I.V. Davydova[1], T.V. Tourte[1], L.S. Namazova-Baranova[1], [2, 3], A.Yu. Simonova[1, 2], L.R. Tarasova[1], V.V. Altunin[1]

[1] Scientific Center of Children's Health, RAMS, Moscow
[2] I.M. Sechenov First Moscow State Medical University
[3] N.I. Pirogov Russian National Research Medical University, Moscow

Experience in the Use of Acetylcysteine in the Treatment of Respiratory Infections in Young Children

Treatment of respiratory infections in early childhood requires extensive use of direct action mucolytic drugs, which include derivatives of acetylcysteine. However, data on efficacy and safety of acetylcysteine in the treatment of both acute and chronic bronchopulmonary diseases in children during the first two years of life are few and contradictory. The article contains the authers' data on the use of granular acetylcysteine for the syrup preparation in the treatment of young children.
Key words: *acetylcysteine, mucociliary clearance, acute respiratory viral infection, bronchial obstruction, bronchopulmonary dysplasia, respiratory function.*

Contact information:

Irina Vladimirovna Davydova, MD, PhD, leading research scientist of the department of new technologies of child growth and development peculiarities studying and outpatient health monitoring at the research institute of prophylactic pediatrics and medical rehabilitation at the Scientific Center of Children's Health, RAMS.

Address: Moscow, Lomonosovskiy Av. 2/62, 119991,

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Respiratory infection is the most widespread pathology in infancy. Specific weight of respiratory diseases in the primary morbidity structure of children is ca. 60% [1]. Acute and chronic bronchopulmonary diseases take one of the top positions among children of all age groups. Anatomico-physiological and functional peculiarities of the respiratory tract of children younger than 3 years of age make this problem especially topical.

The doctor’s main task when treating bronchopulmonary diseases is the respiratory tract clearance of the viscous secretion produced by the ciliated epithelium goblet cells. A range of physiological mechanisms of the human body including the active mucociliary clearance (MCC) and productive cough are concentrated on the respiratory tract clearance. In this situation cough is considered as the reflex organism defense reaction conductive to the removal of the tracheo-bronchial secretion and foreign bodies from the airways at the respiratory tract reflexogenic zones’ irritation. Medicamental suppression of the cough reflex in this case is contra-indicated. Often the secretion character changes from mucous to puromucous and purulent in case of the phlegm congestion in the bronchial apparatus and bacterial inflammation attachment. In the viscous medium the bronchial epithelium cilia work is hampered, phlegm evacuation is disturbed, cough becomes underproductive. Normally, mucus movement speed in the bronchi is 4-10 mm/min on the average, and the more viscous the mucus is the less the speed is, mucociliary clearance reduces by 10-55%. Viscous bronchial secretion may completely block the bronchial lumen which will lead to the disturbance of the ventilation-perfusion interrelations up to the development of the atelectases. Phlegm congestion inevitably leads to the bronchopulmonary inflammation development with the infection overlay and secretory immunoglobulin (Ig) A reduction [2-5].

Expectorants’ action ensures the free sputum discharge from the airways. Mucolytic therapy is called for improving the sputum discharge by improving its flow characteristics; it is concentrated, first of all, on the bronchial secretion viscosity, elasticity and adhesiveness without the considerable volume gain. Mucokinetic effect is put into effect by increasing the mucociliary clearance at the expense of the effective bronchial ciliated epithelium cilia work. Mucoregulatory effect is achieved by mucus hypersecretion reduction at the expense of the influence on the respiratory tract mucous gland [2].

At the moment three drug groups different in the mechanism of influence on the physical and chemical phlegm properties are labeled as **mucolytics**:

- historically, **proteolytic enzymes** (trypsin, α-chymotrypsin, streptokinase, ribonuclease etc.) are the first drugs widely used in medical practice as mucolytics. They reduce viscosity and elasticity of the phlegm at the expense of the destruction of the glycoproteids' peptide bonds of its macromolecules. At the moment they are seldom used because of the serious side effects in form of allergic reactions and hemoptysis risk increase up to the pulmonary hemorrhage development. The only exception is the recombinant α-DNAse (dornase alfa) which is lately prescribed to those suffering from mucoviscidosis;

- **cysteine** derivative amino acids (acetylcysteine, carbocisteine) have been used in clinical medicine since 1960s; have a direct *mucolytic action* which brings on the phlegm viscosity reduction at the expense of the depolymerization at the bronchial secretion proteoglycans' disulfide bond rupture (pic. 1). Acetylcysteine direct action ensures an immediate and pronounced effect [6]. Acetylcysteine is able to dilute not only mucous, but also puromucous and purulent phlegm. In the setting of the phlegm viscosity and adhesiveness reduction the MCC increase takes place, which means that the drugs of this group additionally take a pronounced mucokinetic action. Besides the main mucolytic effect the acetylcysteine has the *antioxidant* and *antitoxic* activity connected with the neutralization of the free radicals generated under the toxic influence on the product cell of the inflammation and the aggressive environmental factors. The drug favors the synthesis of glutathione – the main oxidative body system which increases the cell protection from the free radical oxidation and neutralizes the toxic influence of the inflammation products [7-9]. The same mechanism is enabled in the protective effect in relation to the environmental attacks: city smog, toxic and tobacco smoke etc. [10, 11]. Some foreign researchers cite data about

the *immunomodulatory* and *antimutagenic* properties of the acetylcysteine, and also its *anticancer activity* [12, 13]. The drug's important property is also its *phagocytosis stimulation ability* [13, 14]. Influencing various pathogenesis stages, all given acetylcysteine properties ensure its high performance in relation to the bronchopulmonary system inflammatory process. High acetylcysteine performance is connected with the unique combination of effects on the pathologic process in the setting of the bronchial mucous tunic inflammation;

- **vizicin** derivatives (ambroxol) have a *multiple-factor action*. They activate ciliary beats, thus improving the MCC, reduce bronchial secretion viscosity at the expense of its mucopolysaccharides' chemism change. Moreover, they increase the endogenous surfactant production and inhibit its disintegration [2-5].

Mucolytic drugs are widely used in pediatrics to treat the respiratory tract inflammatory diseases. Indications for the mucolytic therapy prescription may be the inflammatory diseases of the upper airways and the accessory sinuses of nose (rhinites, sinusites, laryngotracheites). Mucolytic drugs also take an important place along with antibiotics and bronchial spasmolytics in the complex therapy of acute and chronic inflammatory diseases of the lower airways. According to the indications peroral, inhalation and endobronchial mucolytic therapy may take place for those suffering from acute and chronic bronchites, bronchiolites, pneumoniae, bronchopulmonary dysplasia, bronchial asthma, congenital and hereditary diseases of the bronchopulmonary system, including mucoviscidosis. As a rule, a mucolytic drug is prescribed as a component of the respiratory tract inflammatory disease complex therapy and is well compatible with any other drugs, except for the ones suppressing the cough reflex. In case of a concurrent prescription of a peroral antibiotic it is advisable to observe a 2-hour interval between its taking and the mucolytic taking [5].

A separate group of drugs often prescribed for the acute respiratory diseases is the **expectorants**, mainly herbal (marsh-mallow, licorice, thermopsis, plantain etc.). Drugs of this group may be used for acute respiratory viral infections (ARVI) and rhinosinusites, diluting the inflammatory secretion of the upper airways and accessory sinuses of nose, thus facilitating its evacuation [5].

When prescribing mucolytic therapy for the small children the rapid progress of severe broncho-obstructive syndrome at the expense of the airway narrowness, propensity for mucus hyperproduction and also abundant vascularization of the bronchial apparatus mucous tunic, which in case of inflammation leads to the rapid edema augmentation. Moreover, the cough reflex may be absent or low-grade in the first life months among children born prematurely and with neurological disorders, which hinders the bronchial drainage function and leads to the phlegm congestion. Thus, mucolytic therapy among small patients has its peculiarities and is conducted with a glance to the cough reflex degree of manifestation, possibility of postural drainage, and also strict observance of the drug-taking time. It is not recommended for children to take mucolytics before day or night sleep to prevent the phlegm congestion in the respiratory tract. Mucolytic effect is increased by the additional fluid intake [3, 5].

In the clinical practice among children of different age groups including newborn children from 10 days of age an acetylcysteine drug is widely used – ACC. One of the drug's unquestionable advantages is the availability of convenient to use dosage forms with different tastes, which children like. Granules for the syrup preparation (orange) are intended for the children of the youngest age group (100-150 mg per day in 2-3 takings for children younger than 2 years of age; 200-300 mg per day in 2-3 takings for children younger than 5 years of age). Effervescent tablets (100mg) with blackberry taste and granules for the preparation of solution with orange taste (100mg) are intended for the children older than 2 years of age.

The course of treatment of acute diseases is 5-7 days. Long-term administration of acetylcysteine is indicated in case of the chronic bronchopulmonary pathology with the viscous phlegm obtrusion of the bronchial lumen, mainly of the puromucous character. Effectiveness and safety of the long-term (3-6 months) courses of mucolytic therapy with acetylcysteine doses considerably bigger than the average therapeutic ones is proved by the results of experimental and clinical studies of the adult patients with chronic obstructive pulmonary disease and chronic bronchites [10, 15-17]. Data on the consequences of a long-term drug administration in the pediatric practice are almost non-existent at the moment.

Acetylcysteine safety and high tolerance of the children older than 2 years of age is proved by many years of the drug administration for treating acute and chronic bronchopulmonary system diseases and confirmed by 34 international clinical studies of 2064 children younger than 17 years of age [18]. In our country the acetylcysteine administration safety acknowledgement was taken by a comparative research of administration of mucolytics of various pharmacological groups to 259 children younger than 15 years of age [4].

Information on the drug's administration to the children of a younger age is little and contradictory. According to the latest data, the reduction of such symptom as cough by 63% on the 6^{th}-7^{th} day of the acetylcysteine treatment was noted among elder children without chronic bronchopulmonary pathology suffering from acute infections of upper and lower airways. Conclusions for the age group of children younger than 2 years of age are not given in the review; it is only noted that in some cases the paradoxical progress of bronchorrhea, but those episodes are not described in the publications. And there are not enough data on the drug's dosage for the newborn children with it. Interestingly, explanations of this phenomenon were not only about mucus hyperproduction in the setting of the adequate outflow impossibility, restrictedly small bronchial diameter, but also about the **dosage effect**. According to the specialists' estimates, at present the dose

recommended to infants is 3 times bigger than the dose for the elder children (45 vs. 16 mg/kg per day) [18]. Dosage effect study for acetylcysteine in different age groups has not yet been conducted.

Data on the safety and effectiveness of acetylcysteine administration to the children younger than 2 years of age suffering from chronic bronchopulmonary pathology were not found in the available literature. At the same time, every pediatrician has had to prescribe this drug more than once to the small children. According to the French pediatricians' data, acetylcysteine derivatives are among the most prescribed drugs for the children younger than 2 years of age [19]; in Spain mucolytics are the 2nd most widespread pharmacological group of drugs prescribed to the children younger than 2 years of age [20]. The situation is present where the international clinical practice is not corroborated by reliable results of the drug's effectiveness and safety based on randomized acetylcysteine clinical trials in the given age subgroup. Of substantial interest is the information on this drug's administration results to both children with ARVI, acute bronchites, bronchiolites and pneumoniae and children with chronic bronchopulmonary pathology. The necessity of the reevaluation of benefits and risks correlation of the administration of mucolytic drugs (acetylcysteine derivatives) by the pharmacological control institutions of the countries where they are registered, especially for the children younger than 2 years of age, is emphasized in the aforementioned review [18]. In the Russian Federation the acetylcysteine administration for the children younger than 2 years of age is only allowed on doctor's orders with the dose of not more than 150 mg/day [21].

Information on the tolerance of the infants to the recommended by the instruction drug doses is contradictory. The limited amount of data on this drug's safety, tolerance and effectiveness among small children was the reason for this clinical functional study project.

The aim of this study was the examination of effectiveness and safety of administration of a mucolytic drug in the form of granules to prepare a 100mg/5ml

syrup among 30 children of the first or second year of life. *N-acetyl-L-cysteine* is a direct action mucolytic drug and is widely used in the therapy of respiratory diseases of children. High acetylcysteine performance is connected with the unique combination of effects on the pathologic process in the setting of the bronchial mucous tunic inflammation.

Patients and methods

The study group included 30 children of 4-22 months of age whose parents gave a written informed consent to the participation. The children conformed to the inclusion criteria and did not have allergic reactions to acetylcysteine in their anamneses. Indication of atopic dermatitis manifestations in the anamnesis was not an exclusion criterion (4 such patients were involved in the study).

The children with acute and recurrent respiratory pathology made up the 1st group (n=15), out of whom 7 children were of the first year of life, and 8 were of 1-2 years of age; moreover, bronchitis relapses were registered only on the second year of life. The 2nd group was made up of children with bronchopulmonary dysplasia (BPD) in the exacerbation period (n=15). Distribution of children by age and clinical diagnosis is given in tb. 1.

Boys were prevalent among the patients with both acute and recurrent respiratory infections; and with bronchopulmonary dysplasia (20 boys out of 30 children involved in the study), which correlates with the literature data on the prevalence of males among patients with respiratory pathology in infancy [22].

The children with acute and recurrent laryngotracheites and bronchites were on the outpatient observation, the children with bronchopulmonary dysplasia in the exacerbation period were on the day hospital observation and in the convalescent stage – on the outpatient observation.

Among those suffering from BPD (7 children of the first year of life, 8 children of 1-2 years of age) 10 children had a classical disease form, and 5 had a "new" one. The obligatory condition for the child's inclusion in the study was the presence of the active cough reflex. The necessity of the postural drainage in the setting of the acetylcysteine therapy and the drug's administration not later than three hours before sleep were specified. Administration of any other mucolytic remedies or drugs suppressing the cough reflex was ruled out.

For the whole study period all patients continued their baseline and symptomatic therapy (including the antibiotic therapy) which they were undergoing before the involvement in the study. The antibiotic therapy was conducted on all children with BPD exacerbation and to 11 children with acute respiratory pathology, and the interval between the antibiotic and mucolytic takings was not less than two hours. Broncholytic inhalers (Berodual, Ventolin) were taken by all children with bronchopulmonary dysplasia and 6 children with acute or recurrent bronchites with physical signs of bronchial obstruction. ACC 100 (granules for the syrup preparation) was prescribed to children of the second year of life in the dose of 2.5ml (50mg) TID; to children of the first year of life the drug dosage was adjusted individually. The children of the first half-year of life were prescribed the drug in the dose of 1.25ml BID or TID (2.5-3.75 ml/day), of the second half-year – 2.5ml BID (5 ml/day).

Besides the clinical examination and application of physical methods of examination the functional diagnostics techniques play a significant role in the bronchial drainage function evaluation. A unique opportunity of the external respiration function evaluation of the small children appeared from the moment of introduction of a new method of testing the indices of air parcel and flow in the setting of acute and chronic bronchopulmonary system diseases [23].

Quiet breathing flowmetry is conducted during the children's natural sleep. At the same time pulse oximetry is conducted with the help of a portable pulse oximeter. While naturally sleeping, a child breathes through the respiratory mask

connected to the pneumotachograph. On the monitor's screen the quantities of air flow and parcel are shown, as well as their curves. After each breath the automatic evaluation of flowmetric parameters and their display on the diagram take place. The scores of these parameters allow an objective assessment of the airways permeability and a detection of the tracheal and bronchial lumen obtrusion with phlegm [23]. As an example we give a "flow-parcel" curve of a child with bronchopulmonary dysplasia without exacerbation, on which a little blockade of peripheral bronchi connected with the fundamental illness (pic. 2) is registered, and a "flow-parcel" curve of a child with bronchopulmonary dysplasia in the exacerbation period in the setting of the ARVI, on which the signs of expiratory upper airway obstruction, besides a little blockade of peripheral bronchi, are registered (pic. 3). Thus, the introduction of the high-technology methods of respiratory function (RF) testing in the wide medical practice may favor the objective assessment of the broncho-obstructive syndrome (BOS) and the possibility of its correction with the help of the mucolytic therapy as well.

All children involved in the study were examined by a neonatologist, a pediatrician and a pulmonologist 3-4 times during the study: in the beginning of the acute or the chronic respiratory infection exacerbation at the drug's prescription; 3-4 days after the disease incursion; on the 7^{th} day (at the exacerbation period end) or on the 10^{th}-14^{th} day of therapy on the occasion of BPD's exacerbation. If necessary, children with bronchopulmonary dysplasia were observed for more than 14 days. The results of the follow-up clinical observation were fixed by a researcher in the "Patient's observation diary": presence of cough, intensity, duration and ability to expectorate phlegm.

Quiet breathing functional analysis was conducted on 10 children once on the 3^{rd}-5^{th} day of therapy 3-4 hours after the morning acetylcysteine dose taking. Point system assessment of the cough character change was done to all children on each visit to a doctor. Each sign was given 0-4 points according to the intensity;

the result was registered in the diary on each examination of a child and talk with the parents.

Study results

The received data analysis showed that all children in compliance with the study inclusion criteria had cough, the intensity of which in the disease incursion fluctuated from frequent (once per hour – 3 points) to very frequent (every 15-20 minutes – 4 points); by the 5^{th}-10^{th} day of treatment the cough completely ceased (0 points) among all those suffering from acute and recurrent respiratory pathology or appeared rarely (4-6 times per day) among children with chronic pathology.

Cough intensity reduction and expectoration ability increase were noted on the 2sn-5^{th} day of acetylcysteine administration with almost all patients in the 1^{st} group (93.5%), and the phlegm expectoration relief increased as the treatment with the help of the drug continued; phlegm was well diluted and easily expectorated by the majority by the 5^{th} day of treatment. The same dynamics was noted in the group of the "chronic patients'" children with the only difference: the cough intensity did not reduce to extremely insignificant (1 point) or complete absence (o points) but remained by the 5^{th}-7^{th} day of therapy on the level of insignificant and moderate manifestations (2-3) with all patients.

The children with chronic pathology had significantly longer cough duration than the patients with acute and recurrent bronchites in the setting of the mucolytic treatment. By the 10^{th} day cough remained with all patients with BPD, with 5 patients it was noted after the 14^{th} day of the disease exacerbation, which required the mucolytic therapy continuation.

Paradoxical bronchorrhea increase was noted among 3 children of the first half-year of life with acute bronchitis (4-6 months of age) at the single drug dose prescription of 2.5ml BID, and that required the double reduction of the single dose. Children of the second half-year of life received the studied drug in the manufacturer recommended dose (2.5ml) BID.

Acetylcysteine administration duration in this age group was also defined by the disease character. Among the children with acute bronchites the mucolytic effect was noted on the 2^{nd}-5^{th} day of treatment, the cough ceased on the 5^{th}-10^{th} day of the disease incursion. Among the children with bronchopulmonary dysplasia the phlegm discharge relief was also reached in the first days of the drug's prescription, but the cough duration was not less than 7-10 days, in some cases – more than 14 days.

On the 3^{rd}-5^{th} day of therapy a single examination of spirometric parameters was conducted on 10 children of different age by the RF (quiet breathing analysis) method 3-4 hours after the morning drug's dose taking to detect the so called swamping syndrome. 3 children out of 10 were of 4-6 months of age and received mucolytic therapy for acute obstructive bronchitis, while 7 (3 children of 6-8 months of age and 4 children of the second year of life) – for the BPD exacerbation.

The most informative RF indicators proved to be the following: relative respiratory volume, peak expiratory rate time (in %), peak expiratory rate volume (in %). The relative respiratory volume appeared to be reduced only with 2 children involved in the study (1 child with acute bronchitis and 1 child with bronchopulmonary dysplasia).

The reduction of time between the exhalation beginning and the peak flow point in % of the total expiratory time (9 out of 10) was noted with almost all examined patients, which is connected with the presence of broncho-obstructive syndrome caused not only by phlegm presence in the peripheral bronchial lumen, but also by bronchospasm together with the bronchial apparatus mucous tunic inflammatory edema. Functional indicators of volume insignificantly reduced only with 2 out of 10 patients (18.2% and 19%), which indicates an effective enough airflow even in the setting of the broncho-obstructive syndrome and the absence of bronchial lumen obtrusion by a large amount of phlegm. Thus, the received functional data allow us to make an assumption about the lack of swamping syndrome among 10

children of the studied group in the setting of the acetylcysteine 100 (granules for the syrup preparation) administration.

CONCLUSION

Administration safety and high acetylcysteine 100 (granules for the syrup preparation) tolerance proved by the previous studies of the children of the elder age groups are confirmed as a result of this study for children younger than 2 years of age. Increase in allergic reactions at the drug's prescription to the children with food allergy clinical manifestations (3 children) was not noted. Only in a case of one child of 8 months of age with acute bronchitis with atopic dermatitis in the disease-free survival the allergic reaction in the form of punctate rash on the body and limbs was noted at the acetylcysteine prescription. As far as in that case the mucolytic was used as a part of a combination therapy involving an antibiotic (Sumamed syrup – 10 mg/kg per day) and neurological drugs, it is not deemed possible to unequivocally assess this reaction.

Bronchospasm appearance in the setting of the acetylcysteine therapy was not noted among children with acute and recurrent respiratory pathology. In the group of patients with bronchopulmonary dysplasia under the presence of the broncho-obstructive syndrome clinical signs mucolytic therapy should be conducted together with a broncholytic, preferably, inhalation one, to improve the bronchial drainage function.

Functional studies conducted on 10 patients suffering from acute, recurrent and chronic (in the setting of BPD) bronchites did not prove the so called swamping syndrome among children 3-4 hours after the single acetylcysteine (granules for the syrup preparation) dose taking. To prove the received results it is necessary to continue studying the drug's influence on the respiratory function of the infant patients with various variants of the respiratory pathology.

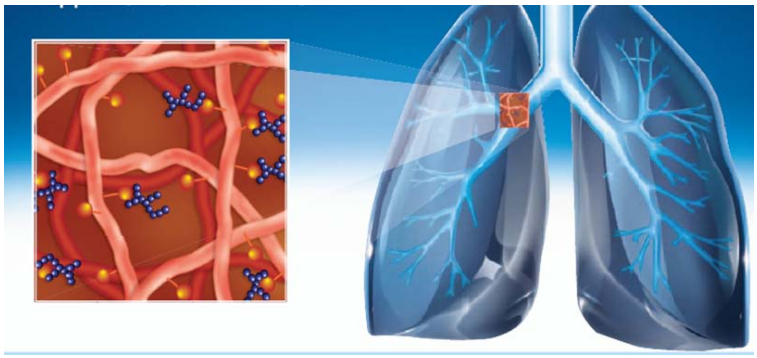
The effectiveness of the acetylcysteine administration to dilute phlegm and improve the bronchial drainage function of the children younger than 2 years of age in the complex therapy of acute, recurrent and chronic (as a BPD manifestation) bronchites is proved by such clinical data as the cough intensity and duration reduction, increase in the expectoration ability. The drug's prescription to the children of this age group should be done in case they have a good cough reflex and not later than 3 hours before sleep, due to the age-related anatomico-physiological peculiarities of the respiratory tract.

Paradoxical bronchorrhea noted among 3 children younger than 6 months of age at the prescription of 2.5ml BID of the acetylcysteine syrup may be connected not only with the mucus hyperproduction and its inadequate outflow, restrictedly small bronchial diameter, but also with the dosage effect. According to the specialists' estimates, at present the dose recommended to infants is 2-3 times bigger than the dose for children older than 1 year of age (30-45 vs. 15 mg/kg per day) [18]. Dosage effect study for acetylcysteine in different age groups has not yet been conducted. A small number of observations does not allow us to make final conclusions, but a correction of the dose, proposed in the annotation, for the age group of 0-2 years of age may be recommended; though for the children of the second year of life the recommended dose (100-150 mg/day) remains the same, while for the children of the first year of life, especially the children of the first half-year of life and prematurely born, the dose adjustment should be conducted individually at 15 mg/kg, considering the child's body weight. Thus, for example, a child with body weight of 5kg should take not more than 1.25ml of syrup TID (75 mg/day).

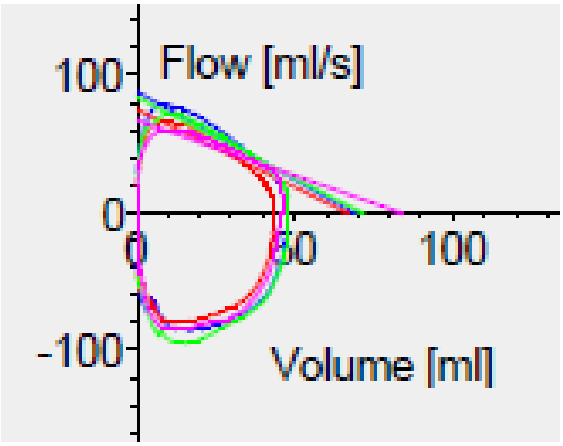
Thus, effectiveness and safety of the acetylcysteine derivatives' administration in pediatric practice to treat those suffering from acute and chronic bronchopulmonary pathology is confirmed by many years of clinical practice and numerous studies conducted all over the world and proved by the clinical functional results of the study conducted. Unique properties of acetylcysteine that combines mucolytic, mucokinetic, antioxidant, antitoxic and anti-inflammatory

effects make it irreplaceable for the multimodality therapy of the respiratory tract inflammatory diseases. The possibility of the RF objective control during the infants' natural sleep, which appeared in the modern stage, allows us to confirm the bronchial drainage function effectiveness in this age group.

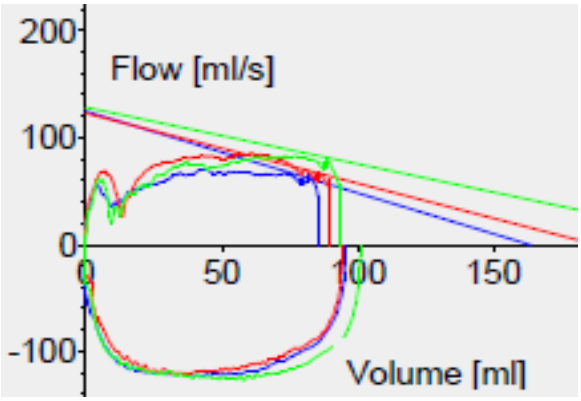
A possibility of administration of such modern drugs as ACC in granules to prepare syrup in the therapy of the bronchopulmonary diseases of the children of the first two years of life favors the improvement of the small patients' condition and faster recovery.



Pic. 1. Acetylcysteine action mechanism



Pic. 2. "Flow-parcel" curve of a child with bronchopulmonary dysplasia without exacerbation



Pic. 3. “Flow-parcel” curve of a child with bronchopulmonary dysplasia exacerbation and signs of expiratory upper airway obstruction

Table 1. Description of the patients by groups

Diagnosis / Age	Acute tracheitis	Protracted laryngotracheitis	Acute bronchitis	Recurrent bronchitis	Bronchopulmonary dysplasia	Total
4-12 months	3	-	4	-	7	14
1-2 years	-	1	3	4	8	16
Total	3	1	7	4	15	30