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## Efficacy of treatment of bronchial asthma attack in teenagers with partial control over the disease

The goal of the research is to evaluate efficacy of treatment of bronchial asthma attack considering hypersusceptibility indices of the respiratory tract to indirect bronchospasmogenic stimulus in teenagers with a partial control over the disease.

The effectiveness of therapy was analyzed according to the severity of bronchial sensitivity to dosed physical activity in 40 adolescents with partially controlled asthma. The patients were randomized. An average age was  $14,3 \pm 0,2$  years, and duration of the disease –  $(8,0 \pm 0,4)$  years. Considering the index of bronchial instability in teenagers with a partial control over the disease, two clinical groups of observation were formed. The first group included 16 teenagers with the index of bronchial instability more than 25%, and the second group included 24 peers with less pronounced bronchial instability (less 25%). All the children were comprehensively clinically-paraclinically examined, including evaluation of severity of bronchial obstructive syndrome, immunological tests I-II levels, inflammatometry of expired air condensate and spirometry with nonspecific provocation testing. Bronchial instability index (BII) was calculated and nonspecific hypersusceptibility of the bronchi to indirect stimulus (physical exercise) was examined by means of testing with physical exercise followed by inhalation of bronchodilators. Nonspecific hypersusceptibility of the bronchi to direct stimuli was examined by means of inhalation spirometric test with histamine series solutions calculating histamine provocation concentration ( $PC_{20}$ , mg/ml) and provocation dose ( $PD_{20}$ , mg), decreasing forced expiratory volume (FEV<sub>1</sub>) to 20% from the initial level.

Evaluation of deobstructive therapy efficacy of bronchial asthma attack in teenagers with a partial control over the disease gives the evidence to consider that during the first days of treatment it should be more active and extensional in teenagers with high bronchial instability, especially in those cases when a child belongs to the cluster of a high risk of development of severe attack of the disease on the basis of the preliminary comprehensive examination. Patients with high bronchial instability received glucocorticosteroids in a comprehensive treatment more often, for example, in 56,3% cases in the form of systemic pharmacological agents. Risk indices of glucocorticosteroid use in patients from I group (BII > 25%) in comparison with II group (BII < 25%) were the following: 1,5 [95%CI: 1,1-4,6], with odds ratio 5,3 [95%CI: 2,5-10,9].

**Key words:** bronchial asthma, children, adolescents, bronchial hyperreactivity, inflammation of the bronchi.

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## Ефективність лікування нападу бронхіальної астми у підлітків із частковим контролем захворювання

Метою дослідження було – оцінити ефективність лікування нападу бронхіальної астми з урахуванням показників гіперсприйнятливості дихальних шляхів до непрямих бронхоспазмогенних стимулів у підлітків із частковим контролем захворювання.

Ефективність лікування аналізували залежно від ступеня бронхіальної чутливості до дозованого фізичного навантаження у 40 підлітків із частково контрольованою бронхіальною астмою. Пацієнти були відібрані рандомізовано. Середній вік становив  $14,3 \pm 0,2$  року, тривалість захворювання –  $(8,0 \pm 0,4)$  років. З урахуванням індексу лабільності бронхів у підлітків із частковим контролем захворювання сформовано дві клінічні групи спостереження. До першої групи увійшли 16 підлітків з індексом лабільності бронхів понад 25%, до другої – 24 однолітки з менш вираженою лабільністю дихальних шляхів (менше 25%).

Усім дітям проведено комплексне клініко-параклінічне обстеження, яке включало оцінку тяжкості бронхообструктивного синдрому, імунологічні дослідження I-II рівнів, інфламометрію конденсату видихуваного повітря та спірографію з бронхопровокаційними пробами. Індекс лабільності бронхів (ІЛБ) та неспецифічну гіперсприйнятливості дихальних шляхів до непрямих стимулів (фізичне навантаження) визначали за допомогою проби з фізичним навантаженням з подальшою інгаляцією бронхолітиків. Неспецифічну гіперсприйнятливості бронхів до прямих стимулів оцінювали за допомогою інгаляційної спірометричної проби з серійним розведенням гістаміну з визначенням провокаційної концентрації гістаміну (ПК20, мг/мл) і дози (ПД20, мг), яка могла обумовити зменшення ОФВ<sub>1</sub> на 20%.

Оцінка ефективності дезобструктивної терапії нападу бронхіальної астми у підлітків із частковим контролем захворювання свідчить про доцільність більш активного та розширеного лікування у перші дні лікування у підлітків з вираженою лабільністю дихальних шляхів, особливо у випадках належності дитини до кластера високого ризику розвитку тяжкого нападу захворювання за даними попереднього комплексного обстеження. Пацієнти з вираженою лабільністю бронхів частіше отримували глюкокортикостероїди у складі комплексної терапії, зокрема у 56,3% випадків – у формі системних лікарських засобів. Показники ризику застосування глюкокортикостероїдів у пацієнтів I групи (ІЛБ >25%) порівняно з II групою (ІЛБ <25%) становили 1,5 [95% ДІ: 1,1-4,6] при співвідношенні шансів 5,3 [95% ДІ: 2,5-10,9].

**Ключові слова:** бронхіальна астма, діти, підлітки, бронхіальна гіперреактивність, запалення бронхів.

**Introduction.** Bronchial asthma (BA) in children refers to the most common chronic diseases considerably forming sickness rate, occurrence of pathology in childhood and further disability [1; 6; 12]. The disease should not be considered as a medical but social issue as well, since it is the most frequent reason of missing school, social maladjustment of a child, reduced quality of life and high cost of treatment [4; 7; 11]. Moreover, the disease of a child involves parents into a number of the above social problems as well. In spite of certain success achieved in the treatment of bronchial asthma, it should be recognized that it does not correspond to the expectations completely assuming anti-inflammatory therapy which is the basis for treatment of the disease [4; 6; 10]. Preventive measures based on the theory of allergic inflammation of the respiratory tract must be considered still less effective [6; 8; 9]. Numerous multicenter investigations demonstrated that nowadays non-atopic forms of the disease take a leading position and cause increase of sickness rate contrary to atopic variants of the disease, especially in the developing countries with insufficient economic level [2; 7; 12]. Today BA is considered as a disease characterized by recurrent episodes of variable bronchial obstruction, chronic inflammation, hypersusceptibility and airway remodeling [6; 8; 9]. It is these specific features of the disease that constitute the cornerstone of the inflammatory paradigm of bronchial asthma. Modern therapy of the disease is directed to these pathogenetic links, which postulates the necessity of long-term use of anti-inflammatory drugs, first of all inhaled corticosteroids [4; 10; 11].

However, it should be noted that the modern integral inflammatory theory requires revision and new conceptual realization or transformation into a novel paradigm. Considering the above characteristics as epiphenomena, such a theory may become the basis for new approaches in treatment and prevention [6].

In fact, the relationship between such specific features of BA as the character and intensity of chronic bronchial inflammation, hypersensitivity, hyperreactivity and airway remodeling remains controversial and insufficiently convincing for clinical application. According to numerous studies, the diagnostic value of these indices in evaluating

disease severity, treatment efficacy, level of asthma control and prevention remains limited [3; 5; 6].

This issue is especially acute among teenagers, when hormonal restructuring of the body, rapid physical development, social adaptation, formation of harmful habits and increasing exposure to adverse environmental factors result in disease modification and realization of genetic susceptibility [7; 11; 12]. It is during this period that BA onset or persistence from early childhood is associated with a high risk of continuation into adulthood [7; 12].

Therefore, investigation of interrelations between bronchial hypersusceptibility (BHS) in teenagers with BA and such disease characteristics as atopy, systemic immunological changes, activity of local bronchial inflammation and detoxification rate of foreign antigens appears to be topical and promising. This is determined not only by deeper understanding of asthma pathogenesis in adolescence, but also by the possibility of applying these indices to solve clinical tasks such as evaluation of disease severity for initiation of basic therapy, assessment of control efficacy, and substantiation of individualized treatment in cases where protocol-based therapy is insufficiently effective [1; 3; 6].

The goal of the research is to evaluate efficacy of treatment of bronchial asthma attack considering hypersusceptibility indices of the respiratory tract to indirect broncho-spasmogenic stimulus in teenagers with partial control over the disease.

**Methodology/Methods.** Forty teenagers suffering from bronchial asthma were comprehensively examined in the Pulmonological and Allergological Department of the Regional Children's Clinical Hospital in Chernivtsi. The patients were randomized. The average age was  $14,3 \pm 0,2$  years, and the duration of the disease was  $8,0 \pm 0,4$  years. There were 12 (30,0%) girls and 28 (70,0%) boys. Twenty-three children (57,5%) were rural inhabitants, while 17 patients (42,5%) lived in Chernivtsi and other urban areas.

Considering the bronchial instability index (BII) in teenagers with partial disease control, two clinical observation groups were formed. The first group included 16 teenagers with BII > 25 %, and the second group consisted of 24 peers with less pronounced bronchial instability (BII < 25%).

All children underwent comprehensive clinical and paraclinical examination, including assessment of bronchial obstructive syndrome severity, immunological tests (levels I-II), inflammometry of expired air condensate [6], and spirometry with nonspecific provocation testing [1; 3]. Bronchial instability index was calculated, and nonspecific bronchial hypersusceptibility to indirect stimulus (physical exercise) was assessed by exercise testing followed by inhalation of bronchodilators. Nonspecific hypersusceptibility to direct stimuli was examined using inhalation spirometric test with histamine solutions, calculating histamine provocation concentration (PC20, mg/ml) and provocation dose (PD20, mg), which reduced forced expiratory volume in one second (FEV1) by 20% from baseline [3; 6].

The obtained results were statistically analyzed using computer software packages STATISTICA (StatSoft Inc.) and Microsoft Excel XP for Windows, applying parametric and non-parametric methods of analysis. Results and Discussion.

Table 1 presents the structure of relieving (deobstructive) therapy used for patients during the first day of staying in the hospital, where teenagers were admitted because of asthma attack.

The presented data demonstrate that practically all the teenagers during the first day of inpatient treatment of bronchial asthma attack according to the protocols of treatment received  $\beta$ -agonists of a short action (Salbutamol, Ventolin) in the form of inhalation using nebulizer as a method of drug delivery. Patients with high bronchial lability more often received systemic glucocorticosteroids in combination therapy, in particular, in 56,3% of cases. Among patients of group II, the use of systemic glucocorticosteroids occurred in 20,8% of children ( $P\phi < 0,05$ ). Risk indices of systemic glucocorticosteroids use in patients of group I (bronchial lability index  $> 25\%$ ) compared with group II (bronchial lability index  $< 25\%$ ) were: relative risk 1,5 [95% CI: 1,1-4,6], when odds ratio 5,3 [95% CI: 2,5-10,9]. Similar results

were obtained concerning administration of Aminophylline, mostly in a parenteral way in the content of infusion therapy, and only 37,5% patients received the drug orally. It should be noted that teenagers from the both clinical groups in 37,5% cases received antibacterial therapy. Anti-histamine drugs in the form of Desloratadine were administered for 87,5% patients of the first group and 75,0% representatives from the second group ( $P > 0,05$ ).

Beclometasone was administered as an inhalation GCS in 36,4% cases, Fluticasone was used in 27,3% cases (with Salmeterol), Budesonide (with Formoterol) – in 18,2% cases, and in 18,2% cases – Fluticasone or Budesonide.

Therefore, during attacks teenagers received standard therapy within the frame of the protocol of BA treatment. At the same time, a part of patients with the signs of general inflammatory response received antibacterial therapy. The teenagers with comorbid allergic diseases or so-called “moist asthma” received anti-histamine drugs of the latest generation.

Table 2 presents an average duration of treatment of bronchial asthma attack in the groups of teenagers with different BII.

The data presented give the evidence to consider that duration of deobstructive therapy in the groups of comparison did not differ considerably. At the same time, teenagers with a high bronchial instability received longer therapy with GCS due to more torpid clinical manifestation of exacerbation to therapy. Thus, risk indices of a longer use of glucocorticosteroids in patients from I group in comparison with II group were the following: relative risk was 2,0 [95% CI: 1,5-2,7], with odds ratio 3,5 [95% CI: 1,9-6,3]. It should be noted that all the teenagers irrespective of intensity of bronchial instability received systemic corticosteroids only during the first days of their treatment in the hospital. Thus, an average duration of treatment with systemic GCS was  $3,1 \pm 0,3$  days (95% CI: 0,6-1,8).

Owing to the fact, that on the whole, deobstructive therapy included combinations of the above drugs, and only

Table 1

Content of deobstructive therapy during the first day of treatment of bronchial asthma attack

Groups of patients	Number of children	Occurrence of cases of drug use (%)			
		$\beta$ -agonists of a short action	glucocorticosteroids (SGCS+ IGCS)	aminophylline	infusion therapy
BII $> 25\%$	16	100,0	87,5	50,0	50,0
BII $< 25\%$	24	87,5	58,3	33,3	33,3
$P\phi$		$> 0,05$	$> 0,05$	$> 0,05$	$> 0,05$

Note. BII – bronchial instability index,  $P\phi$  – Student probability criterion, SGCS – systemic glucocorticosteroids, IGCS – inhaled glucocorticosteroids

Table 2

Duration of administration of deobstructive therapy components for bronchial asthma attack (95%CI)

Groups of patients	Number of children	Duration of drug administration (days of treatment)			
		$\beta$ -agonists of a short action	glucocorticosteroids (GCS)	aminophylline	infusion therapy
BII $> 25\%$	16	$8,8 \pm 0,98$	$9,3 \pm 1,1$	$6,5 \pm 0,54$	$2,7 \pm 0,4$
BII $< 25\%$	24	$8,2 \pm 0,57$	$6,4 \pm 0,64$	$7,0 \pm 0,62$	$3,3 \pm 0,4$
$P$		$> 0,05$	$< 0,05$	$> 0,05$	$> 0,05$

Note. BII – bronchial instability index, CI – confidence interval,  $P\phi$  – Student probability criterion

7 patients (16,6%) received treatment with  $\beta$ 2-agonists of a short action only, the analysis of frequency of relieving drugs administration seems to be reasonable (Figure 1).

The presented data demonstrated that combination of all the above drugs was administered 1,5 times more frequently for teenagers with high bronchial instability, and in the group with low instability of the respiratory tract – combination of  $\beta$ 2-agonists with glucocorticosteroids. The lack of statistically reliable differences by the frequency of use of the presented combinations of pharmacological means might be explained by a small sampling of patients.

Fig.2. presents duration of use of the presented combinations of pharmacological means administered with deobstructive purpose in the groups of teenagers during inpatient treatment of bronchial asthma attack.

The data obtained give the evidence to consider that duration of use of certain combinations of drugs in the process of deobstructive therapy in the groups of comparison did not differ considerably.

Since from the clinical point of view, deobstructive effect of the chosen therapy should occur as soon as possible, Fig.3 presents the efficacy of the above mentioned

combinations of drugs (in points) on the 2<sup>nd</sup> day of inpatient treatment.

The data obtained give the evidence to consider that addition of aminophylline to a complex of therapy intensifies deobstructive effect of  $\beta$ 2-agonists. At the same time, addition of GCS to the combination does not increase considerably deobstructive effect of the given combination of drugs. It might happen due to postponed effect of the given pharmacological agents.

On the whole, analysis of deobstructive therapy gives the evidence to consider that its efficacy is not determined by bronchial instability only, but other factors as well. Considering the fact that these factors cannot be always evaluated from a clinical point of view, it should be noted that “activity” and volume of deobstructive therapy, first of all, must be determined by severity of asthma attack. From this position, prognostication of severity of the attack on the basis of the results of preliminary conducted comprehensive clinical-laboratory examination is of the main priority.

Table 3 presents three clusters of prognosticated severity of asthma exacerbation (in points) considering the results of a comprehensive examination conducted in the period before the attack.

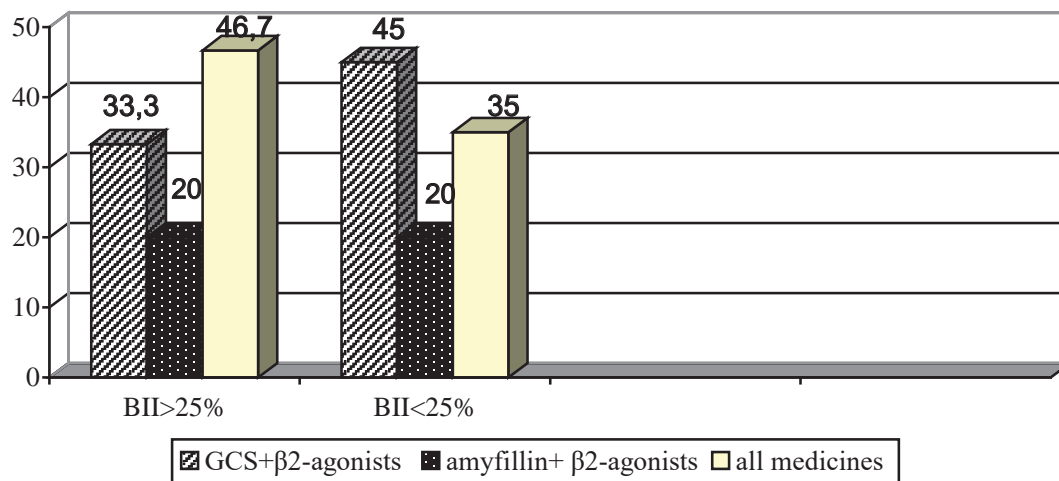


Fig.1. Frequency of use of certain combinations of drugs (%)

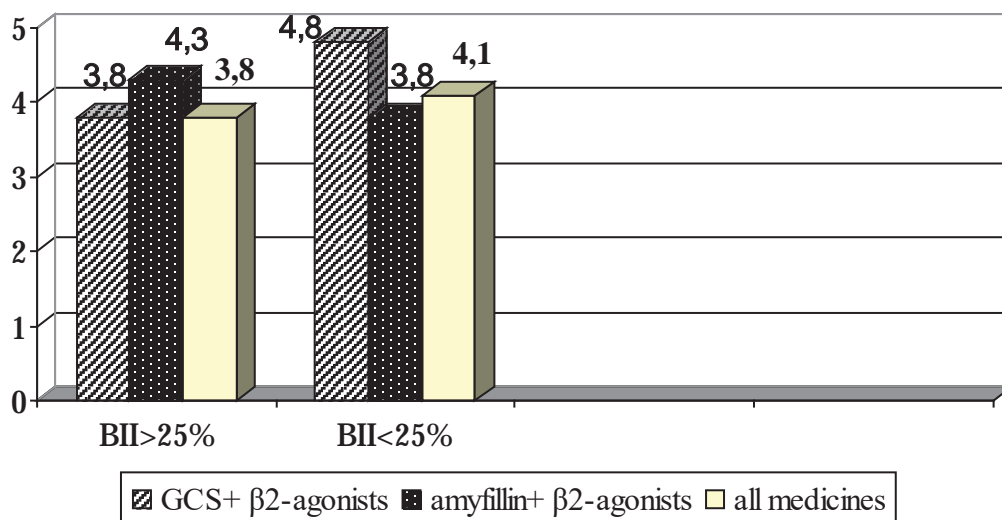


Fig. 2. Duration of use of certain combinations of drugs (days of inpatient treatment)

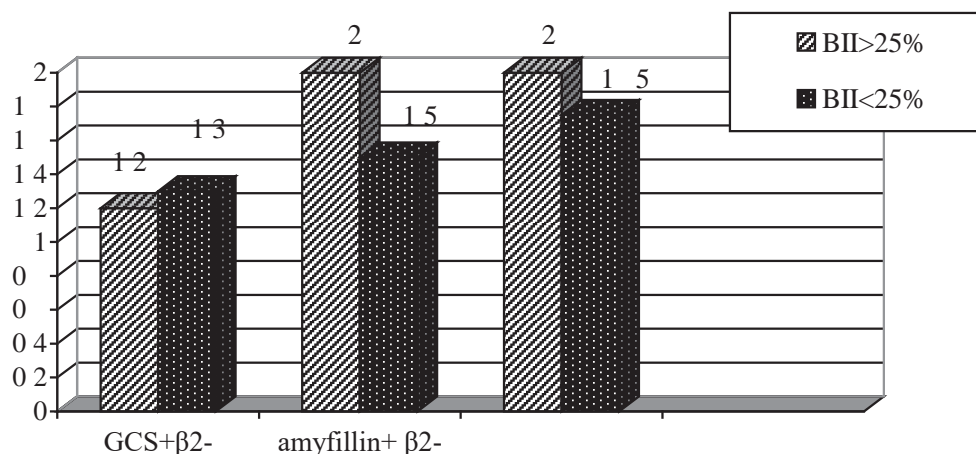


Fig. 3. Efficacy (the score of deobstruction) of combinations of bronchospasmolytics on the second day of treatment

Table 3

Clusters of predicted severity of asthma exacerbation considering the results of a comprehensive examination

Signs	Mild attack (10,1±0,4 points) I cluster	Moderate attack (12,8±1,7 points) II cluster	Severe attack (14,4±0,7 points) III cluster
boys (%)	60,0	83,3	81,8
BA duration (years)	6,8±0,7	7,5±1,7	8,1±1,0
PC20H (mg/ml)	1,7±0,3	0,41±0,1	0,29±0,05
DDC (s.u.)	1,8±0,01	2,4±0,02	2,4±0,08
BSI (%)	5,0±1,2	27,7±3,8	11,8±3,4
BDI (%)	5,1±0,9	1,4±0,5	33,3±3,5
BII (%)	6,7±1,2	29,2±3,2	41,9±3,2
NO metabolites in EAC (mcmol/ml)	41,0±1,7	47,4±6,9	46,7±5,9
Intracutaneous allergic tests with allergen of home dust (mm)	15,0±1,3	9,2±1,9	21,6±2,4

Notes. BA – bronchial asthma, PC20H – provocation concentration of histamine; DDC – dose dependent curve; BSI – bronchial spasm index; BDI – bronchial dilation index; BII – bronchial instability index; EAC – expired air condensate

The data obtained give the evidence to consider that risk of development of severe bronchial asthma attack in teenagers with high nonspecific bronchial hypersusceptibility to histamine and their pronounced instability at the expense of both bronchial spasm in response to physical exercise and deobstructive effect against the ground of β-agonists, in case of high skin sensitivity to allergens of home dust available. Contrary to this, teenagers with lower bronchial sensitivity to histamine, their lower instability, less pronounced skin sensitivity to a complex of allergens of home dust, develop mild or moderate exacerbation.

On the assumption of this, immediate indication of a complete volume of deobstructive therapy with high “activity” of treatment is reasonable in the first case, and in the second case this characteristic of treatment should be more sparing.

#### Conclusion

1) Patients with high bronchial instability received glucocorticosteroids in a comprehensive treatment more often, for example, in 56,3% cases in the form of systemic pharmacological agents. Risk indices of glucocorticosteroid use in patients from I group (BII > 25%) in comparison with II

group (BII < 25%) were the following: 1,5 [95%CI:1,1-4,6], with odds ratio 5,3 [95%CI:2,5-10,9].

2) Evaluation of the effectiveness of desobstructive therapy of asthma attacks in adolescents with partial control of the disease and with high lability of the bronchi suggests that in the first days of treatment therapy should be more active and voluminous with glucocorticosteroids, methylxanthines and β2-agonists, especially in those cases when the child belongs to a cluster of high risk of development of a severe attack of a disease on the basis of preliminary complex examination.

3) At the same time, in the group of patients with low airway lability index, the combination of β2-agonists with glucocorticosteroids was more effective, which was accompanied by a lower probability of developing severe exacerbation of bronchial asthma.

4) The risk of severe asthma attacks should be expected in adolescents with high nonspecific hyperresponsiveness of the bronchi to histamine and marked bronchial lability both due to bronchospasm in response to exercise and desobstructive effect of β2-agonists, if they have evident skin hypersensitivity to house dust allergens.

**Інформація про конфлікт інтересів.** Конфлікту інтересів немає.

**Інформація про фінансування.** Автори гарантують, що не отримали жодних винагород у будь-якій формі, здатних вплинути на результати роботи. Дослідження виконано без фінансової підтримки.

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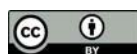
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