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# COMMUNITY-AQUIRED PNEUMONIA IN ASTHMATIC CHILDREN WITH DIFFERENT DURATION OF INHALED CORTICOSTEROID THERAPY

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**Background.** The continuing increase of the prevalence of asthma in the world, the lack of the expected therapeutic effect of current programs, make this phenomenon to be studied. One of the main causes of asthma exacerbation and worsening of the prognosis in the children's population are infectious diseases that occur in connection with steroid therapy used in the asthma treatment. **Aim:** to study the relationship of steroid therapy in asthmatic children with the occurrence of community-acquired pneumonia, that changes asthma symptoms in them. **Materials and methods.** 39 children aged 3-18 years old with atopic asthma who received corticosteroid therapy, were examined. All patients were divided into 4 groups: Group 1 – patients received inhaled corticosteroids for 2 years; Group 2 – for 3-5 years; Group 3 – for more than 5 years; Group 4 – patients with newly diagnosed asthma and a short course of corticosteroid therapy in the remission. **Results.** The frequency of community-acquired pneumonia was analyzed in all groups. Strong positive correlation between the duration of use of moderate and moderate/high dose inhaled corticosteroid therapy in asthmatic children for more than 2 years and the occurrence of community-acquired pneumonia with development of complications (pulmonary hypertension, pulmonary fibrosis, pulmonary bullae, bronchiectasis) in 48.7% them was revealed. **Conclusions.** Strong positive correlation between the duration of moderate and moderate/high dose inhaled corticosteroid therapy in asthmatic children for more than 2 years and the occurrence of community-acquired pneumonia in them was revealed, that necessitates the antibiotics to be included in the medication therapy of asthma.

**Keywords:** children; asthma; inhaled corticosteroid therapy; community-acquired pneumonia; antibacterial therapy.

# ВНЕБОЛЬНИЧНЫЕ ПНЕВМОНИИ У ДЕТЕЙ С БРОНХИАЛЬНОЙ АСТМОЙ И РАЗНОЙ ДЛИТЕЛЬНОСТЬЮ СТЕРОИДНОЙ ТЕРАПИИ

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**Актуальность.** Продолжающийся рост уровня заболеваемости бронхиальной астмой во всем мире, отсутствие ожидаемого терапевтического эффекта современных программ обусловливают необходимость изучения этого феномена. Одной из важных причин, вызывающих обострение бронхиальной астмы и ухудшающих прогноз в детской популяции, являются инфекционные заболевания, которые развиваются на фоне применяемой в лечении бронхиальной астмы стероидной терапии. **Целью** представленного исследования было изучить связь стероидной терапии при бронхиальной астме у детей с частотой возникновения внебольничных пневмоний, изменяющих классическое течение симптомов бронхиальной астмы. **Материалы и методы.** Обследовано 39 детей от трех до 18 лет с атопическим вариантом течения бронхиальной астмы, получавших базисную терапию (ингаляционные кортикостероиды). Все пациенты были разделены на четыре группы: 1-я группа — получение ингаляционных кортикостероидов в течение двух лет; 2-я группа — 3–5 лет; 3-я группа — более 5 лет; 4-я группа — пациенты с впервые диагностированной бронхиальной астмой и с коротким курсом ингаляционной стероидной терапии в стадии индукции ремиссии. **Результаты.** Во всех группах проанализирована частота внебольничных пневмоний. После статистической обработки получена тесная положительная корреляционная связь между длительностью использования средних

и средневысоких доз ингаляционных кортикостероидов у детей с бронхиальной астмой более двух лет и наличием у них внебольничной пневмонии, с формированием у 48,7 % из них осложнений (легочной гипертензии, пневмофиброза, легочных булл, бронхоэктазов). **Выводы.** Тесная положительная корреляционная связь между длительностью получения средних и средневысоких доз ингаляционных кортикостероидов у детей с бронхиальной астмой более двух лет и возникновением внебольничной пневмонии указывает на необходимость назначения таким пациентам антибактериальной терапии.

**Ключевые слова:** дети; бронхиальная астма; ингаляционная кортикостероидная терапия; внебольничные пневмонии; антибактериальная терапия.

## INTRODUCTION

The high prevalence of asthma in the last three to four decades has become a serious public health problem due to the frequent disablement and mortality of patients. According to the Global Initiative for Asthma (GINA) experts, the world prevalence of asthma is about 334 million people. More than 250 thousand people die annually from asthma [11, 12].

Viral infections such as rhinoviruses, respiratory syncytial viruses, influenza viruses, parainfluenza, adenoviruses, as well as bacterial and mycoplasma infections and the development of sensitization to them can initiate bronchial hyperresponsiveness. Infectious agents and their destruction products, especially peptidoglycans, cause the release of various biologically active substances, which include not only histamine, but also components of the kallikrein-kinin system, complement system, and serotonin that lead to vascular changes and impaired microcirculation [3, 8].

Pediatric asthma is a developing disease associated with the maturation of the neuroendocrine, immune, and respiratory systems. Asthma is a combination of the effects of genetic, environmental, and mental factors with dissociative disorders within the neuroimmunoendocrine complex. We revealed the regulatory effect of hormones of the central and peripheral nervous systems on immunogenesis. The central nervous and immune systems interact with each other using neurotransmitters, cytokines, and endocrine hormones [3, 12].

Asthma is a heterogeneous disease characterized by multifactorial dependence and the interaction of numerous somatic and mental components [11, 12]. Etiologically and pathogenetically, various clinical manifestations of asthma are divided conditionally into phenoendotypes. The phenotypes can combine with a possible transformation [3, 12].

Despite the significant successes of modern medicine in the diagnosis and treatment of this disease, stabilization of clinical and functional indicators associated with asthma management is achieved only in 50% to 60% of patients that necessitates the study of the factors that reduce treatment effectiveness. An important place among them is occupied by the infections that contribute to the occurrence of obstructive bronchial conditions, asthma exacerbations, and the occurrence of complications [5, 10].

Obstructive conditions in children are more often associated with a respiratory viral infection. Most obstructive forms of bronchitis are associated with RS-viral, parainfluenza infection [3, 4]. In the last decade, the role of atypical intracellular pathogens, such as mycoplasmas and chlamydia in asthma exacerbations, has been actively studied [1, 4–7, 10, 13, 14].

Mycoplasmas and chlamydiae are common pathogens of severe acute respiratory syndrome in children. Violation of the drainage function of the bronchi with asthma fosters the constant colonization of the bronchial tree by microbiota and selective reproduction of some microorganisms. Mucostasis associated with microorganism-caused inflammation increases the manifestations of bronchial obstruction, worsens the clinical course of asthma, and causes complications. *Mycoplasma pneumoniae* causes not only bronchial hyperreactivity but also gamma-interferon synthesis suppression with the development of a tendency to chronicity and persistence of microorganisms in the epithelium. Secondary catarrhal and purulent endobronchitis associated with damage to the respiratory tract by *Mycoplasma pneumoniae* is observed in 20% to 50% of children with asthma [4–6].

The clinical and differential diagnosis of atypical pneumonia in children presents significant difficulties because of the non-specificity of the manifestations and the peculiarity of the course due to the variability of symptom complexes. More often, the infection is asymptomatic. However, clinical manifestations that are not characteristic of asthma exacerbations, such as signs of intoxication, including an impaired general condition and low-grade fever, chronic paroxysmal dry cough despite basic treatment for asthma, obstructive respiratory dysfunction, scattered dry and chesty small bubbling rales during auscultation, exclude microorganism-caused inflammation. Damage to the respiratory tract by atypical microorganisms

is associated not only with the alveolar, but also with the interstitial-type of lung tissue infiltration with impaired bronchial evacuation function, increased airiness areas, interalveolar septum rupture, false cysts, and the risk of subsequent spontaneous pneumothorax [2, 5].

The final diagnosis can be established based on laboratory results when intracellular pathogens in epithelial cells and their antigens, as well as IgM, IgA, and IgG against atypical pathogens, are detected.

Asthma is diagnosed according to the annually reviewed and updated GINA protocol adopted by the associations of allergists.

It is generally recognized that inhaled corticosteroids (ICS) are most effective in asthma treatment. However, ICS are safer compared with oral steroids. The use of ICS in clinical practice significantly improved the quality of asthma therapy [3, 9].

With asthma, ICS have a powerful anti-inflammatory effect because of their genomic and extragenomic activity. The genomic mechanism involves the binding of specific cytoplasmic receptors at any dosage no earlier than 30 minutes after the formation of the hormone-receptor complex at the start of anti-inflammatory protein synthesis and decreased the synthesis of pro-inflammatory proteins, such as cytokines, enzymes, and adhesion molecules. ICS have direct inhibitory effects on macrophages, T-lymphocytes, eosinophils, and epithelial cells involved in the inflammatory process, reduce the number of mast cells in the airways, inhibit the formation of many mediators by lymphocytes and macrophages, such as interleukins 1, 2, 3, 4, 5, 13, TNF-α, RANTES, and GM–CFS. The non-genomic anti-inflammatory effect of ICS is associated with the stabilization of lysosomal membranes, decrease in cell membrane permeability, decrease in capillary permeability and local blood flow in the inflammation areas, decrease in the swelling of endothelial cells, impairment in the ability of immune complexes to penetrate through the basement membrane, inhibition of fibroblast growth, suppression of collagen and mucopolysaccharide synthesis, vasoconstriction in the focus of inflammation, and decrease in vasopermeability partly due to the inhibition of prostaglandins synthesis [3]. ICS significantly improve the clinical symptoms of the disease.

Despite the high efficiency of ICS in the treatment of children with asthma, the side effects of this therapy, in particular, microbial and viral lesions of the bronchopulmonary system, cannot be ignored. In the presence of structural damage to the lungs in patients with asthma, the prescription of ICS should be justified [15].

Patients with atopic asthma are genetically predisposed to intracellular infections, preconditioning them to a more severe course of non-specific inflammatory lung diseases and exacerbations of chronic bronchopulmonary pathology that leads to bronchiectasis, pneumosclerosis, or deforming bronchitis. With infantile respiratory mycoplasmosis, the incidence of recurrent and chronic pathology of the respiratory system can be 50.6% [4, 5, 13, 14].

*The goal is to study* the relationship between the duration of steroid therapy with pediatric asthma and the incidence of community-acquired pneumonia (CAP).

## MATERIAL AND METHODS

We examined 39 children of ages 3 to 18 years old who underwent treatment for atopic asthma. In 66.7% of cases (26 children), the course was mild persistent; in 33.3% (13 patients), the course was moderate. Asthma was diagnosed according to the adopted protocol [3], which included complaints, a case history of the children, clinical, a laboratory (hemogram with eosinophilia detection, determination of IgE level), and instrumental examination (chest x-ray, ECG, echocardiography; computed tomography and spirography, if medically required). CAP was diagnosed using accepted criteria based on clinical and radiological signs. A serological study was done to determine IgM and IgG against mycoplasma, chlamydia, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and enzyme-linked immunosorbent assay (ELISA) in the blood serum. Polymerase chain reaction (PCR) was used to detect the causative agents of CAP in asymptomatic, latent, and chronic forms of infection.

ECG, echocardiography, and computed tomography (CTG) were performed to identify complications.

All the patients received basic therapy including ICS at low, medium, and medium-high doses. They were divided into four groups. Group 1 included the children who received ICS for two years from the diagnosis of asthma; group 2 received ICS for 3 to 5 years; group 3 received ICS for more than 5 years; group 4 included the patients with newly diagnosed asthma who received ICS for a short time in the remission-induction stage.

The results were analyzed statistically with the calculation of the relative values difference significance ($t$). The coefficient ($r_{xy}$) was calculated to determine correlations. The differences in the studied distributions, such as the incidence of CAP in children with asthma with prolonged ICS course, and the incidence of CAP in patients who did not receive

ICS with the first diagnosed asthma, were detected by calculating the compliance indicator ($\chi^2$).

## RESULTS

We examined 39 children with atopic complaints, including 31 (79.5%) patients with allergic history and physical changes in the bronchopulmonary system characteristic of asthma. The hemogram showed that 71.8% of patients suffered from eosinophilia, 35.9% had an increased level of total IgE in serum. An x-ray of the chest organs showed bloating of the lung tissue and a bronchovascular pattern deformation in all the patients. The study of the external respiration functioning resulted in the detection of ventilation failure of the obstructive type in 52.6% of cases; ventilation failure of the mixed type was found in 26.3% of children older than seven years old. The changes revealed made it possible to diagnose asthma and prescribe the basic ICS therapy.

Groups 1 and 3 included six children (15.4%), group 2 included 12 children (30.8%), and group 4 included 15 children (38.4%). Low doses of ICS were prescribed to 12 patients (30.8%), medium doses of ICS were prescribed to 18 patients (46.1%), and medium-high doses of ICS were prescribed to nine patients (23.1%). All the patients from group 1 received medium doses of ICS. Medium-high doses of ICS were prescribed to all patients from group 3, and low doses of ICS were prescribed to 70% of the children from group 4. In group 2, average doses of ICS were prescribed to 75% of the patients, whereas medium-high doses of ICS were prescribed to 25% of the patients.

CAP was detected in 22 patients with asthma (56.4%). The severity of asthma symptoms in children with CAP was more pronounced in comparison with the children who did not develop symptoms of pneumonia and was characterized by the duration of respiratory manifestations, including bronchial obstruction. In 17 children (43.6%) without signs of pneumonia, bronchial obstruction lasted $5.5 \pm 2.3$ days. In patients with asthma and pneumonia, with symptoms of intoxication, physical changes in the lungs, characteristic of pneumonia, lasted $11.5 \pm 2.0$ days.

When studying the etiology of CAP using an ELISA and determining antibodies against infectious agents, mycoplasma infection (MPI) was detected in 20 children (90.9%), chlamydial infection (CI) was detected in six patients (27.3%), EBV was detected in five patients (22.7%), and pneumococcus (PC) was detected in three patients (13.6%). A combination of several pathogens, such as MPI, CMV, CI, and EBV, was detected in 12 patients (54.5%).

The titer of IgM and IgG against mycoplasma were found in 27 children (72.7%). In the acute period, positive mycoplasma IgM with negative IgG were in nine patients (33.3%), and positive mycoplasma IgM and IgG were observed in eight children (29.7%). No mycoplasma IgM was detected with a positive IgG in three patients (11.1%), and negative IgM and IgG were detected in seven children (25.9%). At 2 to 3 weeks after the initial examination and obtaining positive results, the second study of paired sera was conducted in 12 children (60%) with established mycoplasma pneumonia. A high level of mycoplasma IgM ($\geq 1 : 32$) was maintained in eight of them (66.7%), an IgG titer $\geq 1 : 64$ was found in four children (33.3%) in the absence of an increase in IgM level. The results obtained do not allow excluding the persistent course of mycoplasma infection in 11 patients with asthma (55%).

In group 1, CAP was diagnosed in six patients (66.7%); in group 2, CAP was diagnosed in 11 (91.7%); in group 3, CAP was diagnosed in all patients (100%); in group 4, CAP was diagnosed in one patient (6.7%). A strong positive correlation ($rxy = 0.98$; $p < 0.001$) was found between the duration of ICS in asthma patients and CAP incidence

The introduction of targeted antibacterial therapy (macrolides) into the basic course of asthma treatment has significantly improved the condition of patients by eliminating intoxication and reducing respiratory syndrome manifestations.

The examination of the patients allowed establishing a statistically significant ($p < 0.001$) predominance of CAP in children with asthma who received ICS for more than two years, compared with patients with newly diagnosed asthma who just started on steroid therapy.

Signs of pulmonary hypertension (PH) were first recorded in 19 patients (48.7%) with a moderate (59.1%) and mild persistent course (27.1%) of asthma. The patients complained of fatigue and shortness of breath after light physical activity with increased bronchial obstruction. Heart auscultation revealed tachycardia and pronounced pulmonic component of the second heart sound (P2). During the instrumental examination, the ECG showed signs of venous heart overload. The X-ray of the chest organs showed congestion, smoothing of the heart waist by the second arc. Echocardiography showed an increase in pressure in the pulmonary artery of more than 25 mm.

Probably, the established PH signs can be explained by the Euler–Lillestrand mechanism associated with an increase of pressure in the pulmonary artery with the obstructive forms of chronic bron-

chopulmonary pathology (including asthma). Alveolar hypoventilation and resulting alveolar hypoxia with bronchial obstruction cause spasm of the arterioles of the pulmonary circulation, restrict blood flow through insufficiently ventilated sections of the lung and prevent the shunt of venous blood into the pulmonary circulation, which causes a generalized reduction of arterioles and pulmonary hypertension. At the initial stages, PH symptoms are not pronounced, but if PH is untreated for a long time, it can result in respiratory and heart failure and cause disability or death.

During an exacerbation of asthma provoked by CAP with PH signs, 12 (63.1%) patients from groups 2 and 3 were observed to exhibit long-term clinical signs, such as reduced general condition, severe fatigue, shortness of breath, chest pain, frequent cough with mucopurulent sputum. They also showed radiological signs of interstitial pneumofibrosis, including increased and deformed interstitial components of the pulmonary pattern, fine-meshed and medium-meshed formations in the pulmonary fields, that were also found for the first time. These changes can be explained by the persistent course of mycoplasma inflammation with a primary lesion of the lungs interstitium.

In three children (25%) with PH and pneumofibrosis signs, pulmonary bullae were detected in an observational chest X-ray image and pulmonary bullae and bronchiectasis in a CTG image. They were absent in previous images that were taken three or more years ago at the beginning of the observation. We noted deformation and an increase in the lung pattern due to peribronchial fibrotic and inflammatory changes, cellular lung pattern in the region of the lower segments of the lungs, as well as thickening, unevenness of the bronchi walls, the presence of mucocele. These changes are probably associated with deep damage to the lung tissue in the case of CAP, including an interstitial lesion with interstitial tissue elasticity degradation, excessive stretching of the wall of the inflamed, exudated bronchus, and emphysema site of the lung.

## CONCLUSIONS

1. In children with asthma, we revealed a strong positive correlation between receiving medium and medium-high doses of ICS for more than two years and the occurrence of CAP.

2. The etiology of CAP is represented by MP and CMV infection, as well as by a combination of pathogens that requires the expansion of therapeutic care for children with asthma and targeted antibacterial therapy.

3. A more severe course of asthma has been established in children with CAP. It was characterized by a longer bronchial obstructive episode due to intoxication and complications.

4. It is necessary to monitor the condition and conduct a thorough examination of children who have received medium and medium-high doses of ICS for a long time (more than two years) to improve the diagnosis and treatment of asthma and prevent its complications. If CAP is detected, antibiotic therapy is prescribed.

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