Bronchoobstructive syndrome (BOS) is the most significant problem in pediatric pulmonology department in terms of diagnosis, treatment and further rehabilitation. BOS is not defined as a separate clinical entity, and includes manifestations of asthma, chronic pneumonia, persistent viral upper respiratory tract infection, allergic reactions or intrusive non-productive cough without explicit etiological causes.

BOS is considered to be a set of clinical signs reflecting violation of bronchial patency due to narrowing of the lumen. BOS is the leading feature that brings together a group of acute, recurrent and chronic diseases having the main complex of symptoms, but it is not an independent nosological unit and cannot serve as a diagnosis. However BOS often accompanies respiratory diseases, especially in young children, the appropriate therapy of this condition remains a serious problem in pediatrics.

Causes that contribute to the BOS in children:
- age-related features of the respiratory tract and chest;
- viral and bacterial infection agents (respiratory-syncytial virus, parainfluenza, adenovirus, mycoplasma, etc.);
- characteristics of the local immunity;
- mucostasis, ciliary epithelium dysfunction;
- passive smoking;
- environmental pollution;
- premorbid background (prematurity, allergic history, rickets, malnutrition, etc.).

Child airways are narrow thus inflammatory changes in the airways easily bring to their obstruction; BOS can accompany a variety of respiratory diseases:
- bronchial asthma;
- obstructive bronchitis, bronchiolitis;
- aspiration syndrome, foreign bodies of the trachea, bronchi, esophagus;
- chronic bronchiolitis with obliteration;
- local pneumocerosis (chronic pneumonia);
- congenital malformations of lung, cystic fibrosis;
- bronchopulmonary dysplasia;
- tumors of the trachea and bronchi;
- immunodeficiency proceeding with lung disease;
- external compression of the trachea and bronchi;
- congenital heart disease with hypertension, pulmonary circulation, vascular anomalies, congenital non-rheumatic carditis;
- diseases of the central and peripheral nervous system.

Variety of reasons underlying this symptom is reflected in different therapeutic approaches. Along with the use of antiviral, antibacterial, and mucolytical agents as well as physiotherapy methods that improve the evacuation of sputum from the bronchial tree bronchodilators are used. Bronchodilators are traditionally included in the complex of therapeutic interventions for the treatment of BOS. Bronchodilators appointment has purposes:
- obtaining anti-inflammatory and bronchodilating effect;
- accurate diagnosis by the presence or absence of bronchospasm with $\beta_2$-agonists inhaled.

The presence or absence of bronchial obstruction reversibility is an important differential diagnostic criterion for the choice of appropriate therapeutic tactics for asthma and BOS in children with acute and chronic lung disease [2, 6]. In recent years drugs with prolonged action attract the attention of pediatricians. Reduction of the drug multiplicity tends to be very convenient, especially in the treatment of BOS in children.

The aim of this study was to evaluate the efficacy of formoterol fumarate (Zafiron) of pharmaceutical company ADAMED (Poland) in children with prolonged and relapsing inflammatory bronchopulmonary diseases with concomitant BOS. The possibility of the use of Zafiron as a bronchodilator for the spirography pharmacological test have been studied simultaneously.

The problem of differential diagnosis of various bronchoobstructive conditions in pulmonology is very important, especially in pediatric patients. The diagnosis of BOS is based on data of clinical examination and spirometry. According to up-to-date principles of changes in the bronchopulmonary system interpretation, the most informative parameter is forced expiratory volume in 1st second (FEV$_1$). In our study spirometry had been conducted on calibrated equipment in accordance with the recommendations of the American Thoracic Society and European Respiratory Society Standards.
The severity of obstruction is determined with the help of spirometry:

- mild – FEV₁ > 70 %;
- medium – FEV₁ 50 to 69 %;
- severe – FEV₁ < 50 % predicted.

The main symptoms of BOS are the following: mixed, mainly expiratory dyspnea, appearance of wheezing when child is excited, running, during physical activity, and in severe cases – at rest, dry unproductive cough. In some cases, dry painful cough may be the only symptom of bronchial obstruction.

Formoterol is a selective β₂-agonist. It has a bronchodilating effect in patients with irreversible and reversible respiratory obstruction. Effect of the medication starts quickly in 1–3 minutes, and is maintained during 12 hours after the inhalation [1, 7, 9]. It is shown that formoterol effectively prevents bronchospasm caused by inhaled allergens, physical exercises, cold air, histamine or methacholine [6, 7]. Due to the fact that the bronchodilating effect of formoterol lasts 12 hours after inhalation, maintenance therapy prescribed 2 times a day; in most cases, provides the necessary control of bronchospasm caused by chronic diseases during the day and at night [1, 8, 9]. Formoterol is indicated for prevention and treatment of bronchospasm in patients with obstructive respiratory diseases such as asthma and chronic bronchitis both with and without emphysema, as well as prevention of bronchospasm induced by inhaled allergens, cold air or physical exercises [1, 9].

Materials, Methods and Results
The study involved 30 children with BOS aged 6 to 17 years. Lingering pneumonia was diagnosed in 22 children having frequent dry unproductive cough with no response to antitusives, antispasmodics, and desensitizing agents. Twelve of these patients manifested wheezing with expiratory dyspnea. In 8 patients cough variant of asthma (hidden bronchospasm) was supposed at the admission. Patients with reliably diagnosed asthma in which Zafiron has proven efficacy, especially in combination with inhaled corticosteroids, were not included. All patients underwent external respiratory function (ERF) assessment according to the standard method with following Zafiron inhalation in dose of 12 μg (dry powder in capsules for inhalation use via aerolayzer). Second spirometry was carried out in ten minutes after inhalation for the definition of bronchial reaction to antispasmodic agents and the diagnosis of latent bronchospasm.

After Zafiron inhalation 2–3 % increase in FEV₁ was observed in 6 patients, 7–11 % in 18 patients, and 12–16 % in 6 children (Table 1).

On the second stage Zafiron was differently prescribed in children with lingering pneumonia complicated with BOS and in children with asthma of mild to moderate severity.

Treatment ranged from 14 days to 2 months. Zafiron was administered at a dose of 12–24 μg 2 times a day. Control assessment of respiratory function and clinical data recording were performed at baseline, in 7 and 14 days, 1 and 2 months after initiation of treatment. All children with lingering bronchopneumonia had received standard antibiotic and mucolytic therapy, physiotherapy procedures without any positive clinical response to oral bronchodilators. Inhalation of Zafiron resulted in regression of symptoms in almost all patients on the 2nd and 3rd day after treatment onset. Intensity of compulsive cough attacks and expiratory dyspnea decreased. Changes of ERF parameters after 7 days of Zafiron inhalation are presented in Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Change, %</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>74 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>81 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>88 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>96 ± 4</td>
</tr>
</tbody>
</table>

After 1 month of treatment clinical recovery and spirometric parameters normalization was observed in children with protracted bronchopneumonia. Only 6 children had FER parameters under 80 % with decrease of instantaneous expiratory flow values at medium and small bronchi. These patients continued Zafiron therapy in combination with the appropriate dose of inhaled glucocorticoid. Clinical and instrumental monitoring showed that the chosen treatment strategy was correct. Essentially all patients demonstrated normalization of general condition and ERF parameters, attacks of bronchial obstruction with expiratory component were not observed. No adverse events reported in the literature were indicated.

Further control and the gradual discontinuation of medications were performed in accordance with the GINA protocols.

Discussion
According to numerous published data and those obtained in pulmonology clinic of IPOG NAMS of Ukraine, BOS often complicates the course of inflammatory diseases of the respiratory system in children and adolescents. Etiology of BOS varies: diverse pathogenic microorganisms, viral and microbial associations, fungi of Candida, etc. Inflammatory changes of bronchial wall and hypersecretion possibly influence the symptoms of BOS, as well as the allergic inflammation. In some cases, BOS is considered as bronchial asthma,
having typical symptoms, but in most cases BOS does not manifest so vivid clinical symptoms of that disease. Over the past 3 years the frequency of respiratory diseases complicated with BOS grew up 5 to 7-fold in children.

Given the similar pathogenetic pattern of asthma and BOS, the therapy of these diseases includes β2-agonists, theophyllines, and, less frequently, drugs of other groups. Given the high medication burden in the pediatric patient, β2-agonists with prolonged action are increasingly being used for the treatment of asthma in recent years. Therefore, the use of formoterol in children with chronic inflammatory respiratory diseases and related BOS is attractive in terms of both its bronchodilator and anti-inflammatory effect.

The results of our study confirm that Zafiron is an effective bronchodilator that can be used for the treatment of BOS in children with bronchopulmonary diseases. Formoterol should be considered in patients with bronchial asthma and those with chronic inflammatory respiratory diseases complicated with secondary BOS. Application of Zafiron is one of the key links in the complex therapy of BOS helping to control the disease, restoring bronchial patency in patients with reversible airflow obstruction or improving it in patients with partially reversible obstruction.

References


Abstract. Given the complexity development mechanisms of bronchial obstruction syndrome (BOS), its optimal treatment, especially in children, is still an important issue. New ways of optimization of BOS treatment are need. Selective long acting β2-agonists are in the focus of their bronchodilating properties. The aim of the study was to examine the efficacy and safety of β2-agonist zafiron (formoterol fumarate) in children with BOS.

Thirty pediatric patients (aged 6 to 17 years) with BOS clinical signs and symptoms participated in the study. Zafiron was differentially administered to children diagnosed with mild to moderate bronchial asthma and patients with BOS complicated lingering pneumonia (n = 22). The second group received standard antibiotic and mucolytic treatment though had no therapeutic response to receiving oral bronchodilators. Zafiron efficacy at a dose of 12–24 mg 2 times a day was assessed by a decrease in clinical symptoms and improvement of respiratory function after 7 – 14 days, 1 and 2 months of treatment. After 1 month 24 of 30 children showed clinical recovery and normalization of the respiratory function. During the study no drug-associated adverse events were observed.

Data obtained in this study suggest that zafiron is safe and effective bronchodilator and should be considered in patients with chronic and lingering bronchopulmonary diseases, the course of which is exacerbated with secondary BOS.

Key words: broncho-obstructive syndrome, selective β2-agonists, zafiron.