Asthma.doc

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Progressive increase of number of patients with nonspecific lungs diseases, especially with respiratory allergoses, in pathogenesis of which allergy plays main role, and affection of respiratory organs are on the first plan in clinical picture, is seen from the second half of XX century. Respiratory allergoses - it's a collective concept. It unites allergic affection of upper respiratory tract (small forms of respiratory allergoses: allergic rhinitis, pharyngitis, tracheitis), bronchial asthma (BA), exogenous allergic alveolitis, allergic pneumonia, eosinophillicum pulmonary infiltrate.

Bronchial asthma is the widespread disease all over the world. Epidemiological investigations of last years are evidence of bronchial asthma presence in 4 to 8% of population, in children population this figure increases up to 5-10%. There are more than 100 millions of patients with bronchial asthma in the world. Hereditary predisposition in children with BA varies between 30 to 80% and more, that testifies to unfavorable prognosis as for BA morbidity in future.

Problems of BA diagnostics and treatment obtained international significance. In 1992 by initiative of Institution of Heart, Lungs and Blood (USA) work team of 18 experts from 11 countries prepared "Report on International Consensus of Asthma Diagnostics and Treatment" in which scientific achievements in disease's investigation are presented, and practical approaches of its diagnostics and treatment are determined. According to definition given in report, bronchial asthma - is genetically determined inflammatory disease of respiratory ways, which is characterized with:

- reversible obstruction of bronchi (variability of obstruction)
- presence of allergic process in mucous membrane of bronchi
- disease is interpreted not us episodic (attack-like) but as chronic process, taking place even in asymptomatic periods;
- hyper reactivity of bronchi - increased sensitivity of bronchial tree to various environmental factors.

There are 2 elements having important practical meaning for BA treatment in this definition:

- disease is interpreted not as episodic (attack-like) but as chronic process, taking place even in asymptomatic periods;
- asthma is defined as a disease having allergic inflammatory basis that results from presence of cellular infiltrates containing eosinophiles, tissue basophiles (mast cells), and lymphocytes in bronchial mucous membrane even in mild cases.

Henceforth strategy of therapy tactics was essentially supplemented in "Report of International Work Group at Risk and Safely of Anti-Asthmatic Therapy" in 1994. Work group of experts in 1998 elaborated national program of BA diagnostics and treatment in Kiev. Thus, BA remains actual, widely studied problem at present.

**Etiology of bronchial asthma.**

Sensibilization of an organism to various allergens plays prominent role in BA etiology. Increased sensitivity to allergens is often genetically determined. Inclination to IgE hyper production is transmitted as autosomal-recessive sign. A child has more chances to fall ill (40-60%) if both parents suffer from BA, if maternal heredity is charged - disease appears in 50%, if paternal - in 25% of cases. Polygenic type of heredity is assumed. It has been noticed that boys fall ill 2,4 times more often than girls. Exudative-catarrhal diathesis, child's exema, allergic reactions to food products and remedies, Quinke's edema and nettle-rash are seen in patients with BA trustworthy more often.

At present genes, which control IgE and cytokines production (they are localized on 14th chromosome - 14q12, 14q23, 14q32) and development of bronchial hyper reactivity (genes identified and localized on 5th chromosome - 5g23.31, as well as genes responsible for interleukins 3,4,5,9,12,13 synthesis, glucocorticoids and β2-adrenoreceptors) are mapped. Each from genetic predisposing factors increases probability of BA development, and their combination leads to high risk of disease's appearance at minimal assistance of environmental factors. Risk factors taking part in BA development in children are presented in the table 1.
Different allergens, invading an organism predominantly by inhalation way, are causative factors, which leads to BA attack development. Domestic allergens (especially domestic dust) play paramount role among non-specific allergens. This is compound as for composition and structure antigen, which contains non-specific components (lime, cement etc.) and organic particles, mainly products of domestic human activity: fibers of woollen and plant tissues, desquamated epithelial cell, human and animal's hair. To a considerable extent allergenicity of domestic dust is due to presence of great quantities of microorganisms Dermatophagoides pteronyssinus - from 500 up to 2275 in 1 g. They dwell mainly in bedclothes, soft furniture, carpets, human and animal's hair, and appear in the air during cleaning. Desquamated epithelium and secretion of sebaceous glands are nutrient medium for these mites. Mite itself is allergen as well as its excrements and dead mites.

Pollinergic allergens constitute the second group, as a cause of BA. Grass pollen is the most often cause. In Ukraine there are pollen of timothy-grass, in south regions - ambrosia, absinth, orach. Tree pollen provokes BA rarely: birch, maple, and nut-free. Flower pollen provokes sensitization even more rarely. Epidermal allergens is the next group. At present epidermal allergens are the most disquieting types. Epidermal allergens (domestic animals dusts, e.g. guinea-pigs, rabbits, rats - in diminishing frequency) are the most often causes of allergic diseases' development.

Role of food and drugs allergens in BA development is considered to be possible. Sensibilization to non-bacterial antigens doesn't exclude sensibilization to infectious ones - to microbial in particular (Chlamya) and often to fungal ones. From enormous quantity of natural fungi (about 100 000 kinds) allergic characteristics are detected in 350-300 kinds. The most widespread spore formastr of form fungi, which predominate in atmosphere air (Cladosporium, Alternaria) and in the air of premises (Aspergillum, Penicillum) are of greatest importance in BA etiology. Apart from it, other fungi (Mucor, Rhizopus etc.) having more local circulation, can also be the cause of sensibilization also. All of them discharge tremendous quantity of spores in the air, size of which are from 0,5 to 12 microns, due to it they invade respiratory ways with inspired air deeply.

There is certain sequence of sensitization's development.

Food allergens are the leading sensitization's factors for infants of first months of life, first of all there are milk allergy and formulas on its base, afterwards - yolk and protein of eggs, and seafood. So called asthma of milk precipitates exists in small children, it combines often with inborn hyper reactivity of airways. Sensibilization to food allergens diminishes sensitivity to inhalation, domestic and pollen allergens appears to 3-5 years. Monovalent allergy becomes polyvalent one. Invading of an organism with allergen, predominantly through inhalation, is the necessary condition of BA appearance. However major allergy of majority of patients consistently present in inspired air can't even harmful influence because they collide with natural resistance - system of local protection. Mucus membrane with its mucociliar apparatus (ciliate epithelium and discharge of mucous membrane glands, produced by serous and goblet epithelium cell) are the elements of local protection.

Allen particles, which were not excluded, under the action of various humoral substances. There are substances with antitoxic action: lysozyme, `actinidia' inhibitors (α-antitrypsin, α2-macroglobulin, antithrombin III), proteases and complement system. Antibodies - secretary fraction of γ-globulins and complement - protective antigen against invasion allergens simultaneously and locally with them. Summary effect of all-mentioned mechanisms of local protection provides excretion, neutralization, destruction and elimination of most of pollens presented in inhaled air. Defects in function of broncho-pulmonary apparatus local protection mechanism, beginning with disorders of cilia's mobility and worsening with immunologic inborn or acquired disorders, create the prerequisites for allergens invasion from airway's empty space inside the organism.

Factors negatively influencing upon various protective links condition, so called triggers, are the following - supercooling, dust loading and gas-laden atmosphere, smoking, and broncho-pulmonary infections.

In children recurrent respiratory infections precede appearance of BA attacks in 75-90% of cases. Respiratory viruses affecting airways epithelium provoke disorders of bronchial mucous membrane's protective function, that alleviates allergens invasion through disordered epithelium and promotes bronchial hyper reactivity formation.

**Clinics of bronchial asthma.**

BA exacerbation appears as a result of triggers action - ARI, allergens, physical and psychos emotional load, changes of meteorological situation, ecological impacts, intolerable products, vaccines and sera.

Attack of expiratory suffocation is typical. Attack appears more often at night or at 4-6 a.m. that is connected with circade rhythm of bronchial hyper reactivity. Patient's breathing becomes noisy, participation of abdominal press muscles, scalene muscles, sternomediastinoid muscle in respiratory act is seen. Supra- and substernal spaces, intercostal intervals fall in. A patient feels fear; as a rule he sits leaning with hands against shoulder girdles and is raised and moved ahead, the head is pulled in shoulders, chest is elevated and enlarged at the expense of front-back size. Great majority of children has frequent angustished dry cough, increased BP and tachycardia.

Objectively at the moment of attack broncho-shade of pervasive pulmonary sound, low borders of lungs, narrowing of relative heart dulness borders, plenty of dry diffuse "murical" whistling wheezes at expiration and less of them at inspiration are revealed. In some patients not dry whistling wheezes but moist rales predominate, which can be auscultated both at expiration, and at inspiration. In such case we are speaking about so called "humid asthma". At the moment of attack temperature is normal, but short-term fever may be seen in infants without infectious process. Duration of attack may vary from 30-40 minutes to several hours and even days (status asthmatic). Gradually facilitation takes place, patients begin to expectorate transparent foamy and than dense sputum, breathing becomes not so difficult, the face looks of normal color, but its edema may be preserved for a while. Epithelium cells, eosinophiles, macrophages and crystals of Sharko-Leiden may be revealed under microscope.

More 4 groups of symptoms are the diagnostic criteria of BA:

- symptoms of respiratory discomfort: dry cough, predominantly in the early morning hours or after contact with allergen, its appearance and intensification after physical load, inspiration of strong smells, at meteorological changes;
- symptoms of reversible bronchial obstruction: expiratory dyspnea, broncho-shade of pulmonary sound at percussion, dry whistling wheezes at expiration, and prolongation of expiration;
- extra pulmonary signs of allergy, burdened allergic anamnesis;
- eosinophilia in blood and/or sputum.

Severity of BA course is determined by degree of bronchial obstruction.

**Classification of bronchial asthma.**

Modern BA classification provides for separation of etiological disease's factor, degree and character of bronchial obstruction. Predominantly etiological factor of BA evaluation is reflected in International diseases classification (IDC) of X revision prepared by WHO, Geneva, 1992. Accordingly to IDC-X asthma is divided on:

- predominantly allergic (a rule, connected with established external allergen);
- non-allergic (including idiopathic, that is connected with unestablished internal factors);
- mixed (in presence of signs of first two forms);
- unspecified.

The main moment of any diseases' classification is its orientation at differentiated patient's treatment, and severity of disease is such criterion in BA. In 1998 Problematic commission of children pulmonology in Ukraine adopted BA clinical classification, which provides for following classifications:

**Factors predisposing to BA development:**

- atopia
- bronchial hyperreactivity
- heredity
- other predisposing local factors

**Factors aggravating action of causative ones:**

- viral respiratory infections
- pathological course of pregnancy
- in mother
- prematurity
- irrational feeding
- atopic dermatitis
- various pollutants
- tobacco smoke

**Causative (sensibilizing) factors:**

- domestic allergens (domestic dust, mites)
- epidermal allergens of animals, birds, cock-roaches, and other insects
- fungal allergens
- pollen allergens
- food allergens
- medicinal means
- viruses and vaccines
- chemical agents

**Factors provoking BA exaggeration - triggers:**

- allergens
- viral respiratory infections
- physical and psychosomatic loading
- changes of meteorological situation
- ecological influences (senesobiotics, tobacco smoke, strong smells)
- intolerable products, drugs, vaccines
Criteria of BA severity in children

<table>
<thead>
<tr>
<th></th>
<th>Intermittent bronchial asthma (1 step)</th>
<th>Persistence of bronchial asthma</th>
<th>Moderate degree of bronchial asthma (III step)</th>
<th>Severe degree of bronchial asthma (IV step)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of attacks</strong></td>
<td>3 - 4 times a month</td>
<td></td>
<td>Attacks of moderate severity with exact disorders of external respiration function</td>
<td>E v e r y day constantly</td>
</tr>
<tr>
<td><strong>Clinical characteristics of attacks</strong></td>
<td>Episodical, quickly disappearing, mild</td>
<td></td>
<td>Constant presence of symptoms, severe attacks, asthmatic status</td>
<td></td>
</tr>
<tr>
<td><strong>Night attacks, activity sleep disorders</strong></td>
<td>Absent</td>
<td></td>
<td>Almost every night, the child practically doesn't sleep</td>
<td></td>
</tr>
<tr>
<td><strong>Tolerance to physical load</strong></td>
<td>Not changed</td>
<td></td>
<td>Decreased</td>
<td>Essentially decreased</td>
</tr>
<tr>
<td><strong>Indices of FEV₁, PEF</strong></td>
<td>Not less than 80% of norm</td>
<td></td>
<td>60-80% of norm</td>
<td>Less than 60% of norm</td>
</tr>
<tr>
<td><strong>Changes of bronchial potency during 24 hours</strong></td>
<td>Not more than 20%</td>
<td></td>
<td>20-30%</td>
<td>More than 30%</td>
</tr>
<tr>
<td><strong>Characteristics of remission periods</strong></td>
<td>Normal values of external respiration function between exacerbations</td>
<td>Symptoms are absent, normal function of external respiration</td>
<td>Not complete clinical-functional remission (respiratory insufficiency)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of remission periods</strong></td>
<td>3 months and more</td>
<td>Less than 3 months</td>
<td>1-2 months</td>
<td></td>
</tr>
<tr>
<td><strong>Physical development</strong></td>
<td>Is not disturbed</td>
<td>Is not disturbed</td>
<td>Possibility of retardation and disproportion of physical development</td>
<td></td>
</tr>
</tbody>
</table>

BA exacerbation may proceed as acute attack or lingering condition of bronchial obstruction. BA attack – it's acute episode of expiratory dyspnea, difficult and/or whistling breathing and spastic cough at marked decrease of PEF that is exactly noted by patient and his associates.

Period of BA exacerbation - lingering course of attack's period characterized with prolonged breathing difficulties, which can last days, weeks and months; clinically marked syndrome of bronchial obstruction is present. Acute BA attacks of various severity can be seen in such condition (table 3).

The most severe form of BA is distinguished in separate group - status asthmaticus (SA) - that is connected obviously with peculiarities of clinical manifestations and medical tactics demanding immediate hospitalization of a patient to intensive care unit.

Non-arresting BA attack with duration more than 6 hours or absence of positive dynamics after 3 adrenaline injections with intervals of 20-30 minutes are criteria of status asthmaticus.

Table 3

Criteria for evaluation of attack's severity
Threat of respiratory standstill (status asthmatics)

* * * * *

Threat of respiratory standstill (status asthmatics)

<table>
<thead>
<tr>
<th>Signs</th>
<th>Light</th>
<th>Mild</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Physical activity</td>
<td>Preserved</td>
<td>Limited</td>
<td>Forced position</td>
</tr>
<tr>
<td>Talking speech</td>
<td>Preserved</td>
<td>Limited: separate phrases are pronounced</td>
<td>Jerky speech</td>
</tr>
<tr>
<td>Conscience sphere</td>
<td>Excitement sometimes</td>
<td>Excitement</td>
<td>Mental confusion, hypoxic coma</td>
</tr>
<tr>
<td>Respiratory rate*</td>
<td>Hurried breathing</td>
<td>Expiratory dyspnea is present</td>
<td>Tachypnea or bradypnea</td>
</tr>
<tr>
<td>Participation of auxiliary musculature, retraction of jugular fossa</td>
<td>Feebly marked</td>
<td>Marked</td>
<td>Strongly marked</td>
</tr>
<tr>
<td>Whistling breathing</td>
<td>Registered at the end of expiration as a rule</td>
<td>Marked</td>
<td>Strongly marked</td>
</tr>
<tr>
<td>Pulse rate*</td>
<td>Increased</td>
<td>Increased</td>
<td>Markedly increased</td>
</tr>
<tr>
<td>FEV1, PEF in % of norm or of best patient’s index*</td>
<td>More than 80%</td>
<td>Less than 60-80%</td>
<td>Less than 60%</td>
</tr>
<tr>
<td>PaO2</td>
<td>Norm</td>
<td>More than 60 Hg mm</td>
<td>Less than 60 Hg mm</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Less than 45 Hg mm</td>
<td>Less than 45 Hg mm</td>
<td>More than 45 Hg mm</td>
</tr>
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* Respiratory rate, pulse rate, FEV1, and PEF is necessary to repeat in dynamics of treatment.

Status asthmaticus is caused by deep block of β2-adrenoreceptors due to:

1. long term treatment of the disease with frequent exacerbations, that demanded wide use of sympathomimetics;
2. infectious processes in broncho-pulmonary system;
3. abrupt decrease of glucocorticoids in hormone-dependent patients.

Three stages of status asthmatics are distinguished:

I stage - stage of relative compensation. It is characterized by resistance to sympathomimetics and partially to other bronchodilators. It appears more frequently not at attacks, but gradually and lasts for several days. Pallor of skin, acrocyanosis, inspiratory dyspnea, swelling of chest, persistent cough and dry whistling wheezes on the background of weakened respiratory movement. Discorrespondence between intensity of respiratory wheezes, which can be heard at a distance and by direct lung’s auscultation, attracts attention. Tachycardias, elevated BP, narrowing of heart’s relative dulness borders due to lung’s emphysema, are registered.

II stage of status asthmatics is characterized by increasing respiratory insufficiency of obstructive type. Unusual severity of patient’s condition, pale cyanosis, acrocyanosis, marked tachycardia, dyspnea, liver’s enlargement, and edema. Practically total absence of wheezes at auscultation (“mute lungs”) or very few dry wheezes on limited region seem to be paradoxical. Cough disappears, pulse is frequent and weak, and BP is decreased. Formation of total bronchial obstruction syndrome is typical for this stage of status asthmatic that can lead to hypoxic coma if medical care is delayed. General excitement, sense of fear and asphyxia give place to prostration.

III stage of SA - hypoxemic coma and asphyctic syndrome develop due to decompensated respiratory process, acidosis and marked hypercapnia. Chuchalin A.G. distinguishes 2 types of hypoxic coma - quickly and slowly appearing ones. Prostration, early loss of reflexes and consciousness on the background of generalized cyanosis, increasing tachycardia and dyspnea, which losso inspiratory component, decreasing BP, swelling of cervical veins, and liver’s enlargement are typical for quickly proceeded hypoxic coma. Wheezes are not auscultated anymore, and so called “dead lungs” appear. The same symptoms are typical for slowly proceeded hypoxic coma also, but its appearance is protracted in time.

Bronchial asthma pathogenesis.

It is underlined in modern definition of BA that it is chronic inflammation of respiratory tract with widespread but variable obstruction. W.Osler (1892) pointed at 3 possible mechanisms of respiratory ways obstruction in asthma: spasm of bronchial smooth muscles, inflammation of alveolus, and disorders of nervous regulation of bronchial tonus. The supreme significance among these factors has been given to spasm of smooth bronchial muscles.

- Such opinion existed not only at the end of XIX century but during 75 years of XX century. At the beginning of 1980 year biopsy examinations of bronchial mucous membrane made by Finnish scientists initiated rapt morphological investigations of bronchi in BA. Histological examinations of bronchial mucous membrane’s biopsy revealed its eosinophilic and lymphocytic infiltration and enlargement of subepithelial basal membrane, i.e. marked inflammatory bronchial epithelium damage at all stages of BA, that changed ideas of disease’s origin.
- Inflammatory process forms 4 mechanisms of bronchial obstruction:
  - acute bronchospasm
  - subacute edema
  - chronic formation of mucous plugs
  - irreversible reorganization of bronchus.

Changes of immune answer play key role in BA pathogenesis. In 70-80 yy. of XX century it was believed that allergic reactions development was connected with decrease of Th2 lymphocytes - suppressors (CD8) functional activity.

At present it’s proved that organism’s sensibilization, which lays in the basis of IgE hyperproduction, is connected with changes of Th-1 and Th-2 lymphocytes activity ratio with increased activity of the former. Th-2 lymphocytes activation is caused first of all by influence of allergic stimuli; this process may take place both in antenatal and postnatal periods. Respiratory viral disease during pregnancy can be a cause of Th-2 lymphocytes activation with subsequent IgE hyperproduction in a baby.

Hyperproduction of IL-4, IL-6 and IL-13 connected with Th-2 lymphocytes activation in its turn promote IgE hyperproduction. Process of organism’s sensibilization is finished with fixation of specific relative to certain groups of allergens IgE-antibodies on target cells - mast cells, basophiles in shock organ, in particular in bronchial mucous membranes. Recurring exudation with causal significant allergens induces initialization of IgE-provoked mechanism (reaction of hypersensitivity of 1 type by Gell and Coombs classification) with activation of mast cells, their de-granulation and excretion of allergy mediators (histamine, SRS-A, neutrophile chemotaxis factor, eosinophile chemotaxis factor, prostaglandin F2a, leukotrienes LTD4, LTB4 and others), which realize development of early phase of allergic reaction in the form of bronchial obstruction syndrome, having features of typical BA attack (at the expense of M-cholinoreceptors activation and intensification of guanilatcyclase, increase of cGMP having powerful...
Pharmacokinetic and pharmacodynamic indices of inhaled glucocorticosteroids

In the process of organism’s sensitization and early phase of allergic reaction there is intensified creation of pro-inflammatory cytokines - IL-1, IL-2, IL-5, IL-8, IL-16, TNFα and adhesive molecules, contributing to inflow of cells, taking part in allergic inflammation development, to airways mucus membranes (secretion cytokines). Infiltration originated in bronchial mucous membrane and detachment of eosinophile cation proteins, cation lyosomal proteins of neutrophils, taking place during inflammation lead to bronchial airway’s epithelium damage, intensification of vascular permeability that promote edema and mucus hyperproduction, and - as a result - intensification of obstruction. The same mediators are able to provoke destruction of mast cells membranes repeatedly that is accompanied by excretion of biologically active substances and thus deferred or late phase of allergic reaction is formed, which is pathogenetic basis of bronchial hyper reactivity syndrome. Bronchial hyper reactivity’s development stipulates appearance of recurrent BA attacks not only at action of specific allergic stimuli but an non-specific ones also (physical load, negative and positive emotions, strong smells, chemical substances).

Allergic inflammation of bronchial tree’s mucous membrane and bronchial hyper reactivity connected with it stipulates recurrent and chronic course of the disease.

In 1968 y. American scientist A. Scintevani advanced hypothesis according to which constitutionally blocked block of β2-adrenoceptors (i.e. adenylcyclase) provokes bronchial hyper reactivity in BA that was proved in subsequent investigations. Along with constitutional conditionality of β2-adrenoceptors bronchial hyper reactivity may be connected with Ca2⁺ accumulation inside the cell. This fact was proved by registration of elevated Ca2⁺ concentration in blood cells in the period of BA exacerbation. Apart, changes of phospholipids metabolism with activation of blood phospholipid’s acid synthesis, lipid’s peroxide oxidation and phosphodiesterase, which destroys cAMP, point to disorders of biocomponents characteristics.

Provocative tests are used in a period of BA remission. Provocative inhalation tests with non-specific agents (histamine, metacholine), cold air, and ultrasound are necessary. X-ray of the chest and bronchoscopy are necessary. If BA is of endogenic origin.

Any changes on X-ray of the chest at interictal period of BA are absent. Increased transparence of lung’s fields and flattening of diaphragm’s cupola appear during attack. Segmental and subsegmental atelectasis may appear due to bronchial obstruction with mucous corks.

Total level of Ca in blood’s plasma is usually elevated in severe BA.

Bronchial lability as well as circadian rhythm of bronchial passability which is characteristic in patients with BA is connected with the influence of acetylcholine, that intensifies bronchial obstruction, is typical for many patients with BA.

Diagnostics of bronchial asthma

Diagnostics of BA is based first of all upon analysis of anamnesis and clinical manifestations with obligatory examination of FVD. It allows to evaluate degree of bronchial obstruction and its dynamics under the influence of treatment, and to determine more exactly both degree of attack’s severity and degree of severity of BA itself.

Total blood analysis is normal in uncomplicated BA. Sometimes negligible eosinophilia is present. ESR is normal as a rule, its elevation testifies to addition of infection.

Sputum’s examination. Macroscopically sputum is sticky, viscous and whitish. Cells of Clary’s epithelium, neutrophiles, a lot of eosinophiles as well as elongated bymidral crystals (Shariko-Leiden) released from eosinophiles are seen in sputum at exogenic BA. Amount of eosinophiles is less, neutrophiles predominate if BA is of endogenic origin.

When eosinophiles increase in sputum in BA the level of eosinophiles in blood is increased.

Aldosterone peak in the period of exacerbation and its decrease at BA remission stipulate recurrent and chronic course of the disease.

The total concentration of eosinophiles, neutrophiles, mast cells in sputum, and its percentage in sputum is important for diagnostics of allergic inflammation in BA.

Bronchial hyper reactivity is characterized in patients with BA by phenomenon of “morning PEF collapse”.

Metered-dose bronchodilators (MDBP) and daily bronchial lability (DBL) are the main methods for diagnostics of allergic inflammation in BA. Methodology of MDBP and DBL is mentioned below: 

\[
\text{MDBP} = \text{PEF norm} - \text{PEF min} \\
\text{DBL} = \text{PEF max} - \text{PEF min} \\
\]

- **PEF norm:** Peak-flowmetry is carried with use of individual peak-flowmeters, with construction of peak flow graph and indication of so called “zones of traffic lights” for every patient in order to treat them adequately. As normal meaning of PEF the mean best index, received in a period of remission or in a period of stable best patient’s condition is used.

One of the main points in BA diagnostics at early stages of disease is the exposure of non-specific bronchial hyper reactivity. Test with physical load is one of the most effective ones for it. PEF before load is measured, than physical load is given during 6-8 minutes. Immediately after load and in 5-10 minutes PEF at measured if PEF decreases more than 15% of initial meaning - test is considered to be positive.

Provocative tests are carried in period of BA remission. An index of bronchial obstruction’s reversibility is important diagnostic and prognostic criterion. FEV1 is measured, afterwards the patient inhales one dose of (β2-agonist, and indices of spirometry are repeatedly registered in 15 minutes. The following indices of bronchial obstruction’s reversibility are generally accepted:

- marked (25%) - moderate (15-24%) - slight (10-14%) - negative (10%)

Allergic rhinitis is connected with reaction of respiratory mucous membrane and bronchial hyper reactivity connected with it.

Allergic inflammation of bronchial tree’s mucous membrane and bronchial hyper reactivity connected with it stipulates recurrent and chronic course of the disease.

Differential diagnosis of bronchial asthma

Differential diagnostic of BA is made with conditions for which bronchoscopic syndrome is typical. Obstructive bronchitis, acute bronchiolitis; clinical features of acute respiratory infection, intoxication, absence of atopy are typical.

Foreign bodies of respiratory ways; patients mark precise time of condition’s worsening, which is manifested as acute asphyxia with or without cyanosis and following cough. X-ray of the chest and bronchoscopy are necessary.

Stenosing laryngotracheitis - clinical symptoms appear more frequently in the evening or at night on the background of catarrhal manifestations, fever, hoarse voice, inspiratory dyspnea, and typical barking cough.

Cardiac asthma - is seen in patients with inborn heart disease; enlargement of cardiac borders, murmurs, peripheral edema, liver’s enlargement, bubbling respiration, moist rales, and predominantly inspiratory dyspnea are typical.

Mucoviscidosis - retardation of physical development, absence of atopy, external respiration’s disorders of mixed type, recurrent pneumonia, diarrhoea with steatorrhea, and increased content of sodium and chlorides in sweat are present.

Exogonic allergic alveolitis - a disease provoked by inspiration of organic dust with various allergens which is characterized with diffuse affection of alveolar and interstitial lung’s tissue. Disorders of common condition, respiratory insufficiency, expiratory dyspnea, specific fine bubbling “cellophane” rales are
Flunisolide
inhaled glucocorticosteroids
Pharmacokinetic and pharmacodynamic indices of most often inhaled glucocorticosteroids

**Beclamethasone**
Stepped method of approach to basis prolonged BA treatment in children

Drugs choice and method of their use depend upon severity of the disease, which is indicated as case. The greatest effect of specific hyposensibilization is narrowed. Specific immune therapy is used in cases when contact with allergen is inevitable, and proceedings from possibility of systemic and local reactions on immune therapy indications for its use increasing concentration, is the basis of therapeutic effect. Injection of even minimal allergen’s doses can of blocking antibodies and exhaustion of reagents under influence of small allergen’s doses, injected in bronchospasm. Prolonged forms of theophylline are of wide use in moderate and severe BA.

Cholinolitics effectiveness.

Doses of anti-inflammatory drugs for BA treatment are shown in the table 5.

At present BA anti-inflammatory therapy is expanded due to appearance of leukotriens antagonist - Zafirlucast and Montelucast. These preparations have moderate protective action blocking receptors to leukotriens and thus preventing activation of target cells. They are used predominantly for treatment of mild and moderate BA.

Preparations eliminating bronchospasm, directly influencing upon non-striated bronchial muscles - bronchodilatatives (β-agonists, cholinolitics, myolitics) are also used in BA treatment.

At present sympathomimetics of selective action - β-agonists - are the most widespread and acknowledged. Salbutamol is the most selective one from β-agonists of short action. Salmeterol (Serevent) possesses the same place among preparations of prolonged action.

Doses of anti-inflammatory drugs for BA treatment are shown in the table 5.

**Table 6**

<table>
<thead>
<tr>
<th>Drug’s name</th>
<th>Trade name</th>
<th>Drug’s dose</th>
<th>Chronic treatment</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mild intermittent</th>
<th>Moderate intermittent</th>
<th>Severe intermittent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunisonide</td>
<td>Flixotide</td>
<td>Children from 2 to 10 years old - up to 8-10 mg/day</td>
<td>Children from 10 to 16 years old - up to 20 mg/day</td>
<td>400-600 μg</td>
<td>&gt; 600 μg</td>
<td>200-400 μg</td>
<td>&gt; 400 μg</td>
<td>&gt; 1000 μg</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Azmacort</td>
<td>Moderate doses</td>
<td>Moderate doses 2-4 times/day</td>
<td>Moderate doses 500-1000 μg</td>
<td>High doses &gt; 1000 μg</td>
<td>Moderate doses 200-400 μg</td>
<td>High doses &gt; 400 μg</td>
<td>High doses &gt; 1000 μg</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Fludrocort</td>
<td>Moderate doses</td>
<td>Moderate doses 400 μg</td>
<td>Moderate doses 800-1000 μg</td>
<td>High doses &gt; 1000 μg</td>
<td>Moderate doses 500-1000 μg</td>
<td>High doses &gt; 1000 μg</td>
<td>High doses &gt; 1000 μg</td>
</tr>
</tbody>
</table>

**Table 5**

<table>
<thead>
<tr>
<th>Drug’s name</th>
<th>Trade name</th>
<th>Oral bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunisonide</td>
<td>Flixotide</td>
<td>215%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Azmacort</td>
<td>6.13%</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Fludrocort</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Doses of anti-inflammatory drugs for BA treatment in children

Cholinolitics are used for liquidation of cholinergic bronchospasm’s components, which are connected with acetylcholine action. Ipratropium bromide (Atrovent) has lesser broncholytic action than sympathomimetics. In pediatric practice prescription of ipratropium bromide and combined preparations (cholinolytics + sympathomimetics: Combivent, Berodual) is especially perspective taking into account anatomic-physiological peculiarities of childhood. Influence of cholinergic innervation is known to be more pronounced in large bronchi. Preparations of euphylline have particular place among broncholytics. Theophylline acts directly upon bronchial muscles, inhibits phosphodiesetraterase, promotes accumulation of cAMP, intensifies synthesis and liberation of cathecholamines from adrenal glands, influences upon intracellular absorption and allocation of calcium, and serves as prostoglandin’s antagonist. Theophylline is of interest due to not only bronchodilatative effect but anti-inflammatory and immunomodulative action. Its immunomodulative action is explained by excretion’s inhibition of lymphokines from Th-l (interleukin-2, alpha-interferon, TNF) and Th-2 (interleukin-4, interleukin-5, interleukin-6).

Supportive doses of theophylline for effect’s achievement are twice as much as for liquidation of bronchospasm. Prolonged forms of theophylline are of wide use in moderate and severe BA.

Specific immune therapy is one of the most effective methods in BA treatment. Synthetic activation of blocking antibodies and exhaustion of reagents under influence of small allergen’s doses, injected in increasing concentration, is the basis of therapeutic effect. Injection of even minimal allergen’s doses can provoke disease’s exacerbation in children with high level of sensibilization and polyvalent allergy. Proceedings from possibility of systemic and local reactions on immune therapy indications for its use are narrowed. Specific immune therapy is used in cases when contact with allergen is inevitable, and medicinal treatment doesn’t control BA. The greatest effect of specific hyposensibilization is achieved in children with hypersensitivity to pollen allergens and mites of domestic dust.

BA treatment must be a long one. Choice of the drug, doses, and duration are individual in every patient and depends, first of all, upon severity of case and degree of symptoms expression in concrete case. Help system in accordance with BA severity anticipates stepped method of approach to treatment. Drugs choice and method of their use depend upon severity of the disease, which is indicated as corresponding step (table 6).
# Stepped method of approach to basis prolonged BA treatment in children

## Variant of therapy

### Intermittent asthma

<table>
<thead>
<tr>
<th>Step</th>
<th>Mild - step II</th>
<th>Moderate -step III</th>
<th>Severe -step IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory (pathogenetic) therapy</td>
<td>Inhaled corticosteroids (ICS) in average therapeutic doses (100-400 μg of budesonide)</td>
<td>β₂-agonist of prolonged action or theophylline o f delayed liberation. Prescription of fixed combination in one medicinal form is preferred: Seretid Evohaler 25/50 2 inhalations twice a day, or Seretid Discus 50/100 1 inhalations twice a day</td>
<td>High doses of ICS (more than 800 μg of budesonide)</td>
</tr>
<tr>
<td>Bronchodilators therapy for persistent prescription (is prescribed simultaneously with anti-inflammatory)</td>
<td>Chromoglicate sodium 4 times a day or nedocromil sodium 2 times a day</td>
<td>ICS in therapeutic doses (400-800 μg of budesonide)</td>
<td>I asthm symptoms are controlled not completely - add oral corticosteroids</td>
</tr>
<tr>
<td>Symptomatic therapy</td>
<td>ICS in therapeutic doses (100-400 μg of budesonide)</td>
<td>β₂-agonist of prolonged action or theophylline of delayed liberation. Prescription of fixed combination in one medicinal form is preferred: Seretid Evohaler 2.5 / 2.5 2 inhalations twice a day, or Seretid Discus 5.0 / 2.5 0.1 inhalations twice a day</td>
<td></td>
</tr>
<tr>
<td>Bronchodilators therapy for quick arrest of attack</td>
<td>Inhaled β₂-agonists of short action or theophylline of short action in a dose of 5-7 mg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all steps: after received steady BA control to continue the same treatment program during 3 months then to try gradually withdraw the drugs descending to the previous step etc. If you fail in achievement of BA control during 1 month you must ascend to the higher for severity step.

### Literature

1. International consensus reports on diagnosis and management of asthma. Publication № 92-3091, Bethesda, Maryland 20892, USA National Heart, Lung and Blood Institute, National Institute of Health, 1992.