients were examined in a clinic on schedule four times: at the time of involvement in the investigation, in 3, 6 and 12 months ±14 days. If required (changes in a child's health, questions to doctors), unscheduled visits were conducted.

A chart of visits and diagnostic procedures is presented in Table 1.

Parents performed the control of the symptoms of the disease. Thus, a special diary of self-monitoring was created, where symptoms of the disease were recorded. Besides, notes on drug use were also made in the diary. Final assessment of treatment efficacy was made on a visit to a clinic.

2.2. Total IgE in serum

Serum total IgE was determined using a kit Total IgE-ELISA (Granum, Ukraine), according to a manufacturer's instruction. Results for serum total IgE were expressed as international units (U/mL) and calibrated against the World Health Organization standard for IgE 1 U for total IgE was equal to 2.15 pg/mL. Briefly, in the well plates with the immobilized antigen (specific anti-IgE antibodies) were introduced the diluted serum in ELISA buffer in the ratio 1:1 and incubated for 30 min at 37 ℃. IgE from the sample was bound to the antibodies on the surface of the well. The plates then washed 3 times with PBS to remove unbounded material. The conjugate (second anti-IgE antibodies, labeled with horseradish peroxidase) was introduced into the plate well and incubated again for 30 min at 37 ℃. After that, the plates washed 5 times and added substrate tetramethylbenzidine (TMB) solution. The plates incubated for 20 min at 20–25 ℃ in the dark. The reaction was stopped by addition of Stop solution and absorbance read at 450 nm using a Sunrise microplate reader (Tecan, Austria). The intensity of the color reaction was directly proportional to the number of total IgE in the sample. A piecewise-linear method for calculating values was used. The concentration of IgE in the samples was determined using a calibration curve, where the axis X corresponded to the value of concentration (U/mL) and axis Y corresponded to the value an optical density (OD).

Table 1. A chart of visits and diagnostic procedures.

Procedure	Period of visit								
	Offer to participate in the investigation	Involvement in the investigation (administration of primary rehabilitation measures)	Involvement in the investigation (primary rehabilitation measures were not administered)	6 months ± 1 week from involvement in the investigation	12 months ± 1 week from the involvement in the investigation	Administration of SPC	3 months ± 1 week from the administration of SPC	6 months ± 1 week from the administration of SPC	12 months ± 14 days from administration of SPC
Complaints	+	+	+	+	+	+	+	+	+
Anamnesis	+	+	+	+	+	+	+	+	+
Filling in a form about a child's data	+	+	+	+	+	+	+	+	+
Providing information about investigation	+	-	-	-	-	-	-	-	-
Consent to participate in the investigation	-	+	+	-	-	-	-	-	-
Analysis of a diary of self-monitoring	-	-	-	+	+	-	+	+	+
Total blood count	-	-	-	-	-	+	-	-	+
Determination of serum IgA, IgM, IgG	-	-	-	-	-	+	-	-	+
Determination of total IgE	-	-	-	-	-	+	-	-	+
Determination of IL-4 and INF-γ	-	-	-	-	-	+	-	-	+

+: the procedure was performed; –: the procedure was not performed.

2.3. Determination of immunoglobulins IgA, IgM, IgG

Serum IgA, IgM, IgG for determination of immunoglobulins A, M, G in blood serum IgA, IgM and IgG-ELISA (Granum, Ukraine), according to a manufacturer's instruction. Serum before the study 0.005 mL (mL) of serum is diluted in 1 mL (mL) of sample dilution buffer. The given test system uses the principle of competitive enzyme-linked immunosorbent assay. In the hole of the plate with immobilized antigen (IgA, IgM, IgG) make the test sample and conjugates (anti-IgA, anti-IgM, anti-IgG, labeled with peroxidase). IgA, IgM, IgG from the sample compete with conjugates for bonding with antigen on the surface of the well. After washing, the activity of the enzyme bound on the surface of the well plate, manifested by the addition of substrate, and measured at a wavelength of 450 nm (nm). The intensity of the color reaction is inversely proportional to the amount of IgA, IgM, IgG in the sample.

Carry out calculations using the inversely proportional relationship: CST = ODS/ODTS*CSS, where CST: the concentration of immunoglobulin in the test sample; CSS: the concentration of immunoglobulin in the standard; ODTS: optical density of the test sample; ODS: optical density of the standard.

2.4. Determination of cytokines

Blood was drawn by venipuncture and allowed to clot for 30 min, centrifuged (15 min, 720 × g) and serum was collected, aliquoted and kept frozen at −80 °C until examination. Circulating cytokines were evaluated in duplicates in serum by means of flow cytometry-based method utilizing magnetic microspheres conjugated with monoclonal antibodies using the BioPlex 200 platform with HRF (Bio-Rad, USA), incorporating Luminex xMAP® technology, and validated custom plexes allowing for simultaneous measurement of IL-4 and IFN-γ. The bioassays were conducted according to manufacturer's instructions. Standard curves were drawn using 4- or 5-PL logistic regression and the data were analyzed using BioPlex Manager 6.0 software (Bio-Rad, USA) [13].

2.5. Statistical analyses

Categorical (qualitative) signs were presented as a number of patients and in their percentage. Shapiro–Wilk criterion has been applied to check the normality of distribution. Quantitative data with normal distribution character have been presented as M ± SD, where M is a mean value, SD—standard deviation.

In order to check the significance of difference between groups of categorical (qualitative) signs we have applied the tables of frequency (tables 2*2) and a Pearson χ^2 criterion. A two-sided t-test for unrelated groups has been used to check the significant differences between groups of quantitative data with normal distribution. To check the significant differences between related groups (e.g. indexes during different visits) we have applied a t-test for related groups. A difference between groups was considered significant in case of $p < 0.05$.

For the required sample size calculation, a priori power analysis for a two-sided t-test was provided with such initial data: & = 0.05, power $(1 - \beta) = 0.8$, effect size d = 0.8. With equal sample size in each group, calculated minimal total sample size = 52. Thus, the optimal total sample size was

established in 60 patients, to take into account the possible withdrawal of patients from the study.

All of statistical calculations were performed using software RStudio v. 1.1.442 and R Commander v.2.4-4.

2.6. Ethics approval of research

Danylo Halytsky Lviv National Medical University 20/12/2010 № 10; Nonprofit Communal Enterprise "City Children's Clinical Hospital of Lviv"; 16.Nov.2018 № 6.

3. Results

Patients of both groups were alike by sex, body weight at birth (extremely low: below 1000 g; very low: 1000–1499 g; low: 1500–2499 g, normal: 2500–3999 g, high: over 4000 g), gestational age (immature: 22–36 weeks, full-term: 37–42 weeks, postmature: over 42 weeks), respiratory therapy (artificial ventilation and/or spontaneous breathing with continuous positive airway pressure and supply of free oxygen) in neonatal period, development of recurrent bronchial obstruction syndrome under 3 years of age.

Pairs were alike by percentage of boys (18 (60%); $p > 0.05$). Mean body mass at birth was (1888.2 ± 613.2 g in basic group vs 1929.7 ± 588.2 g in control group; $p > 0.05$) and average gestational age was, respectively, (31.9 ± 3.2 weeks vs 31.8 ± 3.2 weeks; $p > 0.05$). All children in neonatal period had respiratory disorders, respiratory therapy was conducted, and recurrent bronchial obstruction syndrome was diagnosed after three years of age.

Diagnosis of bronchial asthma was verified in 17 (56.67%) patients of the basic group and in 19 (63.33%) in control group, $p > 0.05$. In all children, recurrent episodes of obstructive bronchitis were diagnosed (Figure 5).

In investigated groups, the incidence of drug administration for symptomatic therapy was assessed (β_2-agonists, cholinolytics) between visits (Figure 1). Analysis of drug administration for symptomatic therapy was performed every day by parents, and a doctor summarized the results during visits: 0: did not use; 1: rarely; 2: systematically; 3: often; 4: very often.

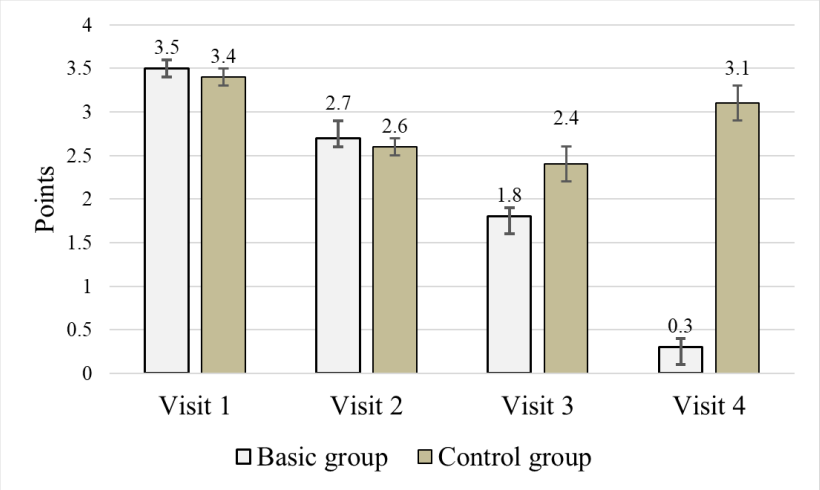

Figure 1. Dynamics of the incidence of drug use for symptomatic therapy.

The study of dynamics of incidence of drug use for symptomatic therapy within groups showed a reliable decrease in their usage during investigation in patients of the basic group: reduction of assessment from 3.5 ± 0.1 to 0.3 ± 0.1 ($p < 0.01$) (mean difference 3.2 (95% CI: 2.80 to 3.60)), while in control group from 3.4 ± 0.1 to 3.1 ± 0.2 ($p > 0.05$) (mean difference 0.3 (95% CI: −0.3 to 0.91)). Comparison of this index between groups at the time of investigation completion showed a reliable decrease in the incidence of drug use for symptomatic therapy in patients of the basic group, compared to control group ($p < 0.01$).

The efficacy of the use of prophylactic complex can be judged based on dynamics of incidence (Figures 2 and 3), mean duration (Figure 4) and severity of episodes (Figure 5) of recurrent bronchial obstruction syndrome.

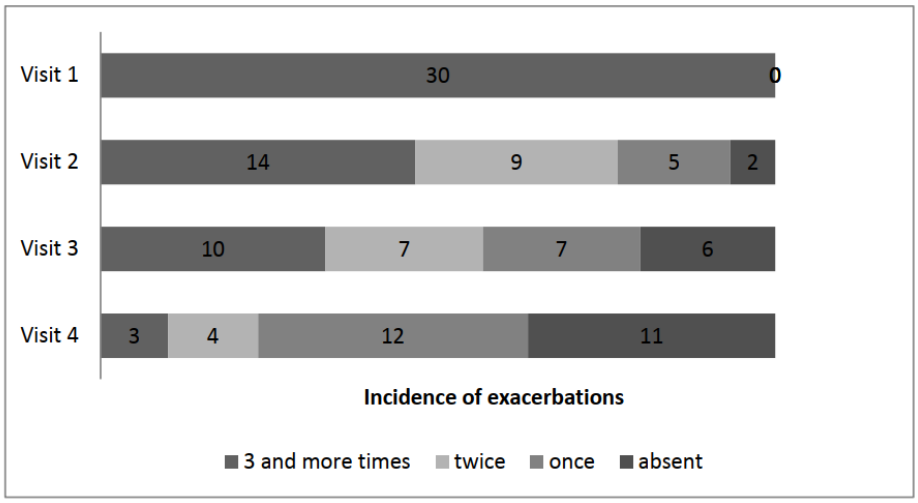

Figure 2. Dynamics of the incidence of recurrent bronchial obstruction syndrome in patients of the basic group.

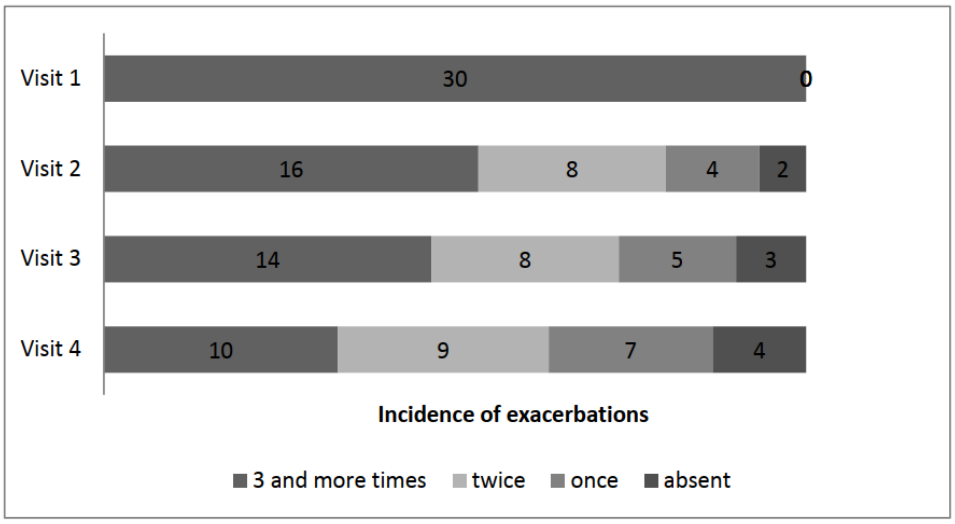

Figure 3. Dynamics of the incidence of recurrent bronchial obstruction syndrome in patients of control group.

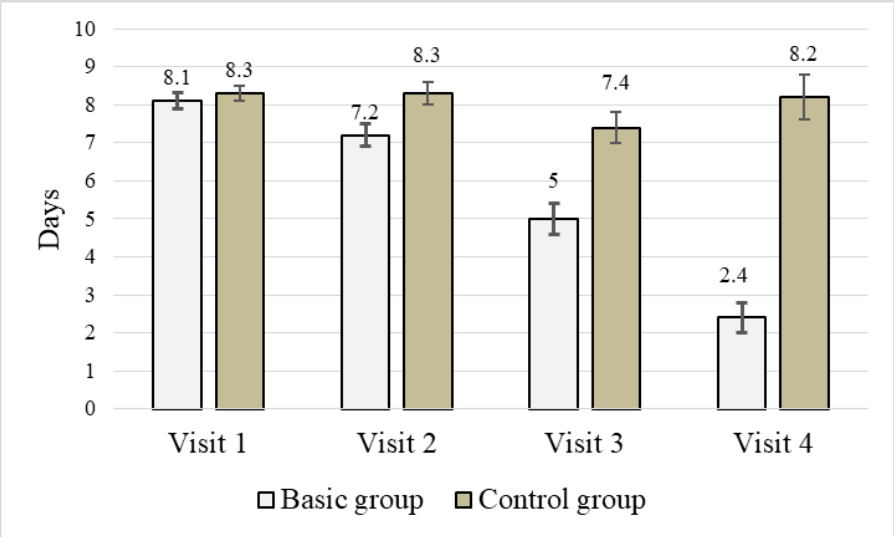

Figure 4. Mean duration of episodes of recurrent bronchial obstruction syndrome.

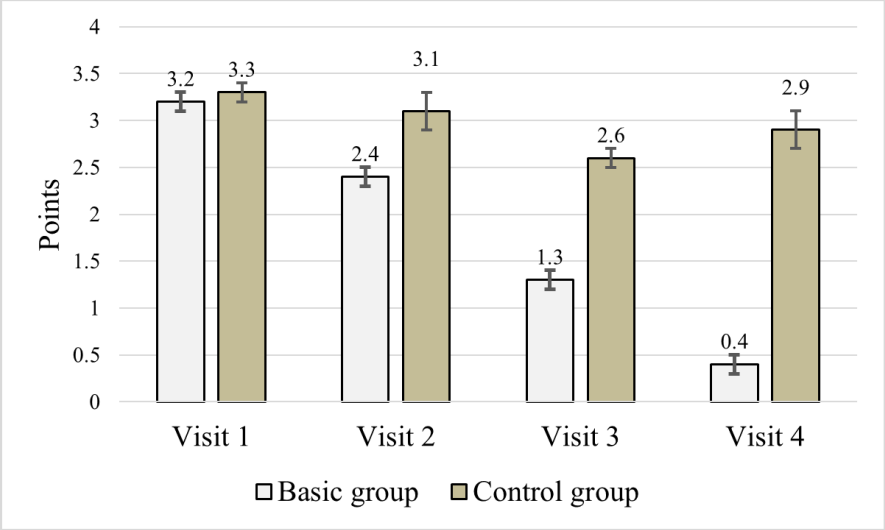

Figure 5. The severity of the episodes of bronchial obstruction syndrome.

Analysis of dynamics of the incidence of recurrent bronchial obstruction in patients of the basic group (Figure 2) and control group (Figure 3) showed that frequent episodes (three and more times) were observed in all patients at the beginning of the research. Whereas, during the last visit, frequent episodes were recorded in 3 individuals (10%) of the basic group versus 10 (33.33%) in control group, $p < 0.05$. In 11 (36.67%) patients of the basic group and 4 (13.33%) of control group, episodes of recurrent bronchial obstruction syndrome were not recorded during the last visit, $p < 0.05$.

At the beginning of the research, mean duration of the episodes of recurrent bronchial obstruction syndrome in patients of both groups was similar ($p < 0.05$), however, decrease in this index was observed during investigation from 8.1 ± 0.2 to 2.4 ± 0.4 in patients of the basic group ($p < 0.01$) (mean difference 5.7 (95% CI: 4.47 to 6.93)), and from 8.3 ± 0.2 to 8.2 ± 0.6 in control group ($p > 0.05$) (mean difference 0.1 (95% CI: −1.54 to 1.74)).

The severity of the episodes of bronchial obstruction syndrome is presented in Figure 5.

In the process of treatment, the severity of episodes of recurrent bronchial obstruction syndrome reduced (Figure 5). The assessment of the severity of episodes of recurrent bronchial obstruction syndrome was determined as follows: 0: absent; 1: mild; 2: moderate; 3: severe; 4: extremely severe.

Throughout investigation, a reliable decrease in the severity of episodes of bronchial obstruction syndrome was observed in patients of the basic group (from 3.2 ± 0.1 to 0.4 ± 0.1; $p < 0.01$) (mean difference 2.8 (95% CI: 2.39 to 3.21)), however, in control group there was no reliable difference (from 3.3 ± 0.1 to 2.9 ± 0.2; $p > 0.05$) (mean difference 0.4 (95% CI: −0.21 to 1.01)). Comparison of the index at the time of investigation completion showed a reliable decrease in episodes of patients in the basic group, compared to control group ($p < 0.01$). Analyzing the efficacy of treatment, we studied the need in administering systemic steroids in patients during recurrent bronchial obstruction syndrome (Figure 6).

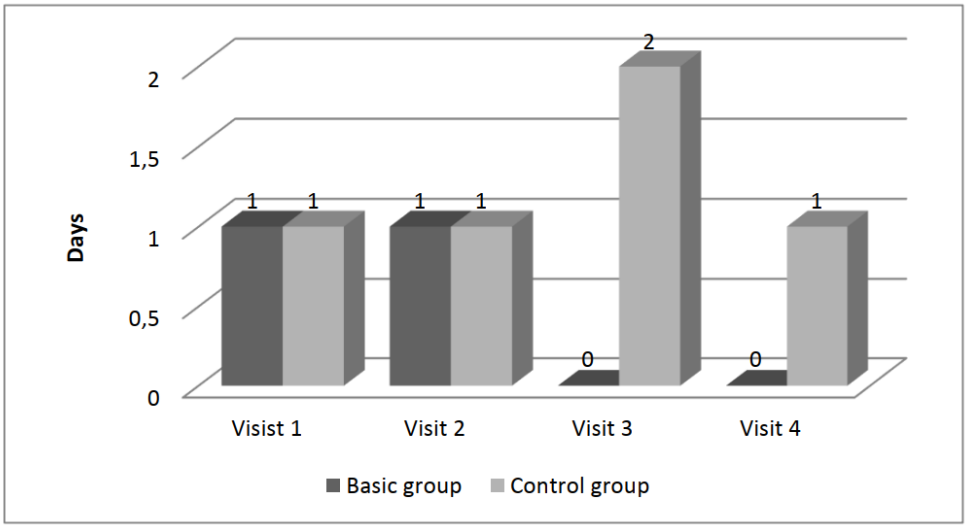

Figure 6. The incidence of administering systemic steroids in patients during exacerbation of recurrent bronchial obstruction syndrome.

The incidence of using systemic steroids during exacerbation of recurrent bronchial obstruction syndrome was the same during the first and the second visits. However, in the group of patients, where secondary prophylactic complex was used, the need in systemic steroids was significantly lower.

Thus, the conducted research enables to state that the use of secondary prophylactic complex promotes stabilization of the disease, its better control and prevents the progression (incidence, severity and average duration of the episodes of bronchial obstruction syndrome decreased).

Simultaneously with clinical assessment of the dynamics of the symptoms of recurrent bronchial obstruction syndrome in children, who received secondary prophylactic complex, a dynamic analysis of the data of immunological examinations was conducted (determination of IgA, IgM, IgG, IgE levels, IL-4 and IFN-γ in blood serum) before and after administration of secondary prophylactic complex.

Dynamic assessment of IgA, IgM, IgG levels in patients is presented in Figures 7–9.

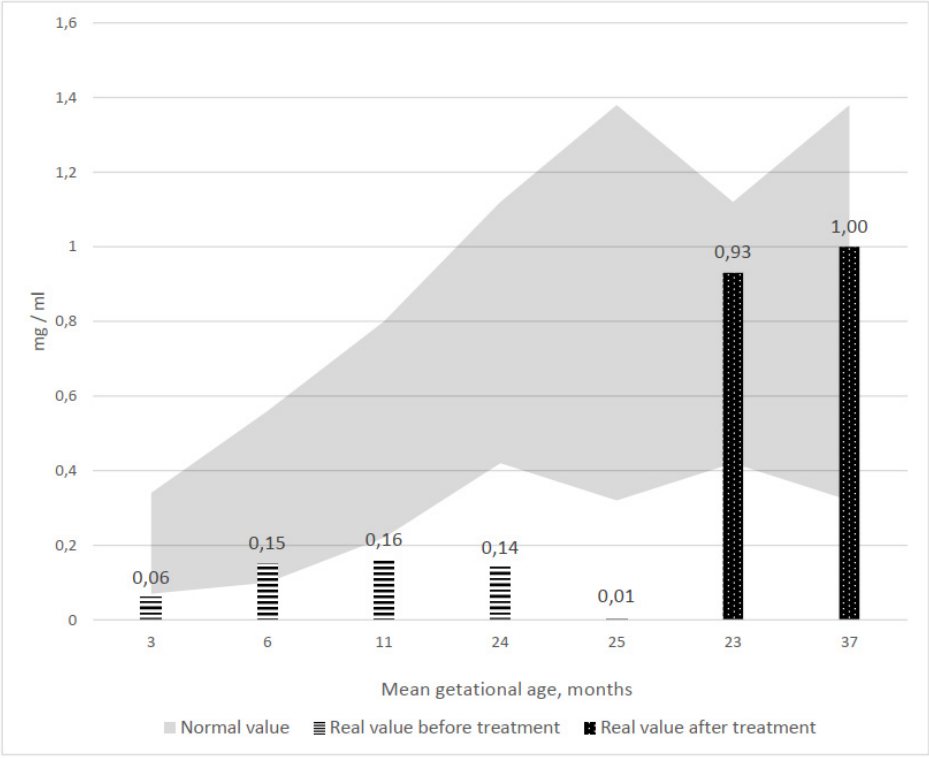

Figure 7. Normal and real value of IgA in children with recurrent bronchial obstruction syndrome before and after administration of secondary prophylactic complex.

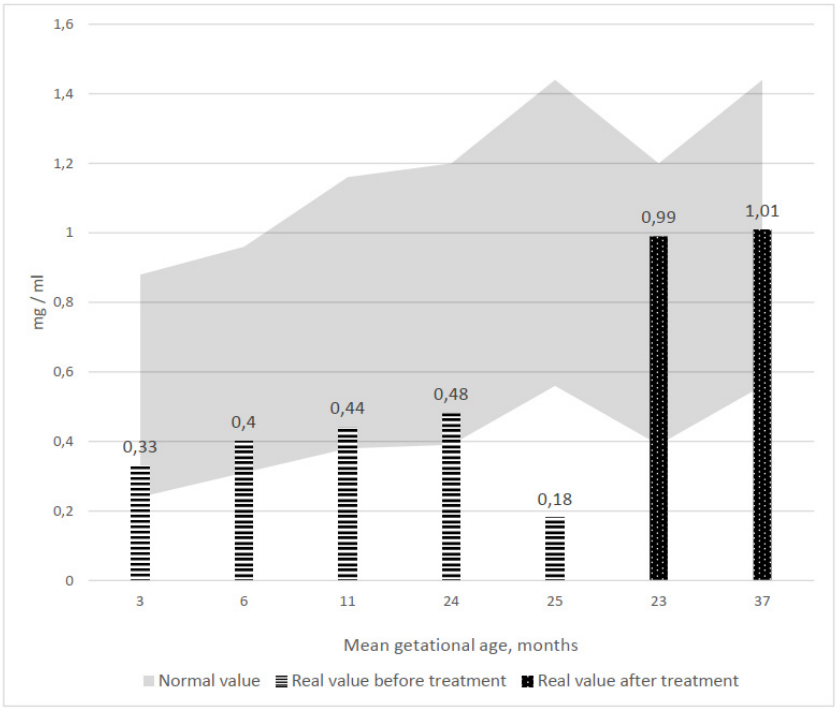

Figure 8. Normal and real value of IgM in children with recurrent bronchial obstruction syndrome before and after administration of secondary prophylactic complex.

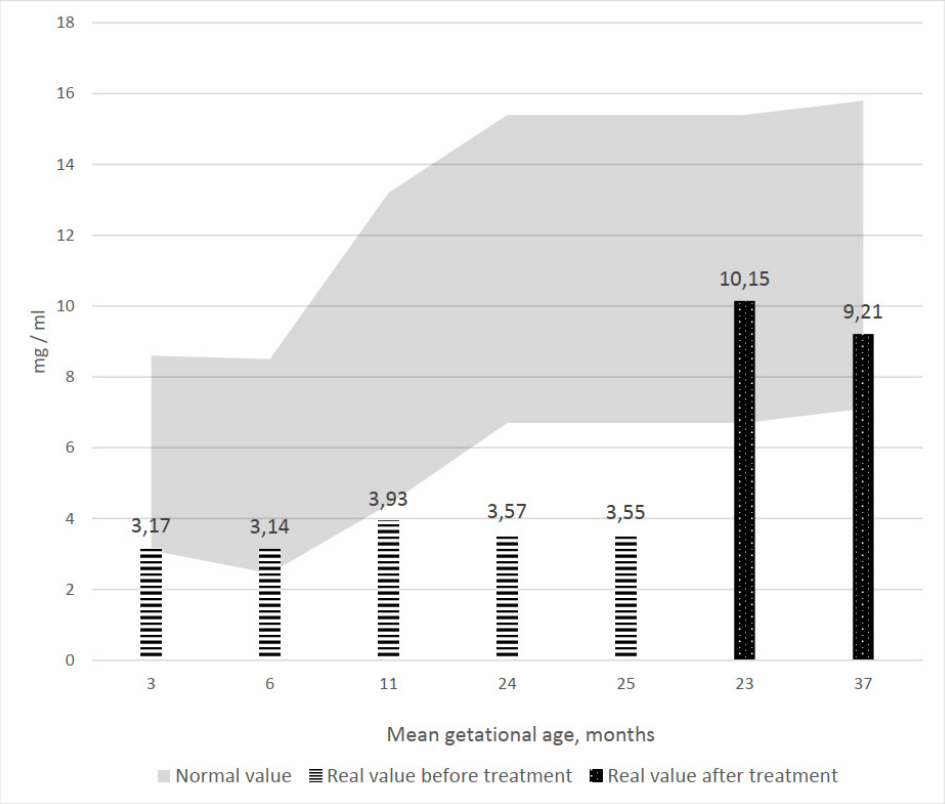

Figure 9. Normal and real value of IgG in children with recurrent bronchial obstruction syndrome before and after administration of secondary prophylactic complex.

Conducted analysis of dynamics of immunoglobulins (Figures 7–9) indicates that a reliably ($p < 0.01$) lower levels of IgA, IgM, IgG compared with normal indices were observed in children with recurrent bronchial obstruction syndrome before administration of prophylactic complex. After completion of prophylactic complex, their level reliably ($p < 0.01$) increased compared with indices before administration of secondary prophylactic complex.

Nosological verification of respiratory pathology, which accompanies bronchial obstruction syndrome, is the most complex in young children, which is associated with heterogeneity of genesis and difficulties of differential diagnosis.

Analysis of dynamics of total IgE level in children with recurrent bronchial obstruction syndrome (Figure 10) did not show a reliable difference before and after administration of prophylactic complex ($p > 0.05$).

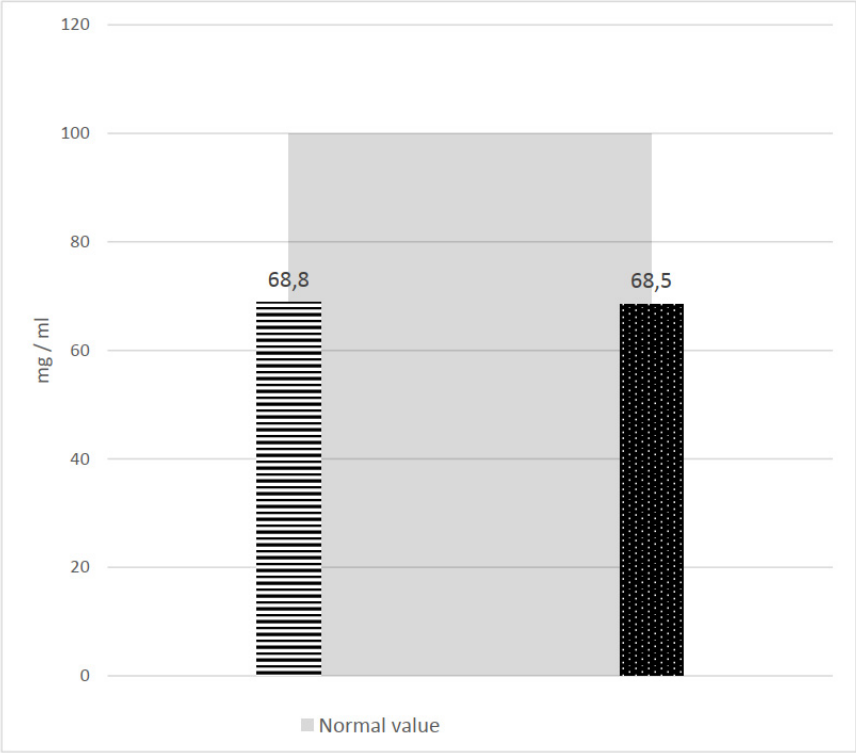

Figure 10. Normal and real value of IgE in children with recurrent bronchial obstruction syndrome before and after administration of secondary prophylactic complex.

Dynamic assessment of INF-γ and IL-4 in patients is presented in Figure 11.

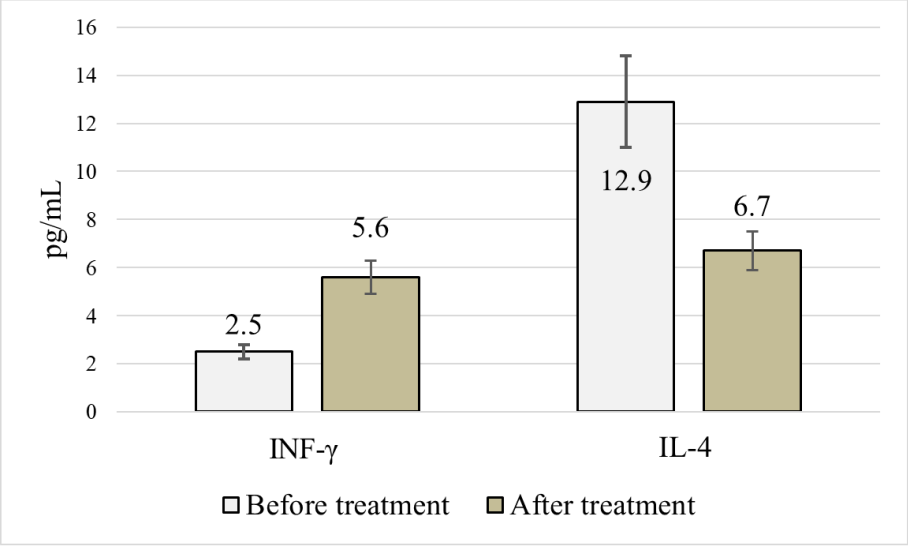

Figure 11. Levels of interleukin-4 and γ-interferon before and after administration of secondary prophylactic complex in a group of children with respiratory disorders in neonatal period.

Due to administration of secondary prophylactic complex, a reliable increase in INF-γ and decrease in IL-4 ($p < 0.01$) was observed. Such immunological indices enable, to a certain extent, to explain the aforementioned clinical efficacy and they can be associated with the influence of Ribomunyl, since the results of the latest investigations revealed new aspects of this drug. It has been proven that administration of Ribomunyl enables to increase IFN-γ production and thus intensify Th-1 immune response. Thus, in children, who were administered secondary prophylactic complex, a positive dynamics not only in clinical, but also laboratory indices (increase in IFN-γ and decrease in IL-4) was recorded.

4. Discussion

The realities of modern life are characterized by an extremely alarming increase in the frequency of respiratory system pathologies from the first months and years of a child's life. In view of this fact, it is extremely important to prevent these pathologies. Lots of reputable national and international organizations are currently working to find the best prevention methods. However, despite numerous studies dedicated to this problem, there are still not enough preventive measures with the proven effectiveness corresponding to the requirements of the evidence-based medicine [5,6,8].

A detailed analysis of the results of researches in the sphere of obstetrics, neonatology, pediatrics, allowed us to see various aspects of this problem, so today we can assert that respiratory disorders and prolonged artificial lung ventilation in the early neonatal period can contribute to the development of serious bronchopulmonary pathologies. Moreover, there are a number of reasons that constantly bring this problem to the forefront. These are, first of all, high mortality rates, the high cost of provision of medical care to such children, as well as disability problems. Therefore, it is extremely important to conduct the active search for factors that contribute to the development of bronchopulmonary pathologies in small children, what will allow to take timely and competent preventive measures and to prevent the development of recurrent and chronic pathologies [3,7].

Thus far, the international policy documents formulated new approaches to the prevention of the recurrent bronchial obstruction syndrome (BOS) and proposed two levels of preventive measures [1].

The primary prevention (first level) involves working with at-risk children for the purpose to prevent the development of the disease. It should begin long before the baby is born and involve the educational work with a pregnant woman and her family.

The secondary prevention (second level) is carried out after the first signs of the disease appeared. Its purpose is to prevent the development of recurrent and chronic pathologies and severe forms of the recurrent BOS and its complications [14,15].

The primary prevention of the recurrent BOS includes the rational feeding, household sanitation, limitation of contacts with infectious factors, early cold exposure training and general strengthening exercises [2,5].

In its turn, the secondary prevention is aimed at preventing exacerbations, and for this purpose the basic therapy and immunomodulating drugs are prescribed for children.

Early examinations are necessary for children with the recurrent bronchial obstruction syndrome to establish the causes of disease relapse. A thorough collection of genealogical, medical, biological, social, hygienic and epidemiological anamnesis, complete analysis of clinical symptoms and assessment of dynamics of the disease are significant. Nowadays, different schemes of secondary

prophylaxis aimed at prevention of exacerbations of the disease are being tested and discussed, which are of great interest in medicine.

What regards the secondary prevention of recurrent BOS, it is advisable to prescribe the basic therapy with the use of inhaled corticosteroids (CS)—fluticasone or budesonide. The use of inhaled CS allows to achieve a high drug concentration in bronchi, has a pronounced local anti-inflammatory effect and virtually no systemic activity [3]. However, the problem of unified recommendations for dosing of inhaled drugs, duration of treatment and methods of control over the topical anti-inflammatory effect still remains unresolved [6]. Therefore, the prescription of inhaled CS and treatment control is a problem that is solved by a physician individually. In general, a patient should take anti-inflammatory drugs for a long time, until a sustained remission is achieved. In particular, the regression of morphological changes takes at least 6 months.

Today, there are different generations of immunostimulative drug of bacterial origin, the clinical effect of which shows itself in a reduction of frequency of acute respiratory viral infections (ARVI) and a significant reduction of the rate of exacerbations of the recurrent BOS, thus making it possible to make the basic therapy less intensive [5].

It is known that the leading role in the development of atopic reactions is played by the balance between Th-1 and Th-2 cells. Children with the recurrent BOS usually have more Th-2 cells, what results in the excessive antibody production [10,16]. It is clear that the factors stimulating the formation of Th-1-response mediators at the same time reduce the atopic tendency that is often present in the mechanism of the recurrent BOS. It was proved that due to increased IFN-γ production, the immune-modulating therapy with Ribomunyl elicits the stronger Th-1-immune response. In addition to the specific vaccine effect, the immune response is restructured, i.e. the Th-1 response becomes stronger.

Since a viral infection is one of the most common triggers, it is necessary to avoid contact with people having ARVI and use a full range of measures aimed to develop the resistance to infection. A positive effect can be expected from administration of immunomodulatory drugs.

Unfortunately, despite a broad range of preventive measures used today, the incidence of the recurrent BOS among children with respiratory disorders in the neonatal period still remains high. Such complicated and ambiguous situation necessitates the development of new schemes of rehabilitation and prevention measures.

5. Conclusions

(1) Administration of secondary prophylactic complex enables, to a large extent, to prevent progression of bronchial obstruction syndrome: to decrease the severity of episodes (from 3.2 ± 0.1 to 0.4 ± 0.1 points; $p < 0.01$) (mean difference 2.8 (95% CI: 2.39 to 3.21)), their duration (from 8.1 ± 0.2 to 2.4 ± 0.4 days; $p < 0.01$) (mean difference 5.7 (95% CI: 4.47 to 6.93)) and reduce the need in using drugs of symptomatic therapy (from 3.5 ± 0.1 to 0.3 ± 0.1 points; $p < 0.05$) (mean difference 3.2 (95% CI: 2.80 to 3.60)).

(2) Positive clinical dynamics of tested complex is confirmed by immunological indices: a reliable increase in IFN-γ level (from 2.5 to 5.6 pg/mL; $p < 0.01$) (mean difference 3 (95% CI: 1.05 to 5.15)), reduction of IL-4 (from 12.9 to 6.7 pg/mL; $p < 0.01$) (mean difference 6.2 (95% CI: 0.68 to 11.72)); and reliable increase in IgA, IgM, IgG ($p < 0.01$).

(3) Administration of secondary prophylactic complex has a practical meaning in prevention of

exacerbations of recurrent bronchial obstruction syndrome in children with respiratory disorders in neonatal period.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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