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Non-controlled bronchial asthma: the contemporary condition of the problem

Key words: *bronchial asthma.*

Among all allergic diseases the most common is bronchial asthma (BA). In the world there are already about 300 million patients with this ailment and in the forecast by 2025 their number will increase by another 100 million. Chronization and deepening of the pathological process in asthma leads to a significant deterioration in the quality of life of patients, decrease their activity, and also causes growth disability and mortality from this illness. According to official statistics in Ukraine, almost 500 patients with asthma suffer from 100 thousand adults, and this disease is diagnosed annually for about 8 thousand people. According to experts, this does not correspond to the actual situation due to existing shortcomings in the diagnosis of this pathology, but in fact the number of patients is much higher [15].

According to modern concepts, BA is a genetically determined disease that is heterogeneous in its clinical manifestations, pathophysiological and immunopathological mechanisms, which is characterized by chronic inflammation of the respiratory tract. Common symptoms of asthma include attacks of breathlessness (shortness of breath), wheezing, chest compression and coughing. In patients, they may be of varying intensity and manifest in combination with variable airway obstruction (Global Initiative for Asthma) [10, 20]. That is why it is now generally accepted to isolate the phenotypes of asthma, which are defined as clinical characteristics of the course of the disease, as well as the features of the systemic and local (in the airways) inflammatory process [10, 20]. It allows to determine the individual characteristics of the patient and assign him personified treatment [6, 10, 13, 16–18, 25–27, 30]. However, there is still no consensus on the phenotyping of asthma [10, 13]. Different authors, when allocating certain of its phenotypes and subtypes, rely on clinical and morphological characteristics, the most significant triggers, the presence of concomitant pathology, as well as unique responses to treatment. Thus, in the materials of GINA [10, 13, 20], there are those phenotypes of asthma that can be easily identified. Distinguish: allergic asthma, non-allergic asthma, childhood asthma / recurrent obstructive bronchitis, late-on asthma, asthma with obstruction and a fixed rate of airflow, obesity asthma, occupational asthma, asthma, severe asthma, and BA-COPD overlapped syndrome. At the same time, the European respiratory community and the American Thoracic Community tend to focus more on a combination of clinical and pathophysiological aspects (so-called eosinophilic / neutrophilic asthma, severe allergic asthma, etc.). In relation to the duration and severity of the disease, specialists are diagnosed with early / childhood asthma, late-on asthma, asthma with frequent exacerbations, asthma with fixed bronchial obstruction, asthma with severe course («refractory», «brittle or lumbar», «steroid-resistant»). [12] Identification of markers of the dominant subtype of inflammation, allows to allocate its eosinophilic, neutrophilic, mixed and agranulocytic variants [10. 13. 20]. The presence of various triggers and some concomitant conditions determine certain features of the clinical picture and the course of asthma. It allows to separate into separate phenotypes: virus-induced asthma, asthma physical activity, aspirin asthma, smoker's asthma, asthma associated with obesity, asthma with obstructive sleep apnea, asthma associated with gastroesophageal reflux disease, and BA-COPD-Overlap [13]. Modern classifications of asthma determine not only the phenotypes of asthma but also the endotypes that they are responsible for. An endotype is a subtype

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of a disease characterized by a unique or distinct pathophysiological (pathogenetic) mechanism, which largely determines the response of patients with therapy [16, 18, 19, 25]. Yes, stand out:

– allergic asthma: eosinophilic, Th2-induced inflammation, with sensitivity to steroids, with sensitivity to anti-IgE, with sensitivity to interleukin-5 (IL-5), with sensitivity to anti-IL-4 / IL-13, with sensitivity to allergen-specific immunotherapy (ASIT);

– endogenous BA: eosinophilic, neutrophilic, associated with autoantibodies / superantigens, with steroid susceptibility, with steroid resistance;

– neutrophilic BA: with the activation of congenital immunity, with increased survival of neutrophils, with resistance to steroids, with anti-oxidant / macrolide susceptibility, with anti-TNF-α sensitivity;

– aspirin BA: eosinophilic, with a violation of the metabolism of eicosanoids / sensitivity to leukotrienes C4, D4, E4, with sensitivity to glucocorticosteroids, with sensitivity to anti-leukotriene drugs;

– BA with respiratory remodeling: with diffuse remodeling, with activation of endothelial-mesenchymal transformation (EMT), etc. [13, 16–18].

The personification of therapy taking into account the phenotypes and BA endotypes consists in directing treatment on the main immunopathological targets, which plays a leading role in the emergence and maintenance (persistence) of the chronic inflammatory process in each individual case – the so-called target therapy (from target – target, English). The development of targeted therapy for asthma was devoted to the numerous projects of the last 2 decades, thanks to which the arsenal of drugs was supplemented with anti-leukotriene, anti-IgE monoclonal antibodies, anti-cytokine monoclonal antibodies, and their appointment to patients with asthma was regulated by international [15, 17, 18, 22, 24, 27, 30] and national recommendations [7, 14]. Due to the fact that BA is a chronic inflammatory disease, the main purpose of modern treatment of patients today is not to cure them (because it is now a long-term future), but to achieve and maintain full control over the disease, namely, achievement and support good control of clinical symptoms over a long period of time, minimizing the risks of future exacerbations of asthma, fixed airway obstruction and unwanted side effects of treatment [7, 14, 20, 24]. According to the GINA (2014) criteria, achieving full control of the asthma implies [10, 20, 22]:

– absence of daytime symptoms or attacks twice or less once a week;

– no restriction of physical activity during the day,

– absence of asthma symptoms, which makes you wake up at night;

– the absence (or only twice or less per week) of the need for symptomatic treatment,

– normal or close to normal pulmonary function,

– absence of exacerbations.

However, despite all the advances in modern pharmacotherapy, even in the United States and Western Europe, the level of adequate control of asthma is low (only 8 to 30%), and the percentage of patients with uncontrolled asthma in different countries ranges from 40% to 67% [23]. According to reports from the Russian Federation, in this country, complete control of asthma occurs in only 5% 20% of patients. Currently, uncontrolled asthma is a special medical and social problem, which is associated with high disability, often severe life-threatening exacerbations, high risk of death of patients, as well as significant economic costs for health care (about 80% of all costs for treatment). bronchial asthma in general [9]. It is worth noting that among the experts there is a certain terminological anarchy, and often one concept is replaced by another. Thus, the term «difficult» («hard», «hard», «difficult»), asthma, difficult («heavy», «severe»), uncontrollable («uncontrolled», «difficult-to-treat») is often used in the scientific literature. «),» Resistant «(« resistant «,» therapy-resistant «),» refractory «asthma. Severe asthma is often identified with severe, severe – uncontrolled, and uncontrolled – with resistance or refractory. In fact, this is a completely different concept: severe BA – an asthma that requires 4–5 steps to maintain control, that is, the use of high doses of inhaled glucocorticosteroids / 2-agonists of prolonged duration, and uncontrolled – an asthma in which the appointment of adequate therapy does not lead before the control of the disease [12, 13, 20]. In turn, the resistant or refractory is considered to be one of the components of uncontrolled bronchial asthma. «Labor» or «heavy» BA in general combines several phenomena and different characteristics, and the general feature of them is that they are all threatening to life. Such terminological confusion essentially complicates both the diagnosis of asthma and the choice of adequate therapeutic tactics [2]. In order to diagnose uncontrolled asthma by experts from the European Respiratory and American Thoracic Community in 2014, the following criteria were proposed:

1. Insufficient symptom control: questionnaires ACQ-5> 1.5, AST <20.

2. Frequent severe exacerbations: 2 or more courses of systemic glucocorticosteroids (GCS) for more than 3 days each year in the previous year.

3. At least one hospitalization, treatment in the intensive care unit, use of respiratory support during the previous year.

4. The volume of forced exhalation for 1 second (FEV1) is less than 80% due to the administration of bronchodilators.

Reasons that can be explained by the lack of control of asthma, are divided into endogenous and exogenous. Exogenous factors include:

– inadequate basic therapy, which is often associated with inadequate qualifications of the doctor, or underestimation of the patient's condition due to the lack of monitoring of clinical and functional parameters, or the misconception of the patient about his ability to achieve control of asthma,

– low compliance

– permanent action of triggers.

The endogenous causes include:

– pharmacogenetic features,

– Reduced sensitivity to glucocorticosteroids

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– genetically determined individually high rates of development of inflammation,

– uncontrolled hyperreactivity of the bronchi.

Among patients with BA refractory to traditional therapy was noted in 5% –20% of patients. They are more likely to seek medical assistance than others. Exogenous (external) causes dominate, however, in reality, these two types of causes often complement each other. Among patients with severe asthma with signs of therapeutic resistance in 20% of cases, glucocorticosteroid resistance is diagnosed, 15% to beta 2 agonists, and 40% to leukotriene receptor antagonists (APL). Almost 10% of patients with a severe course of asthma do not correspond to traditional treatment regimens, note the high incidence of exacerbations, visits to doctors and hospital admissions [9].

A thorough diagnostic examination of patients with asthma with its uncontrolled course allows them to be classified into one of the following three categories:

1. Asthma that is potentially curable, but there is a barrier to it, such as prolonged smoking, constant allergen exposure, or non-compliance with the treatment regimen.

2. Asthma with associated diseases, in the presence of other factors that contribute to general symptoms of the patient, such as dysfunctional breathing, chronic rhinosinusitis, nasal polyps, bronchiectasis, dyspnea or airway obstruction, uncontrolled gastroesophageal reflux disease (GORD), dysfunction of the vocal cord or tracheobronchomania.

3. Heavy refractory asthma – this is an asthma that really does not respond to standard therapy, especially the effects of GCS. These patients have persistent symptoms, frequent exacerbations and severe obstruction of the respiratory tract, even when receiving high doses of inhaled corticosteroids.

Uncontrolled asthma is represented by three main phenotypes:

1. Chaotic unstable or brittle asthma [9, 11, 23, 26, 28].

2. Chronic complicated asthma with constant bronchoconstriction.

3. Fatal asthma.

Among subtypes of uncontrolled asthma distinguish:

– a lumbar (fragile) asthma,
– night asthma
– asthma steroid resistor
– steroid-dependent asthma,
– asthma with fixed broncho-obstruction,
– an asthma-induced infection
– premenstrual asthma
– acute severe asthma
– the status of asthmatics
– fatal asthma.

The lacunae of asthma is diagnosed in patients with severe and unstable asthma, which exhibit a wide variability in peak expiration velocity (PEF or peak expiratory flow), despite high doses of inhaled steroids. Type 1 of frail asthma is characterized by a broad, persistent and chaotic variability of PCV (less than 40% of daily variability over 50% of the time for at least 150 days), despite strong drug therapy. Blast type 2 includes sudden acute attacks without an apparent trigger and a duration of less than 3 hours in patients with apparently normal respiratory function or satisfactory disease control. Steroid-resistant asthma is diagnosed in rare patients receiving high doses of steroids (10–14-day prednisolone ≥ 20 mg twice daily) but the improvement from baseline FEV1 does not exceed 15%.

Steroid-dependent asthma is defined as asthma, which can be controlled only with the use of high doses of oral steroids.

Acute and severe asthma is diagnosed in patients with acute or subacute exacerbation of the disease, which is accompanied by shortness of breath, difficulty in the chest and a pronounced decrease in lung function.

Asthmatic status is characterized by the emergence of acute respiratory failure, which can lead to death (fatal asthma).

It is noteworthy that some of the phenotypes / subtypes of uncontrolled asthma and severe BA coincide (see table): asthmatic status, fatal asthma (asthma), asthma (asthma).

Night asthma has an early morning immersion and a double fall.

Premenstrual asthma is an unstable asthma that occurs 2 to 5 days before menstruation.

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The results of therapy and the achievement of control are often influenced by comorbid (concomitant) diseases that may predispose to treatment, and also determine the phenotype of the disease. The most commonly occurring comorbid states in asthma are diseases of the upper respiratory tract (allergic rhinitis, sinusitis), respiratory infections, chronic obstructive pulmonary disease, psychopathological conditions, obesity, gastroesophageal reflux disease, hormonal disorders, atopic dermatitis, and nicotine addiction. The presence of obesity in patients with asthma associated with a higher degree of severity of its course and a decrease in the effectiveness of therapy with the use of IGS, which significantly impedes the achievement of disease control. Thus, uncontrolled BA combines various clinical, functional and pathophysiological phenotypes of the disease [8, 9], which is associated with different mechanisms of its formation and therefore requires different approaches to diagnosis and prognosis, which can be used both independently and in various combinations. To do this, use questionnaires

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Table 1. Characteristics of uncontrolled and severe bronchial asthma

Characteristics of bronchial asthma	
Неконтрольована	Тяжка
Definition	
– It is an asthma where the appointment of adequate therapy does not lead to the establishment of disease control	– It is an asthma that requires 4–5 steps to maintain control, ie use of high doses of inhaled glucocorticosteroids / DDBA
Criteria	
1. Insufficient control of symptoms: questionnaires ACQ> 1.5, AST <20.	1. Daily breathlessness (in the absence of adequate treatment)
2. Frequent severe exacerbations: 2 or more courses of systemic glucocorticosteroids (GCS) for more than 3 days each in the previous year.	2. Common nocturnal symptoms (in the absence of adequate treatment)
3. At least one hospitalization, treatment in the intensive care unit, use of respiratory support during the previous year	3. Frequent exacerbations (in the absence of adequate treatment)
4. The volume of forced exhalation for 1 second (FEV1) is less than 80% due to the administration of bronchodilators.	4. Visual disturbance of the function of external respiration: FEV1 less than 60% of the proper, daily variability of PEF (over 30%)
Phenotypes	
1. Chaotic unstable or brittle asthma	1. Asthmatic status or severe acute asthma (acute severe asthma or status asthmaticus)
	2. Fatal asthma
2. Chronic complicated asthma with constant bronchoconstriction	3. Sudden hard asthmatic attack
	4. Slow asthmatic attack
3. Fatal asthma	5.Nestrable (crush) asthma (brittle asthma)
	6. Chronic severe asthma

(AST-test, ACQ-5), spirometry and pycthrometry determine the parameters of the external respiration, perform an analysis of induced sputum (which determines its cellular composition, levels of cytokines, other mediators and soluble intercellular interactions molecules, etc.), condensate is studied the air exhaled by the patient (determine the concentration of gases, individual biochemical parameters, the content of cytokines, etc.), carry out the phenotyping of lymphocytes, test blood serum for the content of immunoglobulins, the compartment immune complexes, cytokines, etc., as well as genetic and pharmacological studies [1, 3, 5, 7, 8, 9, 14].

Each of the listed asthma examination methods used to diagnose and predict its uncontrolled course, to identify causes and to determine the mechanisms of therapeutic resistance is not perfect, has its advantages and disadvantages. Often, such a survey requires quite a long time and significant material and technical resources and financial costs. However, the correction of therapeutic tactics in the case of proven resistance to pharmaceuticals makes it possible for such a patient to avoid their appointment, to select effective medicines, their doses and regimens and to speed up the achievement of desired control of the disease.

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