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# Peculiarities of Clinical Effectiveness of the Anti-Inflammatory Treatment in Childhood Asthma Depending On Airway Remodeling Risk

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**Abstract**

**Goal** of research is to assess the features and clinical effectiveness of basic protocol treatment of asthma in school-age children depending on airways remodeling risk.

**Material and methods.** To achieve the goal 116 children suffering from persistent bronchial asthma (BA) were examined in parallel groups selected by means of simple randomized sampling using the "experiment-control" method. Three clinical groups of observation were formed on the basis of detected concentrations of VEGF and MMP-9 in the sputum supernatant of the examined patients. The first clinical group that further is marked as a "high risk group" considering bronchial remodeling formation, the second group marked as a "moderate risk group" of bronchial remodeling and the third clinical group was marked as a "low risk group" concerning respiratory tract remodeling.

The bronchi lability was assessed using graduated jogging with inhalation of 200 mkg of salbutamol test and further

calculation of Bronchospasm Index (BSI, %), Bronchodilatation Index (BDI, %), and of Bronchus Lability Index (BLI, %). To obtain sputum the procedure of its inducing was performed by means of inhalation of serial hypertonic sodium chloride solutions, biological markers of bronchial remodeling in the sputum supernatant were determined in the following way: VEGF, MMP-9. The level of BA control and severity was determined by means of the following questionnaires: by ACT-test, GINA-test, clinical-instrumental evaluation (CIE) scale.

**Results and discussion.** The effectiveness of treatment control of children from the Compared groups was assessed during consistent 3 years using three different assessment scales (ACT-test (Asthma Control Test), clinical-instrumental evaluation (CIE), and GINA-2009 test). The effectiveness of basice treatment assessed according to different constellation tables with different level of sensibility and specificity prouves that the three-year treatment significantly succeeded only in children with low risk of bronchi remodeling. This is reflected in increasing number of controlled asthma cases. At the same time number of cases with partial and absent control changed circumstantial or didn't change at all.

According to our data, at the beginning of stady cases of Low Bronchi Lability in period of complete control of the disease were observed only in group of children with high risk of bronchi remodeling. Meantime, low bronchi lability cases were found in patients suffering from partially controlled asthma from all compared groups in the beginning or in the end of research. These results reliably illustrate increased bronchus rigidity in process of inflammation. Futhermore, in the above groups of patiens we found higher frequency of low bronchi lability with high concentration of Nitrogen Monoxide metabolite in exhaled air condensate in cases of non-complete control over the disease. Assessmen of effectiveness of Basic treatment shows hihger level of complete asthma control in patients with low risk of bronchi remodeling versus groups of high and moderate risk. Hence, effectiveness of the protocol controlling treatment is significantly lower in BA patients with risk of bronchus remodeling. Sign of bronchus inflammation, marked hyper-reactivity, and decreased lability of bronchi diminishing the treatment impact in this cases.

**Conclusions:** High or medium risk level of bronchi structural changes considerably reduces the effectiveness of protocol controlling treatment of patients with asthma. The results of treatment in those groups of children are even less significant in presence of bronchial inflammation, marked hyperreactivity, and decreased lability of bronchi. Long-term controlling anti-inflammatory treatment with inhaled glucocorticoids according to the de-escalation scheme is required for children suffering from asthma with high risk of bronchi remodeling.

**Keywords :** bronchial asthma, children, airways remodeling, sputum.

**Introduction**. Airway remodeling not only determines persistent irreversible bronchi obstruction, but also contributes to acute exacerbation of asthma and to its more severe course [1, 2]. Development of airway remodeling is usually associated with severe persistent asthma characterized by low lack of effect of anti-inflammatory treatment as well as by progressive decrease in ventilatory lung function due to its obstruction. Furthermore, they presume existence of a special subtype of a severe asthma resulting from airway remodeling. This subtype is characterized by prolonged disease course with persistent obstruction of lower respiratory tract [3-6].

At the same time, some researchers report evidence that persistent obstruction in severe asthma is possible without signs of significant structural changes of bronchi. Chronic airway inflammation (which is distinguishing but not the

only feature of asthma) in some susceptible patients causes development of persistent structural changes in bronchi, which are commonly referred to as remodeling. However, in some cases bronchi remodeling could be observed in the very beginning of asthma or even prior to clinical manifestation. That fact questioned the exclusive role of inflammation in alteration of bronchial structures [7-9]. Although the results of research applied to assess effectiveness of treatment and prophylaxis of persistent structural changes in bronchi are divergent, we still can make a conclusion that in most cases of asthma modern anti-inflammatory therapy can prevent remodeling, but is not effective in treatment of already existing one.

Glucocorticoids have an exceptional importance in basic anti-inflammatory treatment of patients with asthma. According to numerous literature data, steroids reduce the risk of bronchi remodeling due to its multiple effects on the key links in the cascade of structural changes [10, 11]. Furthermore, the high doses of steroids (≥800 mg of beclomethasone per day during sixth mounts or 1000 mg of fluticasone per day during sixth weeks) decrease number of vessels in vascular zone of bronchi and reduce the thickness of lamina propria of basal membrane [12, 13]. It is worth noting that addition of fluticasone at a dose of 200 mg per day to high doses of beclomethasone or budesonide does not affect the airway vascularization [14]. Use of inhaled glucocorticoids is probably the most effective in children aged 1 to 3 year since this is the period of the most often development of structural changes in bronchi. Glucocorticoids are proven to reduce the risk of bronchi remodeling or even cure it in cases of early prescription in mild intermittent asthma with reduced response to bronchomotor $\beta_2$-agonist test [15, 16]. At the same time, however, many researchers have questioned the validity of this positive steroid effect on airway remodeling [17-19]. From a practical perspective, it is important that glucocorticosteroids and long-acting $\beta_2$-agonists reduce the VEGF secretion. Thus, treatment aiming at inhibition the VEGF expression during inflammation process is very promising for prevention of bronchi remodeling [20]. From a different perspective suppression of VEGF secretion could lead to emphysema development since this growth factor inhibits the apoptosis of alveolocytes. The delicate balance between the protective action of VEGF on alveoli and its pathogenic effect on bronchi has not been yet thoroughly explored to date [21, 22].

Thus, the modern anti-inflammatory therapy is the only tool to decrease the risk of bronchi remodeling in patients with asthma to date.

**Goal** of research is to assess the features and clinical effectiveness of basic protocol treatment of asthma in school-age children depending on airways remodeling risk.

**Material and methods.** To achieve the goal 116 children suffering from persistent bronchial asthma (BA) were examined in parallel groups selected by means of simple randomized sampling using the “experiment-control” method. Patients were admitted to Pulmonology and Allergology Department of the Municipal Medical Establishment “Regional Children Clinical Hospital” in the town of Chernivtsi.

Three clinical groups of observation were formed on the basis of detected concentrations of VEGF and MMP-9 in the sputum supernatant of the examined patients. The first (I) clinical group that further is marked as a “high risk group” considering bronchial remodeling formation included 37 patients with the content of VEGF above 80 ng/ml, and MMP-9 – above 5,2 ng/ml in the sputum supernatant (including 67,6% of boys with an average age of 12,0±0,46 years). The second (II) group marked as a “moderate risk group” of bronchial remodeling included 41 patients with VEGF above 80 ng/ml in the supernatant, and MMP-9 – less than 5,2 ng/ml, or with the content of

VEGF less than 80 ng/ml, and MMP-9 – more than 5,2 ng/ml (including 61,0% of boys with an average age of 11,5±0,54 years). The third (III) clinical group included 38 BA children. This group was marked as a "low risk group" concerning respiratory tract remodeling. The concentration of VEGF in the sputum supernatant of those patients did not reach 80 ng/ml, and MMP-9 concentration – was not higher than 5,2 ng/ml (including 67,8% of boys with an average age of 11,2±0,52 years).

General clinical description of patients on the time of beginning of monitoring surveillance is set out in table 1. Statistical discrepancies between the I and the III groups according to place of residence have not so far been significant for validity of comparative analysis of results of comprehensive survey in this groups. However, this data were considered in further analysis.

**Table 1**

Duration of asthma in children in I group on the moment of the beginning of the study was 5,8±0,68 years, in II group – 4,4±0,68 years, and in the group of low risk of bronchial remodeling – 4,4±0,63 years (in all the cases P>0,05).

The distribution of BA according to degree of severity among the children from I clinical group was following: severe form occurred in 13,5% of patients, moderate – in 62,2% of children and mild persistent - in 24,3% of patients. In II clinical group a share of patients with severe form of the disease was 19,5%, moderate – 41,5% and mild – 39,0% of patients. In the group of children with a low risk of bronchial remodeling severe persisting course of BA was found in 23,7%, moderate – 34,3% and mild – 42,0% (for all the cases Pφ>0,05). Share of atopic form of asthma was 67, 6% in the I group, 56,1% in children with moderate remodeling risk, and 63,2% in patients from III group (for all the cases Pφ>0,05). Clinical form of asthma was mixed in rest of the children.

Thus, the groups of comparison were matched according to the main clinical characteristics.

The bronchi lability was assessed using graduated jogging with inhalation of 200 mkg of salbutamol test and further calculation of Bronchospasm Index (BSI,%), Bronchodilatation Index (BDI,%), and of Bronchus Lability Index (BLI,%).

To obtain sputum the procedure of its inducing was performed by means of inhalation of serial hypertonic sodium chloride solutions using Pavord I.D. and Pizzichini M.M. method [23]. Biological markers of bronchial remodeling in the sputum supernatant were determined in the following way: VEGF (vascular endothelium growth factor) – three-stage «sandwich»-variant of hard-phase immune enzyme analysis using mono- and polyclonal antibodies (reagents «VEGF-VectorBrest» A-8784, РФ), MMP-9 (matrix metalloproteinase-9) – by means of «sandwich»-ELISA method (reagents "Affymetrix eBioscience" BMS 2016/2/BMS2016/2TEN (Bender MedSystems, GmbH, Austria).

The level of BA control and severity was determined by means of the following questionnaires:

1) By ACT-test (Asthma Control Test), containing 7 questions (3 of them are answered by parents) for children under 11, and 5 – for patients over 12. Every answer was estimated from 1 to 5 points.

2) By GINA-test containing six questions with alternative answers. The absence of daily, nocturnal symptoms, physical restrictions, administration of rapidly acting β2-agonists less than twice a week and FEV1 higher than 80% were estimated in 1 point; the above characteristics and FEV1 less than 80% out of age norm were estimated in 2 points.

3) By clinical-instrumental evaluation (CIE) scale assuming answers to 7 questions estimated from 0 to 4

points, and the indices of FEV1 and peak volumetric rate (PVR).

The results obtained were analyzed by means of computer sets Statistica 6,0 StatSoft Inc. and Excel XP for Windows using parametric and non-parametric analysis methods. Value of the different factor mutual influence on the bronchi remodeling development was evaluated using cluster, multivariate, and regression analysis. In all the cases confidence interval was 95% (95% CI). The effectiveness of treatment was assessed considering the values of relative (RR), attributive risk (AR), and minimal number of patients (MNP) to be treated to achieve a positive result, odds ratio with determination of their 95% CI.

The research corresponds to requirements GCP ICH and to WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects and to Order of Ministry of Health of Ukraine No 690 from 23.09.2009. Protocol of children examination and informed consent of the patient form corresponded to the rules of biomedical investigations and were approved by the Local Bioethical Committee, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", as well as by the Local Medical Committee of the Municipal Medical Establishment “Regional Children Clinical Hospital” (Chernivtsi), in which the patients were treated. All the examinations were performed with prior informed consent obtained from the patients assuring their confidentiality.

**Results and discussion.** The effectiveness of treatment control of children from the Compared groups was assessed during consistent 3 years using three different assessment scales (ACT-test (Asthma Control Test), clinical-instrumental evaluation (CIE), and GINA-2009 test).

The CIE criteria included clinical manifestation of asthma as well as spirographic study data of disorders of obstruction-impaired bronchial ventilation function. According to CIE 10 and less points enabled to identify controlled BA, 11-16 points were associated with partially controlled BA, and poits higher than 17 – with uncontrolled course of BA (see table 2).

**Table 2**

Table 3 shows the results of asthma treatment according to Asthma-Control Test. The total score higher than 20 was indicative of a complete control achieved, from 16 to 19 – a partial control, 15 and less – absent control over the disease [24].

**Table 3**

The results of assessment effectiveness of controlling treatment in groups of children with different risk of bronchi remodeling range show the significant increasing in number of complete control achieved cases in III group only.

According to GINA-test the total score 5 and more was indicative of a complete control over the disease, 6-8 points – a partial control, and higher than 8 points – uncontrolled BA (see table 4).

**Table 4**

The results of GINA test show that the three-year controlling treatment significantly succeeded only in a group of children with low risk of bronchi remodeling (due to increasing in number of cases with complete control over the disease).

Therefore, the effectiveness of basice treatment assessed according to different constellation tables with different level of sensibility and specificity prouves that the three-year treatment significantly succeeded only in children with low risk of bronchi remodeling. This is reflected in increasing number of controlled asthma cases. At the same time number of cases with partial and absent control changed circumstantial or didn’t change at all. Since assessment of controlling treatment according to CIE

criteria appears more flexible, we use it to conduct further analysis.

Bronchial lability, bronchial hypersensitivity to direct bronchospasmogenic agents (like histamine) and inflammation are important substitute (indirect) criteria of asthma treatment effectiveness concerning bronchus remodeling. The intensity of the inflammation process could be assessed according to increasing of Nitrogen Monooxide metabolites in condensate of exhaled air.

Frequency of Low Bronchi Lability in response to graduated physical loading and salbutamol inhalation (BLI<13%) is set out in table 5.

**Table 5**

According to our data, at the beginning of stady cases of Low Bronchi Lability in period of complete control of the disease were observed only in group of children with high risk of bronchi remodeling. Meantime, low bronchi lability cases were found in patients suffering from partially controlled asthma from all compared groups in the beginning or in the end of research. These results reliably illustrate increased bronchus rigidity in process of inflammation.

Table 6 shows the frequency of increased concentration of Nitrogen Monoxide (above 40 mol/l) in exhaled air condensate depending on the effectiveness of Controlling Treatment.

**Table 6**

Given results suggest that cases with increased content of Nitrogen Monoxide in exhaled air occure more ofen with decreasing effectiveness of Controlling Treatment. This data indirectly supports the above assumption, that decreasing of bronchi lability is partially caused by inflammation.

To summarise, three-year controlling treatment was low effective for children with moderate and high risk level of bronchi remodeling. Futhermore, in the above groups of patiens we found higher frequency of low bronchi lability with high concentration of Nitrogen Monoxide metabolite in exhaled air condensate in cases of non-complete control over the disease.

Indices of effectiveness of Controlling treatment in children of high and moderate risk of bronchi remodeling in comparison with low risk group are given in table 7.

**Table 7**

Assessmen of effectiveness of Basic treatment shows hihger level of complete asthma control in patients with low risk of bronchi remodeling versus groups of high and moderate risk. In the meantime, there is a high risk of non-effective Controlling treatment in children from I and II groups (in comparison with III group) and that failure in treatment happened in every second-third child.

Indices of successful basic treatment in children with low bronchi lability (BLI <13%) (as it is one of the surrogate indices of bronchi remodeling) are set out in the table 8. According to these data the treatment of the patients with high and moderate risk of bronchi remodeling and with low lability of airways associate with absence of control during tree-year treatment. At the same time mentioned bronchi lability in patients with low risk of bronchi remodeling could serve as an indirect marker of successful controlling treatment. Apparently, it would be logical to assume that low bronchi lability shows its rigidity level as well as absents of hyperresponsiveness caused by airway inflammation.

**Table 8**

The data from table 9 (the effectiveness of controlling treatment in compared groups depending on content of Nitrogen Monoxide metabolites in exhaled air condensate (over 40 mkmol/l)) implicitly confirm the hypothesis above. Increasing of Nitrogen Monoxide metabolites in exhaled air could be the surrogate index of more manifested eosinophilic inflammation in bronchi. According to data from table 9, increased content of Nitrogen Monoxide metabolites in exhaled air of patients

with high and moderate risk of structural changes in bronchi shows the low effectiveness of basic treatment. Meanwhile in children with low risk of bronchi remodeling high concentration of mentioned compounds usually is a marker of successful treatment of asthma. To some extent, this can be explained by fact that basic anti-inflammatory treatment in case of combination of bronchi remodeling with inflammation reduces clinical manifestation of bronchoobstruction only insignificantly (due to decreasing of airway inflammation itself). However, in patients with low risk of bronchi remodeling reducing of the inflammation leads to substantial improvement due to elimination of reversible links of bronchoobstruction.

**Table 9**

Hence, effectiveness of the protocol controlling treatment is significantly lower in BA patients with risk of bronchus remodeling. Sign of bronchus inflammation, marked hyper-reactivity, and decreased lability of bronchi diminishing the treatment impact in this cases.

**Conclusions**

1. High or medium risk level of bronchi structural changes considerably reduces the effectiveness of protocol controlling treatment of patients with asthma. The results of treatment in those groups of children are even less significant in presence of bronchial inflammation, marked hyperreactivity, and decreased lability of bronchi.
2. Long-term controlling anti-inflammatory treatment with inhaled glucocorticoids according to the de-escalation scheme is required for children suffering from asthma with high risk of bronchi remodeling.

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Table 1

General Description of the Childrens Groups

| Clinical groups | Number of patients | Frequency, % | | | Age (years) |
|---|---|---|---|---|---|
| | | Gender | | Rural Dwellers | |
| | | Boys | Girls | | |
| I (high risk) | 37 | 67,6 | 32,4 | 67,6 | 12,0±0,46 |
| II (medium risk) | 41 | 61,0 | 39,0 | 61,0 | 11,5±0,54 |
| III (low risk) | 38 | 67,8 | 32,2 | 44,7 | 11,2±0,52 |
| Pφ,t | | >0,05 | >0,05 | I:III <0,05 | >0,05 |

Table 2

Effectiveness of Treatment Control in Children from the Compared Groups (according to Clinical-Instrumental Evaluation)

| Clinical groups | Number of patients at the beginning of study | Frequency, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | Full Control | | Partial Control | | No Control | |
| | | A* | B* | A | B | A | B |
| I group | 37 | 8,1 | 14,3 | 32,4 | 38,1 | 59,5 | 47,6 |
| II group | 41 | 27,5 | 21,4 | 15,0 | 21,4 | 57,5 | 57,2 |
| III group | 38 | 14,3 | 43,8 | 25,0 | 12,5 | 60,7 | 43,8 |
| P | | I:II <0,05 | I,II :III<0,05 | II:I <0,05 | I:III <0,05 | >0,05 | >0,05 |

*A – initial control level, B – control level after 3 years

Table 3

Trends in the Asthma Control Level in children the compared groups (according to Asthma-Control Test)

| Clinical groups | Number of patients at the beginning of study | Frequency, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | Full Control | | Partial Control | | No Control | |
| | | A* | B* | A | B | A | B |
| I group | 37 | - | - | 25,0 | 57,1 | 58,3 | 42,9 |
| II group | 41 | 25,6 | 33,3 | 17,9 | 33,3 | 56,4 | 33,3 |
| III group | 38 | 16,7** | 42,8 | 25,0 | 35,7 | 58,3 | 21,4 |
| P | | >0,05 | >0,05 | >0,05 | I:II,III <0,05 | >0,05 | I:III <0,05 |

*A – initial control level, B – control level after 3 years, ** III A:Б <0,05

Table 4

The Results of Controlling Treatment in Children from the compared groups (according to GINA)

| Clinical groups | Number of patients at the beginning of study | Frequency, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | Full Control | | Partial Control | | No Control | |
| | | A* | B* | A | B | A | B |
| I group | 37 | 3,1 | - | 34,4 | 37,5 | 62,5 | 62,5 |
| II group | 41 | 3,0 | - | 27,3 | 33,3 | 69,7 | 66,7 |
| III group | 38 | 8,8** | 14,3** | 28,9 | 21,4 | 58,8 | 64,3 |
| P | | >0,05 | - | >0,05 | I,II:III <0,05 | >0,05 | >0,05 |

*A – initial control level, B – control level after 3 years, * II A:IIIБ <0,05

Table 5

Frequency of Low Bronchi Lability (BLI<13%) in Children from the Compared Groups depending upon the Effectiveness of Basic Treatment

| Clinical groups | Number of patients * | Frequency, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | Full Control | | Partial Control | | No Control | |
| | | A** | B** | A | B | A | B |
| I group | 37 | 14,3 | - | 42,8 | 66,7 | 59,5 | 47,6 |
| II group | 41 | - | 16,7 | - | 16,7 | 100 | 66,7 |
| III group | 38 | - | - | 25 | - | 75 | - |
| P | | - | - | I:III <0,05 | I:II <0,05 | I:III >0,05 | >0,05 |

*In the beginning of monitoring, **A – at the beginning of the tree-year treatment, B – at the end of the tree-year treatment

Table 6

Frequency of Clinical Cases with Content of Nitrogen Monoxide more than 40 mol/l in Exhaled Air Depending upon the Effectiveness of Controlling Treatment

| Clinical groups | Number of patients * | Frequency, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | Full Control | | Partial Control | | No Control | |
| | | A | B | A | B | A | B |
| I group | 37 | 14,3 | - | 14,3 | 33,3 | 71,4 | 66,7 |
| II group | 41 | 20,0 | 11,1 | - | 22,2 | 80,0 | 66,7 |
| III group | 38 | 20,0 | 100,0 | 20,0 | - | 60,0 | - |
| P | | >0,05 | - | I:III>0,05 | I:II >0,05 | >0,05 | I:II>0,05 |

* A – initial control level, B – control level after 3 years

Table 7

Effectiveness of Patients Basic Treatment depending upon the Risk Level of Bronchus Remodeling

| Control Level | Compared Groups | Risk Reduction | | MNP* |
|---|---|---|---|---|
| | | Absolute Risk (ARR) | Relative Risk (RRR) 95% CI | |
| Full Control (CIE <10 points) | 1:3 | 4,0 | 8,7 (3,94-16,06) | 11,5 |
| | 2:3 | 8,6 | 18,7 (11,54-27,71) | 5,36 |
| No Control (CIE >17 points) | 3:1 | 19,0 | 45,1 (35,14-55,43) | 2,21 |
| | 3:2 | 10,2 | 30,6 (21,78-40,67) | 3,26 |

*MNP – minimal number of patients to be treated to achieve a positive result

Table 8

Effectiveness of Basic Treatment in cases of Low Bronchi Lability in children from the compared groups

| Control Level | Compared Groups | Risk Reduction | | MNP* |
|---|---|---|---|---|
| | | Absolute Risk (ARR) | Relative Risk (RRR) 95% CI | |
| Full Control (CIE <10 points) | 1:3 | 85,7 | 85,7 (77,21-91,95) | 1,17 |
| | 2:3 | 83,3 | 83,3 (74,48-90,05) | 1,2 |
| No Control (CIE >17 points) | 3:1 | 32,2 | 42,9 (33,04-53,25) | 2,3 |
| | 3:2 | 16,7 | 25,0 (16,9-34,71) | 4,0 |

*MNP – minimal number of patients to be treated to achieve a positive result

Table 9

Effectiveness of Controlling Treatment in Children from the compared groups

| Control Level | Compared Groups | Risk Reduction | | MNP* |
|---|---|---|---|---|
| | | Absolute Risk (ARR) | Relative Risk (RRR) 95% CI | |
| Full Control (CIE <10 points) | 1:3 | 41,7 | 55,6 (45,3-65,59) | 1,8 |
| | 2:3 | 74,9 | 99,9 (95,91-100,0) | 1,0 |
| No Control (CIE >17 points) | 3:1 | 46,7 | 70,0 (60,0-78,82) | 1,4 |
| | 3:2 | 35,5 | 64,0 (53,73-73,34) | 1,6 |

*MNP – minimal number of patients to be treated to achieve a positive result