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EFFICACY OF PRIMARY REHABILITATION MEASURES ASSOCIATED WITH THE DEVELOPMENT OF RECURRENT BRONCHIAL OBSTRUCTION SYNDROME IN YOUNG CHILDREN WITH RESPIRATORY DISORDERS IN NEONATAL PERIOD

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ABSTRACT

The aim: To improve primary prophylactic measures associated with the development and progression of recurrent bronchial obstruction syndrome in young children, who had suffered respiratory disorders in neonatal period.

Materials and methods: Algorithm of primary prophylactic measures implied adequate balanced nutrition, sanation of living conditions, restriction of contact with infectious agents, sanation of chronic foci of infection, systematic training and general fitness. The investigation included 160 young children (1 day – 3 years of age). The basic group (n=80) involved children, who had experienced respiratory disorders in neonatal period and received appropriate respiratory therapy (artificial ventilation and / or spontaneous breathing with continuous positive airway pressure and supply of free oxygen), control group – children, who did not have respiratory disorders and respiratory therapy (n=80).

Results: Conducted investigation throughout 12-month monitoring enabled to record the development of recurrent bronchial obstruction syndrome in 43 children (respectively, 30 – 37.50% patients of the basic group versus 13 – 16.25% of control group; p 0.05), could not be obtained.

Conclusions: Comparative analysis within groups did not show a reliable difference in the development of recurrent bronchial obstruction syndrome in children (p>0.05), which can be explained by partial following of doctor's recommendations. There is the need in further study of the issue involving more patients for a longer period of monitoring.

KEY WORDS: respiratory disorders, young children, neonatal period, bronchial obstruction syndrome, primary rehabilitation measures, efficacy

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INTRODUCTION

In the recent years, respiratory pathology remains an urgent problem in clinical pediatrics, which has not only medical, but also social meaning [1-7]. Statistic data prove that among total pediatric morbidity, diseases of respiratory organs constitute half of all disorders [7]. Respiratory disorders are most commonly recorded in premature chil- dren (30 - 80% depending on gestational age); however, they also occur in full-term children (5 - 10%) [3].

Frequently, respiratory pathology starts from the first days of a child's life, which is largely because nowadays children, who in neonatal period required continuous respiratory maintenance (artificial ventilation, sponta- neous breathing with continuous positive airway pres- sure, oxygen therapy) for different reasons, survive [2, 4]. In the recent decades it has been proven that not only diseases of the respiratory system in neonatal period,

but continuous respiratory therapy itself (in particular, artificial ventilation) often result in the formation of recurrent and chronic bronchopulmonary pathology in the future [5]. Moreover, there are data that in early age of each third child, who is on artificial ventilation in neo- natal period, recurrent and chronic bronchopulmonary

diseases (bronchial asthma (BA), bronchopulmonary dysplasia (BPD), recurrent pneumonia, recurrent bron- chitis) occur, development of which is closely associated with the pathology of neonatal period [3, 6].

THE AIM

To improve primary prophylactic measures aimed at the development and progression of recurrent bronchial obstruction syndrome (BOS) in young children, who had suffered respiratory disorders in neonatal period.

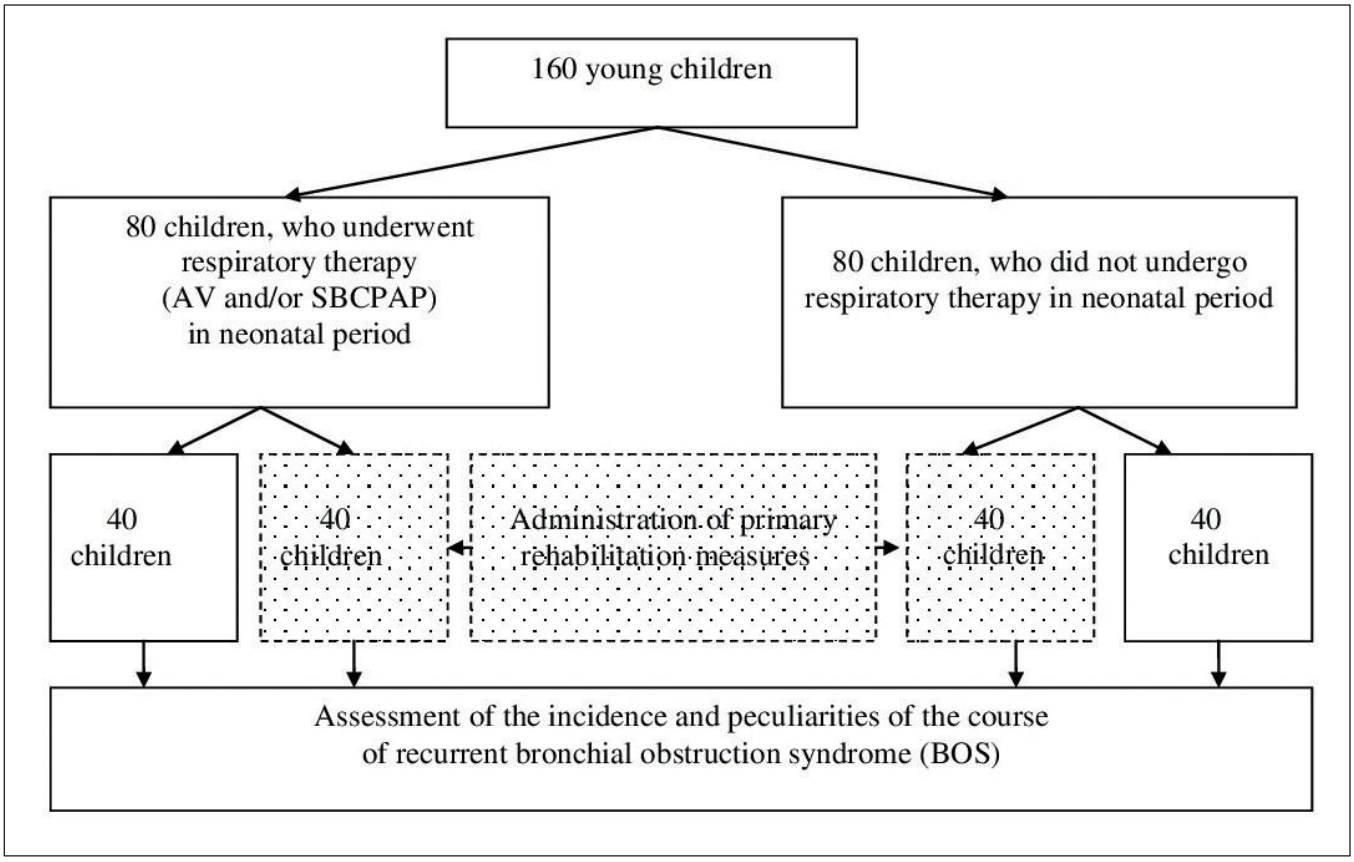


Fig. 1. A scheme of organization of the investigation

MATERIALS AND METHODS

General clinical (study of anamnesis, data of objective examination and dynamic monitoring); modern statistic analysis. In the presence of clinical indications, total blood count, radiological examination of the thoracic organs was administered; bronchoscopy, echocardi- ography, USS of the thymus, and Mantoux test were performed in some clinical cases, doubtful for diagnosis. If required, children were examined by an otolaryngol- ogist, neurologist and other specialists.

Overall, 160 young children (1 day – 3 years), who were treated in departments of reanimation and in- tensive therapy for neonates, pathology of newborns and premature babies, pediatric and allergological departments of Communal Nonprofit Enterprise "City Children's Clinical Hospital of Lviv" were involved in the research.

The basic group included children, who had expe- rienced respiratory disorders in neonatal period and received proper respiratory therapy – artificial lung ventilation (ALV) and/or spontaneous breathing with continuous positive airway pressure (CPAP) and supply of free oxygen (n=80), control – children, who did not have respiratory disorders and respiratory therapy (n=80).

Administration of primary rehabilitation measures was performed randomly in 40 patients of the basic group and 40 – in control group. In the rest of the patients (40 in each group), a suggested complex of measures was not used.

The scheme of organization of the investigation is presented in fig. 1.

STATISTICAL ANALYSES

Categorical (qualitative) signs were presented as a num- ber 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.

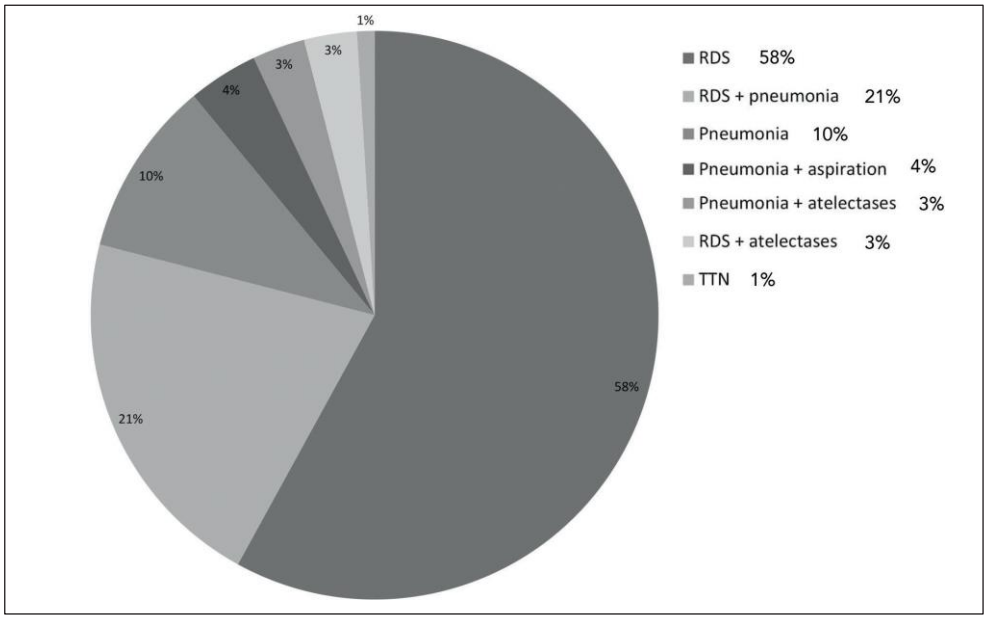
In order to check the significance of difference be- tween groups of categorical (qualitative) signs we have applied the tables of frequency (tables IV) and a Pearson x^2 criterion. A two-sided t-test for unrelated groups has been used to check the significant differences between groups of quantitative 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 $p < 0,05$.

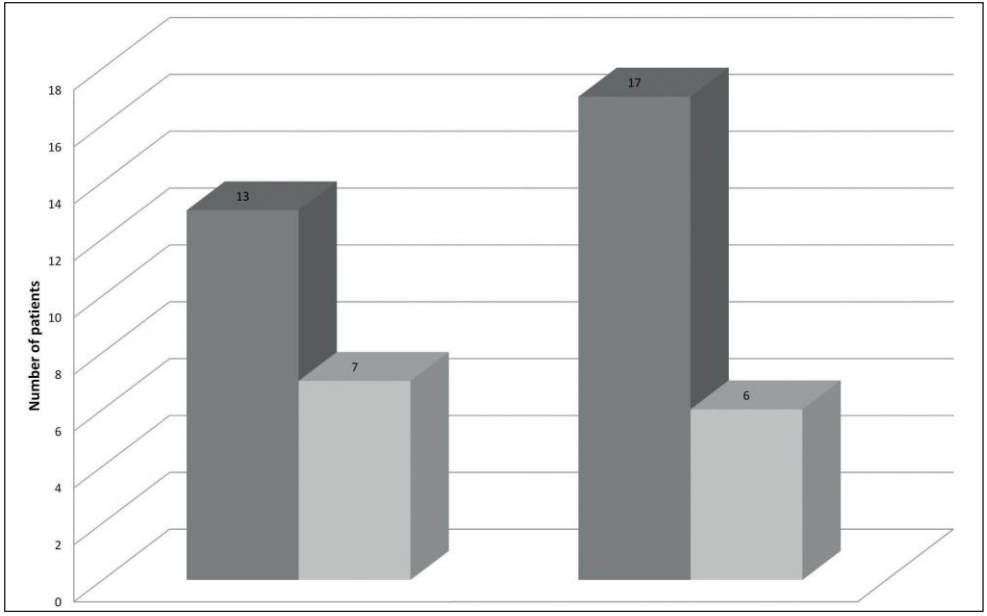
All of statistical calculations were performed using software RStudio v. 1.1.442 and R Commander v.2.4-4.

Fig. 2. Structure of the diseases, which were the cause for conduction of respiratory therapy

Fig. 3. Verification of nosological forms of recurrent bronchial obstruc- tion syndrome in children

Fig. 4. Development of recurrent bronchial obstruction syndrome in children with the administration of primary rehabilitation measures





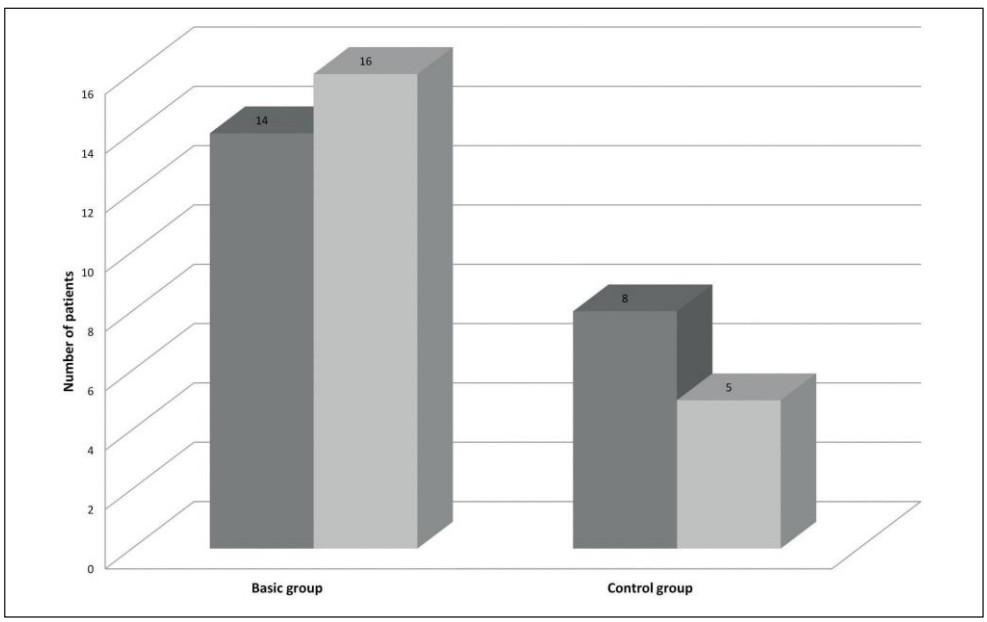


Table I. Distribution of children of the basic group by gender and age at the start of the investigation

Gender	Age at the time of investigation, weeks						Total	
	0 – 1		1 – 2		2 – 3			
	absolute	%	absolute	%	absolute	%	absolute	%
Girls	17	37	12	54.5	5	41.7	34	42.5
Boys	29	63	10	45.5	7	58.3	46	57.5
Total	46	100.0	22	100.0	12	100.0	80	100.0

Table II. Distribution of children in control group by gender and age at the start of the investigation

Gender	Age at the time of investigation, weeks						Total	
	0 – 1		1 – 2		2 – 3			
	absolute	%	absolute	%	absolute	%	absolute	%
Girls	11	28.9	15	55.6	7	46.7	32	40
Boys	27	71.1	12	44.4	8	53.3	48	60
Total	38	100.0	27	100.0	15	100.0	80	100.0

Table III. Variations of respiratory therapy applied in children of the basic group

Type of respiratory therapy	Number of patients	
	absolute	%
Artificial ventilation + spontaneous breathing with continuous positive airway pressure + supply of free oxygen	50	62.5
Spontaneous breathing with continuous positive airway pressure + supply of free oxygen	30	37.5
Total	80	100

Table IV. Distribution of patients in the basic group depending on the duration of conducted respiratory therapy

Duration of respiratory therapy (hours)	Number of patients	
	absolute	%
below 72	5	6.25
72 – 120	15	18.75
120 – 150	10	12.5
over 150	50	62.5

Table V. Distribution of children by age at the time of manifestation of bronchial obstruction syndrome

Group	Age at the time of investigation, weeks						No development of BOS		Total	
	< 12		12 – 24		24 – 36					
	absolute	%	absolute	%	absolute	%	absolute	%	absolute	%
Basic	23	28.75	17	21.25	5	6.25	35	43.75	80	100
Control	16	20	9	11.25	4	5	51	63.75	80	100

RESULTS

Distribution of children by gender and age at the start of the investigation is presented in tables (I and II).

Formed groups reliably did not differ by percentage of boys (46 [57.5%] in the basic group versus 48 [60%] in control group; p>0.05), mean body mass at birth (2025.2±79.3 g in basic group versus 2226.5±64.1 g in control group; p>0.05) and mean gestational age (respectively, 33.1±0.4 weeks versus 34.6±0.3 weeks; p>0.05).

Percentage of premature children was approximately the same in the groups (71 [88.8%] versus 69 [86.3%]; p>0.05) and patients born in multiple pregnancy (re- spectively, 13 [16.3%] versus 10 [12.5%]; p>0.05.

Endogenous surfactant was administered to 16.3% (13) of children in the basic group. This medicine was not administered to children of control group (p<0.01).

Antenatal steroid prophylaxis (p<0.05) was conduct- ed for 9 [11.3%] parturient women of the basic group and 4 [5%] women from control group.

Variations of respiratory therapy, applied in children of the basic, are presented in table III.

According to the data of world literature, the pri- mary cause for conduction of respiratory therapy in newborns is respiratory distress syndrome (RDS). Our analysis proved such statistic pattern. In particular, in the structure of nosologies, which were the reason for conduction of respiratory therapy, percentage of children with RDS constituted 58%, 21% – RDS + pneu- monia, 10% – pneumonia. Other causes accounted for 10%, among them being aspiration + pneumonia, pneumonia + atelectases, RDS + atelectasis, transient tachypnea of the newborn (TTN) (fig. 2).

Duration of conducted respiratory therapy among patients of the basic group is presented in table IV.

Our analysis enabled to detect single development of bronchial obstruction in children under 3 years of age in 9 (11.25%) patients of the basic group and 11 (13.75%) – in control group ($p>0.05$). Simultane- ously, two exacerbations were observed in 6 (7.5%) children of the basic group and 5 (6.25%) – control group ($p>0.05$). In these cases, BOS was referred to as acute obstructive bronchitis. Conduced investigations enabled to record the development of recurrent BOS (3 and more episodes of bronchial obstruction) in 30 (37.50%) patients of the basic group and 13 (16.25%) – control group ($p<0.05$). Thus, at least one episode of BOS occurred in 56.26% of patients in the basic group and 36.25% – in control group. Among them, recurrent episodes were recorded in 37.61% of the basic group and 22.5% – control group.

In 10 children of the basic group, who had undergone continuous respiratory therapy, the development of BPD was observed. Moreover, under 3 years of age, transformation of the disease to BA was observed in 3 (30%), to obstructive bronchitis – in 2 (20%) cases, 2 (20%) individuals suffered from frequent acute respiratory viral infections, 1 (10%) – recurrent laryn- gotracheitis, and convalescence occurred in 2 (20%) patients. Thus, the development of recurrent bronchial obstruction syndrome (bronchial asthma and obstruc- tive bronchitis) was observed in 50% young patients, who had been diagnosed with BPD in neonatal period.

Analyzing anamnestic data of children in both groups, special attention was paid to determination of age, at which first episodes of bronchial obstruction were manifested in a child. Distribution of children by age at the time of manifestation of BOS is presented in table V. Conducted analysis of atopia development in children enabled to reveal that the development of atopic der- matitis was the most common in children of the basic and control groups (29.3±4.4 % of children in the basic group and 27.8±3.7 % in control group; $p>0.05$). There were also recorded allergic rhinosinusitis (in patients of the basic group – 9.3±3.3 % versus 64±2.1 % in control group; $p>0.05$), severe urticaria (respectively, 4.1±1.2 % versus 5.6±1.8 % in control group; $p>0.05$), rarely – insect sting allergy and reactions to medicines ($p>0.05$). Based on investigated factors that influence the devel- opment of recurrent BOS in children with respiratory disorders in neonatal period, we have elaborated a complex of primary rehabilitation measures, aimed at prevention of the development of recurrent bronchial obstruction syndrome in such children. The suggested complex included the following measures.

1. Adequate balanced nutrition, which implied a choice of substantial food rich in calories with op- timal amount of proteins, fats, carbohydrates and vitamins. Maximally continuous maintenance of breastfeeding was encouraged. If a child developed symptoms of allergy and breastfeeding was impossi- ble, hypoallergenic formula and / or hypoallergenic diet (individual according to nutrition diary) was administered.
2. Sanation of living conditions that was implemented by avoiding contact with everyday allergens – daily humid cleaning and airing of the rooms, elimination of dust collectors (soft toys, cabinets with books, carpets), avoidance of a child's contact with epidermal allergens.
3. Restriction of contact with infectious agents – san- ation of chronic foci in a child and family members, early anti-epidemic measures and limited atten- dance of organized children's groups.
4. Systematic hardening of the body. At first, a child was administered series of hardening in the air, then – in water. The process of body hardening started only under conditions of complete wellbeing of a child in warm season following the principle of gradual increase in load.
5. General physical therapy, which included exercises on a fitball and massage of the chest. A specialist performed the massage twice a year with a course of 14 days. Aqueous procedures and swimming were performed with gradual decrease in water temperature (approximately by one degree every two weeks), the incidence and duration of which was determined by the age and mood of a child.

To assess the efficacy of primary prophylactic measures, patients were examined in a clinic three times: at the start and in 12 months ± 14 days from the moment of administration of primary prophylactic measures.

During a visit, complaints were recorded and routine systematic examination was performed. In the pres- ence of clinical indications, total blood count and X-ray examination of the thoracic organs was administered, and Mantoux test was performed in some clinical cases, doubtful for diagnosis. If required, children were ex- amined by an otolaryngologist, neurologist and other specialists.

Parents controlled the symptoms of the disease. Final assessment of efficacy of rehabilitation measures was performed during scheduled visits to a clinic based on anamnestic data and objective examination of a patient.

During each visit, an individual conversation with a child's parents about the importance of following doctor's recommendations was conducted.

Comparison of clinical efficacy of primary prophylac- tic complex was performed within the group (compared with patients who did not receive it) and with control group.

The conducted investigations throughout 12-month monitoring enabled to record the development of re-current BOS in 43 children (respectively, 30 – 37.50 % of patients in the basic group versus 13 – 16.25 % in control group; $p<0.05$). The analysis of the record of nosolog- ical forms in patients of the basic group, conducted within the group, showed that recurrent episodes of obstructive bronchitis were diagnosed in 13 (43.33 %), bronchial asthma – in 17 (56.67 %) children (fig. 3).

Thus, the development of recurrent bronchial ob- struction syndrome was much more common among the patients, who had experienced respiratory disorders in neonatal period and received respiratory therapy compared to the patients, who had not experienced such problems ($p < 0.05$), and was mostly caused by BA.

However, we did not manage to obtain the results, which could confirm the efficacy of suggested primary rehabilitation measures, since comparative analysis within groups did not show a reliable difference in the development of recurrent BOS ($p>0.05$), fig. 4.

DISCUSSION

Nowadays the respiratory pathology remains a top- ical issue in clinical paediatrics, which has not only medical but also social significance [2]. Statistics con- firm that respiratory diseases account for half of all diseases among the overall paediatric incidence rate [3]. Respiratory disorders are most often registered in

premature infants (30-80% depending on gestational age), but they also occur in full-term infants (5-10%) [7]. Moreover, in recent years, respiratory pathology differs in many respects from those that doctors dealt with even 10 years ago, which is largely due to changes in the pathomorphosis of diseases [3, 5]. Professional literature contains information about the connection between conducted respiratory therapy in neonatal period and further formation of recurrent and chronic bronchopulmonary pathology, which is often accom-panied by the development of bronchial obstruction syndrome (BOS) [3].

Respiratory pathology often occurs from the first days of a child's life, which is mostly because at present children who needed long-term respiratory support for various reasons in the neonatal period: ALV, CPAP, oxygen therapy more and more often survive. In recent years, it has been proven that not only diseases of the respiratory system of the newborns, but also long-term respiratory therapy (including ALV) often lead to the development of recurrent and chronic bronchopul- monary pathology in the future [2]. In particular, there is evidence that at an early age, every third child who underwent ALV in the neonatal period, develops re-current and chronic bronchopulmonary diseases (BA, BPD, recurrent pneumonia, recurrent bronchitis), the development of which is closely related to the neonatal pathology [6].

To date, a link between ALV in the neonatal period and the subsequent development of airway hyperreactivity, which is clinically manifested by recurrent BOS has been proven [3]. Early examinations are necessary for children with recurrent BOS to establish the causes of disease relapse. Collection of genealogical, medical, biological, social, hygienic and epidemiological anamnesis, com- plete analysis of clinical symptoms and assessment of dynamics of the disease are very important [8].

There are several debatable issues in the organization of adequate monitoring and treatment of BOS in young children with respiratory disorders in the neonatal peri- od. In particular, the specific contribution of factors that are decisive in its development (respiratory disorders, aggressiveness of respiratory therapy, immaturity of the child's lungs, genetic predisposition, adverse environ- mental effects) is discussed [4]. It is important to find possible ways to prevent the development of recurrent or chronic bronchopulmonary pathology.

A detailed and in-depth analysis of this set of issues will help to study the features of recurrent BOS in chil-dren who have suffered from respiratory disorders in the neonatal period and develop a preventive strategy for its development, which will prevent disease or im- prove prognosis, reduce chronic morbidity and disabil-

ity. The above situation has determined the relevance and purpose of our study.

Primary prevention (first level) involves working with children at risk of the development of the disease. It should begin long before the baby is born and include educational work with the pregnant woman and her family.

Secondary prevention (second level) is performed after the first signs of the disease appear to prevent the formation of recurrent and chronic pathology.

In the literature, there is tertiary prevention (third level), which involves working with sick children and is aimed at preventing the development of severe cases of recurrent BOS and their complications [2, 7].

One of the main directions of the preventive strategy of recurrent BOS is the selection of a balanced diet. The main task in the nutrition of infants is to ensure breastfeeding.

It is not always possible to organize primary pre- ventive measures before the birth of a child. Oppor- tunities expand significantly after the birth of a child. The answers to the question of whether breastfeeding can prevent the development of obstructions are full of contradictions. The lack of convincing data on the preventive effect of breastfeeding is because children for ethical reasons can not be artificially randomized to breastfeeding or artificial feeding. [1].

First of all, those foods that can provoke an exacerba- tion of recurrent BOS in the baby should be excluded from the diet of the nursing mother. It should be noted that the anamnestic data, mother's observations while keeping a food diary, elimination and food challenge tests can identify causative allergens in the vast major- ity of patients. On this basis, it is possible to choose an elimination diet for each patient individually. A properly elaborated diet not only limits the intake of allergens but also has a non-specific hyposensitizing effect and improves the condition of the digestive system, which, in turn, increases immunological tolerance to food allergens [5].

If for various reasons, breastfeeding is not possible, the selection of artificial feeding should be approached carefully. It is clear that formulas containing whey pro- tein or casein hydrolyzate are much less sensitizing to the child's body, and a high degree of protein hydrolysis leads to almost complete loss of the ability to cause an allergic reaction. At present, there are a large number of formulas on the market with partial or complete whey protein or casein hydrolyzate.

Developing an individual diet for children over 1 year is a difficult task. Such food is difficult to choose, even more, difficult to implement. Children become more independent, begin to attend organized children's

groups, which significantly complicates the organiza- tion of dietary nutrition. However, certain rules must be followed when choosing a diet for such children. First of all, before receiving the results of allergy tests, it is recommended to prescribe an empirically selected diet, which excludes causative (selected on the basis of a food diary) allergens. It is inadmissible to indulge in the wide exclusion of all known obligate allergens from the diet, it is necessary to identify the "culprit" allergen individually and at the same time provide its equivalent replacement to maintain the completeness of the child's diet. The organization of nutrition of such patients involves limiting the consumption of foods with high sensitizing activity [3].

It is possible to transfer the child to a usual food without essential restrictions in 10-12 months after the total disappearance of manifestations of recurrent BOS. However, foods that should be excluded should be introduced gradually, alternately, slowly [1].

Along with a balanced diet in the treatment of chil- dren with recurrent BOS, it is important to properly or- ganize the life of the child and care for him / her. First of all, exposure to inhalation and contact allergens should be eliminated or limited. The room where the child lives should be frequently ventilated and wet cleaned twice a day. The number of dust collectors (carpets, upholstered furniture) in the apartment should be sharply limited. Pets are not allowed in the apartment. It is necessary to limit the child's contact with irritants (use of natural wool clothing, irritating hygiene products). The stimulus may be high or low temperature [4].

Limiting contact with infectious factors is the elimi- nation of chronic foci of infection, timely anti-epidemic measures, limited attendance of organized children's groups and places with large crowds (public transport, market, playground) [9].

Coldwater treatment is recommended in the settings of the overall health of the baby in the warm season. First, the child is prescribed sessions of cold air treat- ment, and then – cold water with adherence to the principle of gradual increase in load [2].

Strengthening exercises include exercise ball and chest massage. Massage is performed by a specialist twice a year [4].

Unfortunately, despite the whole range of preventive measures used today, the rate of recurrent BOS remains high. It is possible that soon some preventive principles will be improved or changed. It comes as a natural result because scientists continue their active search. Probably our immediate prospect and greatest hope are to conduct immunomodulation with Th1 immuno- adjuvants, DNA vaccines and cytokine-related antigens (interleukin-12 or interferon-gamma) [10].

The leading role in the development of atopic reactions is played by the balance between Th-1 and Th-2 cells. It is proven that children with the recurrent BOS usually have more Th-2 cells, what results in the excessive antibody production [7]. 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 [6]. Thus, prevention in young children who had respira- tory disorders in the neonatal period is one of the most basic measures of paediatrics.

Currently it has been proven that the cause of insuffi- cient efficacy of any therapeutic or preventive measures is, primarily, partial following of all recommendations. Not always, patients and their close relatives properly accept information from health care providers. Thus, we paid special attention to individual training of par- ents, which was conducted during each visit to a clinic. We tried to form correct notion about the essence of bronchial obstruction syndrome, risk factors of its oc- currence and conditions of progressing in each child. Such work can promote the formation of parents'active position in further treatment of their child.

CONCLUSIONS

1. The development of recurrent bronchial obstruction syndrome occurred much more frequently among the patients, who had experienced respiratory dis- orders in neonatal period and received respiratory therapy compared to the patients, who had not suffered such problems ($p < 0.05$), and was basically caused by bronchial asthma (56.67 %).
2. Theefficacyofsuggested primaryrehabilitationmeasures could not be proven (comparative analysis within groups did not show a reliable difference in the development of recurrent bronchial obstruction syndrome; $p>0.05$).
3. The likely cause of insufficient efficacy of any ther- apeutic or preventive measures is partial following of doctor's recommendations, thus, it is necessary to form an active position of parents in the process of a child's treatment.
4. The efficacy of primary rehabilitation measures concerning the development of recurrent bron- chial obstruction syndrome in young children with respiratory disorders in neonatal period requires further study involving many patients throughout a continuous monitoring period.

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Ethical Committee or Institutional Animal Care and Use Committee Approval: Danylo Halytsky Lviv National Medical University 20/12/2010 № 10; Nonprofit Communal Enterprise "City Children's Clinical Hospital of Lviv"; 16.Nov.2018 № 6. We are grateful to the children and their parents for participating in the study.

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Conflict of interest:
The Authors declare no conflict of interest.

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