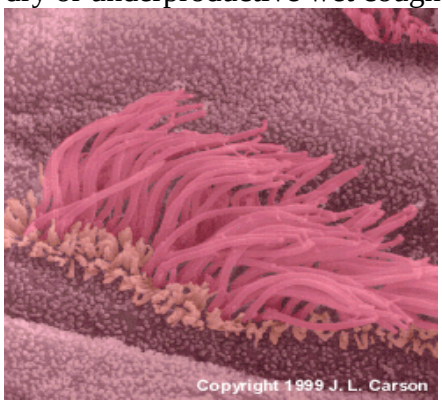
I.V. Davydova, T.V. Turti, V.V. Altunin
Scientific Center of Children's Health, Moscow, Russian Federation

Mucolytic therapy in infants

Author affiliation:
Irina Vladimirovna Davydova, PhD, head of the department of studies of new technologies in children's development peculiarities and outpatient health level monitoring of the research institute of preventive pediatrics and medical rehabilitation at the Scientific Center of Children's Health
Address: 2/1, Lomonosovskiy Av., Moscow, 119991, **tel.:** +7 (499) 134-01-67, **e-mail:** davydova@nczd.ru
Article received: 02.04.2013, accepted for publication: 30.09.2013.

When prescribing mucolytic therapy for bronchopulmonary diseases to infants, it is necessary to consider not only peculiarities of a small child's respiratory tract, but also action of mucolytic drugs. The authors exemplify their data on efficacy and safety of the use of mucolytics in children under 2 years of age with acetylcysteine.
Keywords: *frequently ill children, acute respiratory infections, mucociliary clearance, bronchoobstructive syndrome, acute bronchitis, recurrent bronchitis, bronchopulmonary dysplasia, acetylcysteine, external respiration function.*

One of the most frequent and regular symptoms of acute respiratory infections in childhood is cough. It is well-known that a child normally expectorates several times a day. In that case cough is a physiological mechanism aimed at clearing respiratory tract of clusters of mucus and foreign microparticles penetrating body at breathing (harmful air impurities, dust, tobacco smoke). Cough character alteration (it becomes longer, more frequent and intense) and failure of ability to expectorate sputum are observed in case an infectious-inflammatory process develops in the bronchopulmonary system. Usually, the onset of acute respiratory infections is characterized by dry or underproductive wet cough with scant sputum.



Pic. 1. Bronchial epithelial cilia (electron microscopy).

In the setting of a mucociliary clearance disorder at inflammation of the respiratory tract's mucous tunic, cough acts as a defense reaction aimed at improvement of the bronchial drainage function. The doctor's main goal in this situation is to create conditions for effective expectoration. Inefficacy of cough may result from high sputum viscosity, insufficiently pronounced cough reflex, insufficiently profound respiration and other causes [1, 2]. Drug suppression of cough reflex is contraindicated in such situations. Character of secretion often changes from mucous to mucopurulent and purulent in case of bacterial inflammation and sputum stagnation in the bronchial tree. Performance of the bronchial epithelial cilia is hindered, sputum evacuation is disturbed and cough becomes inefficient in the viscous environment. Normally, sputum advance rate in bronchi is 4-10 mm/min at the average; the rate decreases

significantly and mucociliary clearance reduces by 10-55% with sputum viscosity increase (pic. 1). Viscous bronchial secretion can completely block the bronchial lumen; this results in the disorder of ventilation-perfusion interrelation to the extent of development of atelectases. Sputum stagnation inevitably results in the development of bronchopulmonary inflammation in the setting of infection overlay and reduction in the secretory immunoglobulin A content [2-4].

The bronchial drainage dysfunction is especially relevant in infants with anatomico-physiological and functional respiratory tract peculiarities. It is well-known that bronchopulmonary pathology is one of the most widespread in this age group. Up to 2/3 of diseases in infancy are acute respiratory infections. 4-12 episodes of respiratory infections per year are observed in the frequently ill children. Acute respiratory viral infections in 30% of cases are complicated by a bacterial superinfection; this results in the development of inflammatory diseases of paranasal sinuses and respiratory tract [5, 6].

Such anatomico-physiological peculiarities of infancy as high vascularization of mucous tunics, which leads to the rapid inflammatory edema, and respiratory tract narrowness result in rapid development of diseases. Moreover, cough reflex may be obliterated or not present at all in the children born prematurely and with neurological disorders; this hinders bronchial drainage function and may result in sputum stagnation. Clinical functional disorders of bronchial permeability in premature children of 0-6 months of age and children with bronchopulmonary dysplasia of 0-1 years of age have been confirmed by the results of the authors' own long-term trials [7-9]. Mucolytic therapy in these patients has certain peculiarities and is conducted given cough reflex intensity, possibility of postural drainage and regimen factors. It is advisable not to use mucolytics in children before diurnal or nocturnal sleep in order to avoid sputum congestion in the respiratory tract. Mucolytic effect is aggravated by additional liquid intake [2, 10].

The scientists distinguish between 4 groups of drugs, which may be prescribed to children with ineffective expectoration [10]:

- Drugs suppressing cough reflex (central and peripheral antitussive drugs);
- Sputum-diluting mucolytic drugs (direct mucolytics, mucokinetics, mucoregulators);
- Expectorants stimulating processes of sputum discharge from respiratory tract (primarily, phytogenic);
- Combined drugs.

It must be mentioned that in a vast majority of cases cough treatment should not come to cough suppression only. Dry poignant cough, which leads to severe sleep disorders, physical and psychological discomfort and exhaustion, or the child's preparation for bronchopulmonary trials are indications to the prescription of antitussive drugs. In all other cases antitussive drugs are contraindicated, and even harmful in view of much sputum in bronchial lumen, as in that case they may cause congestion unless expectoration is effective [1, 2, 10].

Mucolytic therapy is intended for ensuring sputum discharge by improving its flow properties; it is primarily aimed at reduction in viscosity, elasticity and adhesiveness of bronchial secretion without significant increase in its volume. Mucokinetic effect is achieved by increasing mucociliary clearance by means of effective performance of bronchial ciliated epithelial cilia (see pic. 1). Mucoregulatory effect is achieved by reducing mucus hypersecretion by means of affecting the mucus-producing glands of respiratory tract [3].

Mucolytic drugs are widely used in pediatrics to treat inflammatory diseases of respiratory system. Inflammatory diseases of the upper respiratory tract and paranasal sinuses (rhinites, sinusites, laryngotracheites) may indicate prescription of mucolytic therapy. Along with antibiotics and bronchial spasmolytics, mucolytic drugs have an important role in the complex therapy of acute and chronic inflammatory diseases of the lower respiratory tract. According to the indications, the patients with acute or chronic bronchites, bronchiolites, pneumonias, bronchopulmonary dysplasia, bronchial asthma, congenital and hereditary diseases of bronchopulmonary system, including mucoviscidosis, may receive oral, inhalation and endobronchial mucolytic therapy. Mucolytic drugs are most often prescribed as a component of the complex therapy of a respiratory tract's inflammatory disease and are well compatible with

any other drugs, excluding cough reflex suppressants. In case an oral antibiotic is also prescribed, it is advisable to maintain 2 hours between its intake and intake of a mucolytic [10].

We studied possibility of using mucolytic drugs in infants through the example of acetylcysteine. It is well-known that the amino acid cysteine derivatives (acetylcysteine, carbocisteine), which have been used in clinical medicine since 1960, cause direct mucolytic action and result in the reduction in sputum viscosity by means of depolymerization at opening of disulfide bonds of bronchial secretion's proteoglycans. Mucociliary clearance increases in the setting of sputum viscosity and adhesiveness reduction, i.e. drugs of this group additionally have a vivid mucokinetic effect. It is important to mention that drugs of this group also have antioxidant, antitoxic and anti-inflammatory properties.

Acetylcysteine (ACC) is a widely used drug in the therapy of respiratory diseases in children of the first years of life. The drug has a unique combination of effects on the pathological process at bronchial mucous tunic's inflammation. Apart from the main, mucolytic effect, we have already mentioned acetylcysteine's antioxidant activity associated with a nucleophilic thiol SH-group, which easily yields hydrogen, thus neutralizing free radicals. The drug promotes synthesis of glutathione – the main oxidative system in the body, which increases protection of cells from free-radical oxidation and neutralizes toxic exposure to the products of inflammation [11-13]. The same mechanism is present in the protective effect against aggressive environment: city smog, toxic and tobacco smoke etc. [14, 15]. 35 years of acetylcysteine application in clinical practice proved its useful therapeutic capabilities.

Acetylcysteine has a pronounced antitoxic effect at intoxication with various non-organic and organic compounds, including paracetamol and cyclophosphamide. Several foreign researchers cite data on immunomodulating and antimutagenic properties and antitumor activity of acetylcysteine [16, 17]. Another important property of the drug is its capability to stimulate phagocytosis [17, 18]. All the mentioned acetylcysteine properties provide high efficacy of the drug against inflammatory process in the bronchopulmonary system by affecting various levels of pathogenesis.

Acetylcysteine may be prescribed to children of all age groups, including infants of 10 days of age. Availability of user-friendly pharmaceutical forms makes the drug irreplaceable in the therapy of infants. Syrup granules with orange taste are intended for younger children (100-150 mg per day BID-TID to children of 0-2 years of age, 200-300 mg per day BID-TID to children of 2-5 years of age) [19]. The treatment course at acute disease takes 507 days. Long-term acetylcysteine application is indicated at the chronic bronchopulmonary pathology accompanied by bronchial lumen obstruction with viscous, primarily mucopurulent, sputum. Efficacy and safety of long-term (3-6 months) acetylcysteine mucolytic therapy courses in the dosage considerably exceeding the therapeutic average have been confirmed by experimental and clinical studies of adult patients with chronic obstructive pulmonary disease [14, 18, 20]. There are almost no data on the consequences of long-term application of the drug in pediatric practice.

Safety and good tolerance to acetylcysteine in children over 2 years of age is proved by a range of clinical trials both in Russia and abroad and by many years of using the drug to treat acute and chronic bronchopulmonary system's diseases [4, 10, 21]. Data on the drug's application in younger children are scarce and inconsistent. Thus, according to the latest "The Cochrane Collaboration" review, which included data on the results of 34 clinical trials of safety and efficacy of acetylcysteine and carbocisteine application at acute upper and lower respiratory tract infections in children without chronic bronchopulmonary pathology; 63% reduction in such a symptom as cough was revealed in older children 6-7 days after the treatment had begun [22]. The review does not feature conclusions about the group of children under 2 years of age; however, paradoxical aggravation of bronchorrhea was mentioned in several cases (these episodes were not registered in the publications). Interestingly, this phenomenon took place due not only to mucus hyperproduction with no possibility of adequate discharge, restricted by small diameter of bronchi, but also to the dosage effect. According to the specialists' calculations, the dosage recommended to infants is 3 times higher than the dosage for older children (45 mg/kg

per day to 16 mg/kg per day) [22]. Acetylcysteine dosage effect has not been studied yet in different age groups.

We have not found data on safety and efficacy of acetylcysteine use in children under 2 years of age with chronic bronchopulmonary pathology in the available literature. At the same time, every pediatrician has had to prescribe this drug to infants rather often. According to French pediatricians, acetylcysteine derivatives are among the most often prescribed drugs for children under 2 years of age [23]; in Spain, mucolytics are the second most widespread pharmacological group of drugs prescribed to children under 2 years of age [24]. This results in the situation when the international clinical experience is not supported by the reliable results of the drug's efficacy and safety based on randomized clinical acetylcysteine trials in this age subgroup. Moreover, information on the results of application of this drug both in children with acute respiratory viral infections (ARVI), acute bronchites, bronchiolites and pneumonias and in children with chronic bronchopulmonary pathology is of considerable interest. The need in risk/benefit reevaluation of the use of mucolytic drugs (especially for children under 2 years of age) – acetylcysteine derivatives – by pharmacological control establishments of the countries where such drugs are registered was emphasized in the aforementioned review [22]. In the Russian Federation, acetylcysteine may be used in children under 2 years of age only on doctor's orders in the dosage less than 150 mg per day [19].

Introduction of the high-technology methods of studying respiratory function in medical practice in the present conditions allows us to objectively evaluate bronchoobstructive syndrome and correct it by means of mucolytic therapy or otherwise. Quiet breathing flowmetry plays a significant role in evaluation of the bronchial drainage function; it is a new method of studying velocity parameters of air volume and flow at acute and chronic diseases of the bronchopulmonary system in infants during natural sleep. Pulse oximetry is conducted simultaneously with flowmetry. Quantitative values of these parameters allow objective evaluation of airway permeability and revealing signs of tracheal and bronchial lumen obstruction with sputum. We present a flow-volume curve in a child with bronchopulmonary dysplasia out of exacerbation, where a slight disorder of peripheral bronchial permeability associated with the primary disease is registered (pic. 2), and a flow-volume curve in a child with bronchopulmonary dysplasia (BPD) at disease exacerbation in the setting of ARVI, where, along with a slight disorder of peripheral bronchial permeability, signs of expiratory respiration obstruction on the level of the upper respiratory tract are registered (pic. 3), by way of example.

Clinical trial of an acetylcysteine-based drug as a mucolytic in 30 children from 4 months to 1 year 10 months of age with acute and recurrent bronchites (n=15) and BPD exacerbation (n=15) demonstrated its efficacy and safety [25].

Quiet breathing flowmetry in 10 children of this group with acute and recurrent bronchites and BPD exacerbation did not reveal the so called "boggy syndrome" in patients 4 hours after the singular acetylcysteine dose intake (syrup granules); it was confirmed by the lack of reduction in volume functional parameters. Cough intensity and duration reduction and improvement of the expectoration ability in the setting of the drug's use indicated improvement of the bronchial drainage function in patients of the group under study [25].

Thus, efficacy and safety of use of acetylcysteine derivatives in pediatric practice for treating patients with acute and chronic bronchopulmonary pathology is confirmed by the long-term clinical experience and numerous trials conducted all around the world is out of doubt. Unique properties of acetylcysteine (it combines mucolytic, mucokinetic, antioxidant, antitoxic and anti-inflammatory effects) make it irreplaceable for the complex treatment of the respiratory tract's inflammatory diseases. Obviously, multicenter randomized post-approval clinical acetylcysteine trials in infants are crucial to the full-scale application of the drug. Without any doubt, it is also necessary to specify the drug's dosage and appraise safety of long-term acetylcysteine therapy for this category of patients. The possibility of objective respiratory function's control during natural sleep ought to help to obtain reliable data on efficacy of the bronchial drainage function in this age group. Such trials could promote wider use of mucolytic drugs, including

acetylcysteine, in pediatric practice. The possibility of using such modern pharmaceutical forms as ACC syrup granules for therapy of bronchopulmonary diseases in children of 0-2 years of age promotes improvement of the small patients' condition and faster recovery.

Pic. 2. Flow-volume curve in a child with bronchopulmonary dysplasia out of exacerbation.

Pic. 3. Flow-volume curve in a child with bronchopulmonary dysplasia exacerbation and signs of expiratory respiration obstruction on the level of the upper respiratory tract.

REFERENCES

1. Zharkova N. E. *Russkii meditsinskii zhurnal – Russian medical journal*. 2006; 6: 1171–1174.
2. Klyachkina I. L. *Consilium medicum – Consilium medicum*. 2008; 10 (3): 124–128.
3. Namazova-Baranova L. S., Alekseeva A. A., Torshkhoeva R. M., Vishneva E. A., Levina Yu. G. *Praktika pediatra – Pediatrician practice*. 2011; december: 5–9.
4. Namazova-Baranova L. S., Nisevich L. L., Volkov K. S., Vazhnova I. M. *Pediatricheskaya farmakologiya – Pediatric pharmacology*. 2008; 5 (3): 64–71.
5. Baranov A. A., Al'bitskii V. Yu. *Mediko-sotsial'nye problemy sovremennogo sirotstva* [Medical and Social Problems of the Contemporary Orphanhood]. Moscow, Soyuz pediatrov Rossii, 2009. pp. 62–71.
6. Namazova-Baranova L. S., Torshkhoeva R. M., Botvin'eva V. V., Tagizade T. G., Taranushenko T. E. *Pediatricheskaya farmakologiya – Pediatric pharmacology*. 2006; 3 (1): 13–17.
7. Davydova I. V., Yatsyk G. V., Lukina O. F. et al. *Pediatricheskaya farmakologiya – Pediatric pharmacology*. 2008; 5 (6): 42–44.
8. Davydova I. V., Yatsyk G. V., Tresorukova O. F. *Rossiiskii pediatricheskii zhurnal – Russian pediatrical journal*. 2008; 6: 10–13.
9. Namazova-Baranova L. S., Turti T. V., Davydova I. V. et al. *Floumetriya spokoinogo dykhaniya u detei pervogo goda zhizni. Metodicheskie rekomendatsii* [Flowmetry of Breathing in Infants. Methodical Recommendations]. Moscow, Pediatr", 2012. 31 p.
10. Volkov K. S., Nisevich L. L., Namazova-Baranova L. S., Filyanskaya E. G., Alekseeva A. A., Barannik V. A. *Voprosy sovremennoi pediatrii – Current pediatrics*. 2013; 12 (1): 112–116.
11. Ushkalova E. A. *Farmateka – Pharmateca*. 2007; 17: 30–36.
12. Aruoma O. L., Halliwell B., Hoey B. M. et al. The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide and hypochlorous acid. *Free Radic Biol Med.* 1989; 6 (6): 593–597.
13. De Flora S., Cesarone C. F., Balansy R. M. et al. N-acetylcysteine. The experimental background. *J Cell Biochem*. 1995; 22: 33–41.
14. Droge W. Cystein and Glutathione Deficiency in AIDS Patients. *Pharmacology*. 1993; 46: 61–65.
15. Lu Q., Bjorkhem I. et al. N-acetylcysteine improves microcirculatory flow during smoring: new effects of an old drug with possible benefits for smokers. *Clin Cardiol.* 2001; 24: 511.
16. Kelly G. S. Clinical applications of N-acetylcysteine. *Alt Medical Review*. 1998; 24 (2): 114–127.
17. Ostroumova M. N., Kovalenko N. G., Bershtein L. M. *Eksperimental'naya onkologiya – Experimental oncology*. 1999; 16: 96–101.
18. Grandjean E. M., Berthet P., Ruffman R. et al. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: meta-analysis of published double-blind, placebo-controlled clinical trial. *Clin Therapy*. 2000; 22: 209–221.

19. *Instruktsiya po meditsinskomu primeneniyu preparata ATsTs (N-atsetil-L-tsistein). Proizvoditel' «Geksal AG»* [Instructions for Medical Use of the Drug NAC (N-acetyl-L-cysteine). Manufacturer "Ghexal AG"].
20. Lui R., Nair D., Ix J. et al. N-acetylcysteine for the prevention of contrast-induced nephropathy. A systematic review and metaanalysis. *J Gen Intern Med*. 2005; 20: 193–200.
21. Stey C., Steurer J., Bachmann S. et al. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. *Eur Respir J*. 2000; 16: 253–262.
22. Duijvestijn Y. C. M., Mourdi N., Smuchny J. et al. Acetylcysteine and carbocysteine for acute upper and low respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease (Review). *Cochrane Database Syst Rev*. 2010; 9: 1–22.
23. Chalumeau M., Cheron G. Assathiany R., Moulin F. et al. Mucolytic agents for acute respiratory tract infections in infants: pharmacoepidemiologic problem? *Archives de Pediatrie*. 2002; 9: 1128–1136.
24. Ergreteau L., Gaillard D., Jouet J. B. et al. Effect of carbocysteine on mucus and respiratory mucosa in children with recurrent bronchitis. *Eur Respir J*. 1992; 5: 301.
25. Davydova I. V., Turti T. V., Namazova-Baranova L. S. et al. *Pediatricheskaya farmakologiya – Pediatric pharmacolog*. 2012; 9 (2): 67–73.