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СОВРЕМЕННОЕ ПРЕДСТАВЛЕНИЕ О ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЕ

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Modern Understanding of Severe Bronchial Asthma

Резюме

В обзоре приведены современные данные о тяжелой бронхиальной астме. Частые обострения астмы значимо снижают качество жизни пациентов, становятся причиной потери трудоспособности, инвалидизации и летального исхода. Гетерогенность тяжелой бронхиальной астмы укладывается в понятия фенотипа и эндотипа, идентификация которых в клинической практике имеет ограничения, но является необходимой для персонализированной терапии. Анализ литературы, отражающей опыт в ведении данных пациентов, необходим для формирования целостных представлений о тяжелой бронхиальной астме и разработки путей оптимизации терапии.

Ключевые слова: *фенотип, эндотип, тяжелая бронхиальная астма*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The review provides data on severe bronchial asthma. Frequent exacerbations of asthma significantly reduce the quality of life of patients, cause disability, disability and death. The heterogeneity of severe bronchial asthma fits into the concepts of phenotype and endotype, the identification of which in clinical practice has limitations, but is necessary for personalized therapy. Analysis of the literature reflecting experience in patient data management is needed to form holistic perceptions of severe bronchial asthma and develop ways to optimize therapy.

Key words: *phenotype, endotype, severe bronchial asthma*

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AV — artificial ventilation, BA — bronchial asthma, BMI — body mass index, COPD — chronic obstructive pulmonary disease, CT — computed tomography, FAO — fixed airflow obstruction, FEV_1 — forced expiratory volume in 1 second, FVC — forced vital capacity, GCs — glucocorticosteroids, GERD — gastroesophageal reflux disease, PFT — pulmonary function test, SBA — severe bronchial asthma.

Introduction

Despite considerable progress in medication treatment, uncontrolled bronchial asthma (BA) remains the main challenge in managing patients with this disease. Patients with severe bronchial asthma (SBA) make up a special group among patients with no disease control. GINA Steps 4 and 5 therapy is ineffective despite high compliance with treatment, correct inhalation technique and management of comorbidities. Therefore, a thorough analysis of the pathogenesis and clinical features of BA course is required. The analysis of literature sources reflecting the experience in managing these patients is essential to form a comprehensive idea of SBA and develop methods to improve treatment.

Epidemiology and socio-economic burden of SBA

Frequent BA exacerbations significantly reduce the quality of life of patients, resulting in labor capacity loss, disability and death [1–3]. Management of patients with BA in developed countries accounts for about 2% of public health costs [4]. In particular, 12% of patients admitted to the emergency room of large hospitals are the patients with BA exacerbation. The socio-economic burden of BA increases in proportion to the severity of this disease. It is known that more than half of the funds (according to some data, over 80%) allocated for BA management overall are spent on treating patients with severe BA [2]. The numerous studies devoted to the pharmacoeconomic search for SBA control methods also highlight the existing problem. However, the amount of financial contributions is not a guarantee of their effectiveness [4].

There is evidence that socio-economic consequences of SBA in Japan are lower than in European countries [5]. This is due to healthcare organization and the geographical features of the country that allow providing access to specialized medical care equally for the entire population of the country. In the United States, epidemiological studies are being conducted to analyze environmental and social factors that affect the prevalence of asthma, as well as its racial features [6]. The number of attacks in adults was found to depend on income: the patients with an income of 250% of the poverty datum line were more likely to report the onset of symptoms than the patients with an income of 450% of the poverty datum line.

According to the Federal State Statistics Service (Rosstat), more than 1 million people were diagnosed with bronchial asthma in the Russian Federation in 2014; the mortality rate was 1.3% [7]. About 6.9% of adults and 10.9% of children in our country suffer from this disease [2]. In 2014, a national register of patients with SBA was created. The analysis of information in this register allows optimizing the management of such patients. According to a clinical trial conducted in Russia, patients with SBA constituted 14–20% of all patients who initially sought medical attention [2].

Elderly patients are undoubtedly a special group among patients with SBA. The severity of disease in this group of patients is associated with a large number of comorbidities and a long history of asthma. In one study, Joe G. Zein et al. (2015) suggested that the severity of asthma in elderly patients is associated primarily with age-related changes in the lungs [8]. The following was discovered: the dependence between the duration and severity of asthma was found in young patients, however, it was not identified in elderly patients; the risk of SBA increases by 7% every year between the age of 18 and 45; however, after the age of 45, no such correlation was observed. Gender-related differences were described: after the age of 45, the disease severity in men depends on BA duration, whereas such correlation is not characteristic for women of this age group. The authors attributed the differences to the fact that oxidative stress reactions in young individuals are more intense, accelerating age-related changes in the lungs, and the functional activity of inflammatory cells in elderly patients is significantly reduced. The authors emphasize that age-related characteristics of this disease should be analyzed due to the growing elderly population.

Uncontrolled and true severe bronchial asthma

The uncontrolled course of this disease has remained remains the main challenge in the management of patients with bronchial asthma (BA) for a long time. According to GINA-2020, uncontrolled asthma has one or both of the following signs [1]:

1) Poor control of symptoms.
2) Frequent exacerbations (≥ 2 per year) that require systemic glucocorticosteroids (SGCs), or one exacerbation that requires hospitalization.

Patients with uncontrolled asthma include both patients with difficult-to-treat asthma and patients with true severe asthma. It is critical to distinguish between these terms since the management of patients will be different depending on the particular group to which they belong. In the case of patients with difficult-to-treat BA, the disease course remains uncontrolled despite the treatment according to GINA Steps 4 and 5. The diagnosis of severe bronchial asthma (SBA) is a subgroup of difficult-to-treat BA and can be made in case of uncontrolled disease course despite appropriate therapy, high degree of compliance, correct inhalation technique, and the management of comorbidities.

The prevalence of SBA is 3–10% [1], while disease control is generally not achieved in about 50% of BA patients [2, 9]. In one study conducted in the Netherlands, the prevalence of difficult-to-control asthma that required treatment according to Steps 4 and 5 was 17.4%. However, only 20.5% of patients in this group complied with the correct inhalation rules and demonstrated good compliance. Therefore, they were classified as an SBA group that included only 3.6% of the entire patient population [10]. In other words, in most cases of uncontrolled asthma, modifiable factors can be found that can help improve the course of the disease.

It is confirmed by a trial conducted in Denmark, where only 12% of patients with difficult-to-control disease met SBA criteria [11]. The authors of this trial also emphasized that a clear distinction between SBA and difficult-to-control BA can be a major challenge in real clinical practice. The group of patients who could not be certainly referred to a particular category constituted 32% of patients with uncontrolled BA. This group included patients who performed inhalation procedures correctly and had good compliance with treatment. At the same time, the impact of trigger factors persisted, and no control of comorbidities was achieved. In addition, this "uncertain" group also included patients diagnosed with BA only based on clinical data with no objective evidence of airflow variability. The importance of multidisciplinary management of patients with difficult-to-control asthma is emphasized since the lack of control of comorbidities irreversibly worsens BA course. The authors raise the question of the need for consensus on the duration of managing comorbidities before starting biopharmaceuticals. SBA and difficult-to-treat BA should be distinguished primarily to justify targeted therapy [11].

The study of A-N. Van Der Meer et al. (2016) demonstrated that among the patients with severe BA admitted to a specialized center for BA management, only 17% of patients needed targeted therapy [12]. For 83% of patients, after a multidisciplinary and multivariate assessment, an individual management plan was drawn up and submitted to the attending pulmonologist. In one Belgian study [13], only 24% of patients treated with omalizumab met all SBA criteria, according to national guidelines. Those were the patients who regularly received basic treatment and had two severe exacerbations during such treatment over the previous year. It is noteworthy that omalizumab therapy was more effective in patients who met all SBA criteria. For example, the number of patients who needed GCs decreased by 22% in the group of SBA patients compared with 8% in the group of patients with difficult-to-treat BA. Similar results were obtained for the number of hospitalizations and admissions emergency care departments [13].

It should be noted that SBA is a retrospective diagnosis [1]. According to the ERS/ATS (The European Respiratory Society / American Thoracic Society) joint recommendations, a specialist should observe the patient for at least three months in order to adjust modifiable factors and verify the diagnosis definitively [14]. It is also important to take into consideration that the severity of disease can change; therefore, disease control in patients with BA should be assessed [1].

SBA is advisably diagnosed sequentially by answering the following questions [1, 15, 16]:

1. Is the diagnosis correct?
2. What is the severity of the disease?
3. Is the treatment optimal?

Then a multivariate assessment of the clinical case is required, which includes the identification and management of comorbidities, taking into consideration social conditions and environmental factors, determining asthma phenotype, and assessing the individual features of the patient [16]. All this results in an individual plan for the management of a BA patient.

For each patient not responding to high-intensity therapy, other diseases should be ruled out and the diagnosis of BA should be confirmed. According to various data, the frequency of an alternative diagnosis in SBA cases ranges from 12 to 50% [17]. Diseases with symptoms similar to those of asthma include chronic obstructive pulmonary disease (COPD), tracheobronchomalacia, central type lung cancer, obstructive sleep apnea, bronchiectasis, allergic bronchopulmonary aspergillosis, tuberculosis, cystic fibrosis, alpha-1 antitrypsin deficiency, vocal cord dysfunction, obliterative bronchiolitis, congestive heart failure, eosinophilic lung diseases [18]. In particular, 70% of BA patients reportedly have vocal cord dysfunction. Allergic bronchopulmonary aspergillosis is found in 2–32% of patients with asthma. Even

though most of these patients respond well to treatment with GCs, antifungal agents should be used in some cases of steroid resistance.

Disease history, age at BA onset, typical symptoms, their frequency, the severity of exacerbations, and association with comorbidities are subject to analysis. It is noteworthy that the risk factors for exacerbations differ depending on disease severity. In the 2018 study, Kang H-R. et al. demonstrated that, in contrast to moderate asthma, age and comorbidities (except for allergic rhinitis) in SBA did not affect the frequency of exacerbations [19]. Regardless of disease severity, the administration of GCs was a risk factor for exacerbations, and the frequency of hospitalizations in the previous year was more important for patients with SBA. This study also demonstrated the increasing role of compliance with medication treatment depending on disease severity.

Special questionnaires can help assess the patient's condition. However, according to an Australian study, their use in actual clinical practice is limited: for example, only 31% of physicians used a questionnaire to assess BA control [20]. The subjective evaluation of control by both the physician and the patient generally does not match the results of the asthma control test (ACT) in about a third of cases [21]. Notably, this value is higher among patients receiving treatment Steps 4 and 5 therapy: 41% of patients who received Step 4 therapy and 48% of patients who received Step 5 therapy considered their asthma to be controlled, despite the fact that ACT score was less than 20, which corresponded to uncontrolled asthma. The same trend is observed among health care professionals. Physicians tend to underestimate the severity of the condition of patients with severe and difficult-to-treat BA.

Questionnaires with sensitivity of 80–90% seem to be the most cost-effective method to evaluate comorbidities [15]. Therefore, it is possible to make an individual plan of patient's assessment, and recommend consultations on an interdisciplinary basis, to avoid excessive health care costs [15].

The variability of airflow obstruction is an integral part of the diagnosis, although it cannot always be proven in cases of SBA. Maximum doses of albuterol (4–8 inhalations) are considered justified in order to detect a 12% increase in forced expiratory volume in 1 second (FEV_1) [15].

When confirming the diagnosis of SBA, the optimality of the treatment should be evaluated. In several cases of SBA, additional therapy (tiotropium bromide, macrolides, antifungal therapy) is prescribed, right up to the use of expensive biological agents [20]. At this stage it is critical to evaluate inhalation technique and the degree of compliance to avoid unnecessary ramping up of treatment and lower the risk of adverse events.

Patients with SBA require a multidisciplinary approach, as well as comprehensive and systematic assessment. The task of an interdisciplinary team is to identify patients with a high risk of hospitalization, adjust risk factors, and provide long-term care. In the 2016 study, Hannah Burke et al. demonstrated that such an approach reduced the number and duration of hospitalizations in patients with frequent BA exacerbations [22]. Improved quality of life and disease control were also reported [16]. A multidisciplinary approach requires specific knowledge and skills. Phenotyping and prescription of targeted therapy in BA were implemented in practice relatively recently; therefore, special attention should be paid to the training of medical personnel [20].

Non-drug factors in the management of patients with SBA

Properly selected therapy does not ensure optimal disease control. BA management is a dynamic and complex process, where the active participation of both the physician and the patient is important [16, 23]. Medication treatment is the key in the management of BA patients. However, it is difficult to achieve success with no proper attention to educating the patient, developing the right ideas about the disease and the goals of treatment, as well as correcting other non-drug factors such as continued exposure to the trigger, untreated comorbidities, obesity and smoking [1, 9].

The importance of non-drug factors was demonstrated in the study conducted by Hedenrud T. et al. (2019). It revealed that BA patients face challenges throughout all stages of treatment [23]. In this study, patients were interviewed using a special questionnaire. Basic problems included the inaccessibility of medical care (difficulties in making an appointment with a physician, lack of required medicines in pharmacies), as well as the lack of proper awareness of patients about the signs of their disease and the goals of treatment. The forgetfulness of patients and difficulties in inhaling drug products also play a certain role. Future studies are expected to include quantitative evaluation to define the prevalence of certain factors in the population of BA patients and identify the relationship between these problems and the socioeconomic status of patients [23].

The most common problems hindering disease control are incorrect inhalation technique (80%) and poor compliance (50%). About 50% of patients make mistakes when using a dry-powder inhaler; this figure reaches 80% in metered-dose inhalers [24]. Proper inhalation technique minimizes side effects that may be caused by poor compliance [25]. For example, the study performed by A.S. Melani et al. (2013), which included more than 1600 patients, showed that at least one critical error in inhalation technique, regardless of the type of inhaler, was associated with increased emergency department visits, number of hospitalizations, and the prescription of SGCs [26]. There is a direct relationship between inhalation technique and treatment success and, therefore, the

patient's satisfaction and their sense of a positive effect of the treatment, which improves therapy compliance [26].

In a study conducted by Lia Jahedi et al. (2017), patients with correct inhalation technique had better awareness of their disease and motivation for treatment, which underlines the importance of awareness-raising when managing BA patients [27]. Unfortunately, only 28% of physicians regularly assess inhalation technique when seeing patients, although according to the literature, a physician should give instructions to the patient at least three times and clearly demonstrate all stages of inhalation [24]. It is regular assessment and adjustment of skills that can exactly improve the control of disease symptoms and the quality of life of patients [26].

SBA clinical profile and phenotypes

The group of patients with SBA is heterogeneous. While standard therapy is effective in most patients with mild to moderate asthma, the management of a patient with severe asthma requires a case-by-case approach [28]. Such patients require targeted therapy, taking into consideration the disease phenotype. Phenotype means visible features of an organism attirbutable to the interaction of its genetic component and environmental factors [29]. The Clinical Guidelines "Bronchial Asthma" of the Ministry of Health of the Russian Federation identify five SBA phenotypes [30]:

– allergic BA,
– BA with fixed airflow obstruction (FAO),
– non-allergic BA,
– late-onset BA,
– BA with obesity.

Each phenotype has its own specific clinical, functional and laboratory features. However, according to the study performed by Sergeeva G.R. et al. (2015), in 83% of cases one patient has the signs of two or more phenotypes [31]. In addition, a phenotype can change over time and transform into another one.

Allergic SBA is the most common and easily recognizable SBA phenotype. The prevalence of severe allergic asthma is about 40–80% [6, 31, 32]. Disease onset occurs in early childhood, with hereditary burden and allergic comorbidities in most cases. The most common comorbidity is allergic rhinitis. The main differences from non-allergic asthma are the following: positive skin reactions and dependence of symptoms on contact with an allergen. Such patients are often characterized by polysensitization. Monosensitization is found only in 16% of cases. The most common allergen is house dust mite; sensitization to it is found in 35–86% of patients [32]. This phenotype is characterized by eosinophilic inflammation; patients respond well to treatment with inhaled glucocorticosteroids (IGCs). However, the long course of the disease, polysensitization, constant contact with an allergen, and high IgE levels can contribute to the development of fixed airflow obstruction, which leads to significantly decreased results of pulmonary function test (PFR) [32].

Non-allergic SBA is more common in adults and is not associated with allergies. The profile of airway inflammation in patients with this phenotype may be eosinophilic, neutrophilic, mixed, or low granulocytic. Patients with non-allergic asthma may not respond to treatment with IGCs depending on the type of inflammation. Non-allergic asthma is more likely to have a severe course than allergic asthma, which deteriorates the quality of life [33]. Pathology of the upper respiratory tract and the skin is less common in the group of patients with non-allergic BA. However, the prevalence of these diseases is higher compared to the control group. Therefore, patients with non-allergic BA also have a systemic component of the disease that requires further analysis. FeNO (nitric oxide fraction) level in exhaled air increases in proportion to the prevalence of rhinitis and dermatitis in the group of these patients [33].

Late-onset SBA. Late onset of SBA is considered to be the onset of respiratory symptoms in patients over the age of 40 years with no previous history of asthma. However, the age range is not exactly defined. This phenotype is more common among women and is associated with several comorbidities, changes in psychological status (depression, anxiety, dementia), development of eosinophilic-neutrophilic inflammation with a predominance of the latter component. It should be mentioned that late-onset BA is heterogeneous in regard to causative factors [34]. Results of the comparative study performed by Daniel J. Tan et al. (2016) revealed no significant differences in the severity of asthma between patients with early and late onset despite the different duration of the disease. At the age of 44, no prevalence of these phenotypes was also distinguished [35]. The differences included etiological factors and the effect on pulmonary function. The duration of the disease plays the key role in the decrease of PFT results, whereas for patients with a late onset, such factors are smoking and age-related changes in lungs [34, 35].

SBA with fixed airflow obstruction (FAO). Fixed bronchial obstruction is characterized by FEV_1/FVC ratio of less than 0.7 after adequate bronchodilation (salbutamol 400 μg), with the diagnosis of COPD absent or ruled out for this patient. SBA criteria are met by 71.7% of patients with FAO [36]. FAO is the result of bronchial wall remodeling due to persistent inflammation, long disease history, frequent exacerbations, and steroid resistance [37]. FAO risk factors also include a history of atopic dermatitis, artificial ventilation (AV), contact with mold, and elderly age [37, 38]. In contrast to the patients with no obstruction, the FAO patients are characterized by a significant decrease in spirometric parameters, increased FeNO level, high eosinophil and neutrophil count in induced sputum, and significantly higher rate of eosinophilia (≥ 3%) [39].

SBA in obese patients. It is known that obesity not only increases the risk of BA, but also worsens disease course and may even contribute to steroid resistance [40]. Obesity leads to the development of comorbidities that aggravate the course of asthma (for example, GERD, type 2 diabetes mellitus, arterial hypertension), maintains chronic systemic inflammation, and also negatively affects lung volume [32]. A 15% reduction in body weight significantly improves asthma control, lung function and quality of life [41].

In a recent study, SBA phenotypes were divided based on the CT of the lungs [42]. The patients were divided into three groups according to the changes found. Group 1 was characterized by remodeling in large airways (lobar, segmental, subsegmental bronchi); basic pathological patterns included the thickening of the bronchial wall, mucus plugs, and bronchiectasis. Group 2 was characterized by changes in small airways; basic pathological patterns included emphysema, air trapping, and changes in subsegmental bronchi. Group 3 included patients with no apparent changes. It is noteworthy that CT demonstrated at least one pattern of pathological changes in 80% of patients with SBA. A relationship was found between the thickening of the bronchial wall and the count of eosinophils in peripheral blood, as well as between the presence of mucous plugs and the eosinophil level in sputum; these facts allow us to interpret these changes in proximal airways as an indicator of eosinophilic inflammation in SBA [42].

Group 1 was the largest and included 44% of all patients. Absolute and relative levels of peripheral eosinophils in this group were significantly higher than in groups 2 and 3. Group 2 was dominated by male patients, often with a history of smoking. Bronchial obstruction was most pronounced in this group: patients required more treatment compared to other groups. In general, group 2 can be described as an asthma: COPD combination, recently classified as a separate subtype of SBA. Patients of group 3 required oral GCs as maintenance therapy significantly less often than the other two groups.

Regarding clinical signs, such as the age of BA onset, body mass index (BMI), the presence of atopy, total IgE level, the number of exacerbations in the previous year, there were no correlations with CT changes, and no differences between groups were found.

Therefore, remodeling in airways may be based on various pathogenetic processes, and one specific SBA phenotype may be underlain by different endotypes [32, 43].

SBA endotypes

A disease endotype characterizes the pathogenetic features of inflammation in airways and is determined based on genetic and molecular parameters [43, 44]. In contrast to the disease phenotype, endotypes are more determinated subgroups of patients [44], although they can also change over time [45]. It seems reasonable to divide the variety of SBA immunopathological processes into two large groups: Th2-type inflammation and non-Th2-type inflammation.

Th2-type inflammation is found in half of patients with BA and in 37% of patients with SBA [44]. The trigger mechanism for Th2-type inflammation is the interaction of the respiratory tract epithelium with environmental factors and the subsequent synthesis of signal substances – alarmins – by epithelial cells. Alarmins include interleukin-33 (IL-33), interleukin-25 (IL-25), and TsLP (thymic stromal lymphopoietin) (Fig. 1). It was demonstrated that most BA patients have a deficiency of E-cadherin and claudin-18, which are responsible for the strength of bonds between epithelial cells. This results in easier penetration of allergens and microbial antigens through epithelial barrier [44]. It should be noted that the decreased expression of E-cadherin is associated with epithelial-mesenchymal transition, which underlies the remodeling of the bronchial wall [40]. The development of Th2-type immune response requires the synthesis of such key cytokines as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13). Their main sources in airways are Th2 lymphocytes and type 2 innate lymphoid cells (ILC2). ILC2 are innate immune cells, and their activation does not require interaction with an antigen and its recognition. Therefore, ILC2 activation underlies non-allergic eosinophilic inflammation [43]. IL-33 and IL-25 play a leading role in ILC2 activation, while TsLP stimulates mainly antigen-presenting cells, specifically dendritic cells that interact with T and B cells and trigger allergic inflammation. It is notable that ILC2 synthesize IL-5 and IL-13 5–10 times more than Th2 lymphocytes, as well as a small amount of IL-4 [48]. IL-4, IL-5, and IL-13 have synergistic effects that cause the attraction of effector cells to the inflammation site, as well as structural and functional changes in the bronchial wall [43, 44].

IL-4 is crucial for the differentiation of naive Th lymphocytes into Th2 lymphocytes. Together with IL-13, it mediates subepithelial fibrosis, thereby participating in the processes of airway remodeling [43]. IL-13 is described as a key effector cytokine that plays an important role in many aspects of BA pathogenesis, including B cell switch to IgE production, mucus hypersecretion, goblet cell hyperplasia, and bronchial hyperreactivity. IL-5 is the main cytokine responsible for the recruitment and survival of eosinophils and, to a lesser extent, of mast cells and basophils. Eosinophils are the main effector cells of Th2-type inflammation; their degranulation and release of substances such as eosinophilic cationic protein and eosinophil-derived neurotoxin are associated with the development of fixed airflow obstruction that determines the severe course of the disease [46].

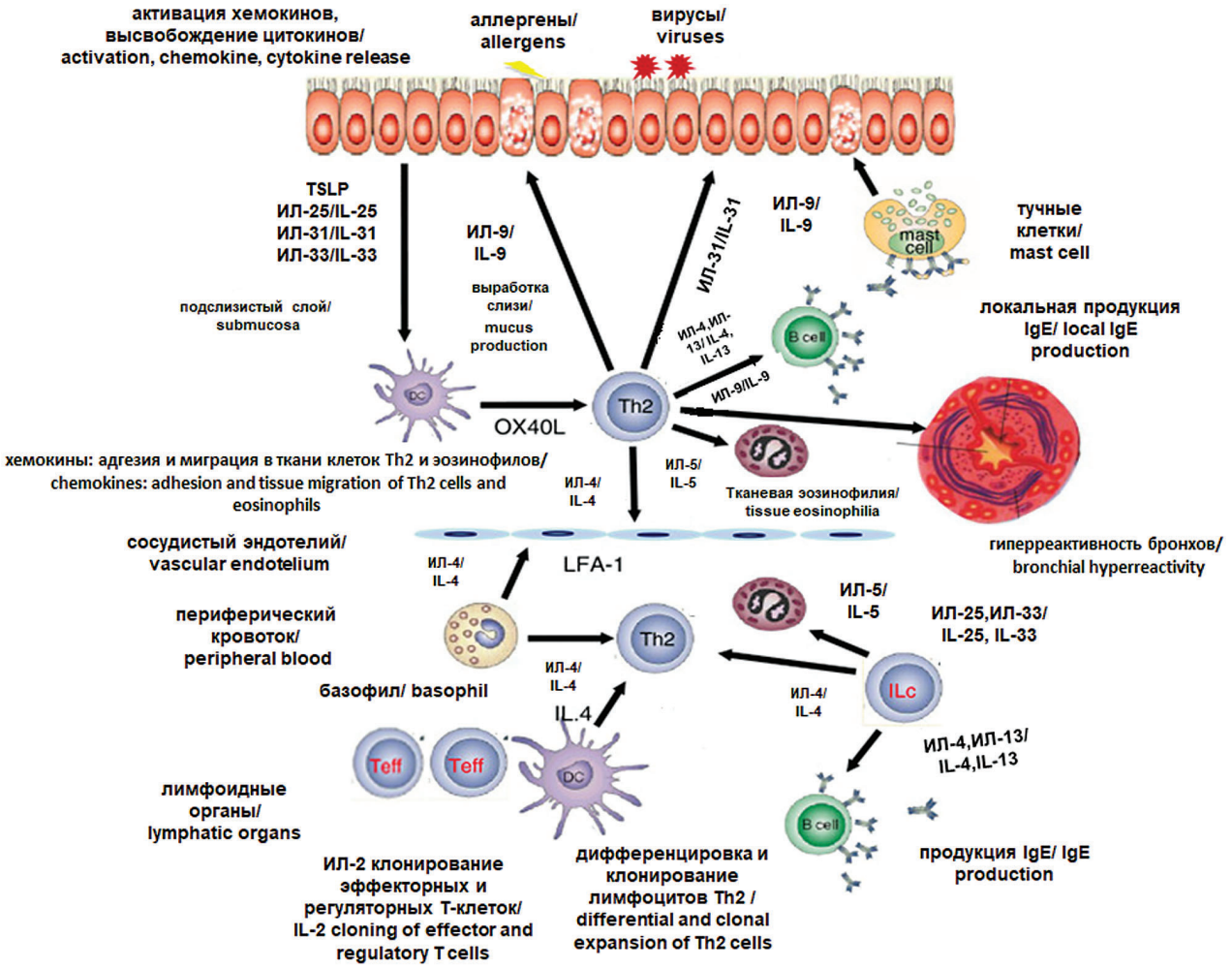

Figure 1. *Mechanisms of allergic inflammation in asthma [47].*
Note: B cell — B-lymphocyte, DC (dendritic cell) — dendritic cell, IgE — immunoglobulin E, ILc (innate lymphoid cell) — innate immunity lymphocyte, LFA-1 (lymphocyte function-associated antigen 1) — integrin LFA-1, OX40L — receptor ligand OX40 (CD252), Teff — T-effector, Treg — T-regulator, TSLP (thymic stromal lymphopoietin) — thymic stromal lymphopoietin

Non-Th2-type inflammation is characterized by the absence of signs of Th2-type inflammation in sputum and peripheral blood and is associated with molecules such as interleukin-1ß (IL-1ß), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17A/F (IL-17A/F), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) [45]. Various authors estimate the prevalence of non-Th2-type inflammation in all BA patients to be 40–70% [45]. In the structure of non-T2 asthma, neutrophilic and low granulocytic inflammation are distinguished depending on the detection of an inflammatory cell pool in induced sputum samples. Activation of Toll-like receptors leads to the differentiation of naive Th lymphocytes into Th1 and Th17 lymphocytes that produce IL-8, IL-1ß, IFN-γ, and TNF-α, facilitating the recruitment of effector cells, mainly neutrophils [45].

The role of neutrophils in SBA is diverse. However, their participation in oxidative stress reactions and ability to synthesize transforming growth factor beta (TGF-ß), a powerful inducer of epithelial-mesenchymal transition [40], are of special significance. IL-17, IL-6, and IL-8 are described as key non-Th2-type inflammatory cytokines. It is noteworthy that cytokines of the IL-17 family can promote both the migration of neutrophils into the respiratory tract and the induction of Th2-type immune response cytokines, thereby affecting the development of eosinophilia [47]. The role of cytokines of the IL-17 family in the pathogenesis of BA is multifaceted and ambiguous. However, there is evidence in the literature that an increased level of IL-17 is an independent risk factor for SAD, and the presence of single nucleotide polymorphisms in the IL-17 gene is associated with the development of allergic diseases [47].

Although low granulocytic inflammation is characterized by the absence of sputum eosinophilia and neutrophilia, an increased amount of inflammatory cells in patients with low granulocytic inflammation was demonstrated compared to relatively healthy individuals [44]. Bronchial hyperreactivity in patients with a low granulocytic type of inflammation is thought to be associated not only with exposure to inflammatory cytokines: it was demonstrated in animal models that treatment with nerve growth factor (NGF) induced bronchial hyperreactivity to the same extent as allergen sensitization [44].

Low granulocytic inflammation is thought to be most common in cases of well-controlled asthma and is associated with better pulmonary function parameters. However, about 20% of patients with low granulocytic inflammation have a severe course of the disease, which is refractory to ongoing therapy [48]. Signs of airway remodeling in this group of patients suggest the existence of mechanisms for the development of fixed airflow obstruction regardless of the severity of inflammation, which was also demonstrated in animal models. Smooth muscle cells play a leading role in airway remodeling in the cases of low granulocytic inflammation [48].

It should be noted that endotypes are closely related to disease phenotypes. Approximately 25% of patients with SBA have severe eosinophilic inflammation and late onset of the disease [49]. Allergic and aspirin-induced SBA are also phenotypes with Th2 endotype [44]. A recent cluster analysis revealed Th2 endotype in cases of late-onset eosinophilic asthma associated with chronic rhinosinusitis with nasal polyps, which was characterized by high expression of specific IgE to Staphylococcus aureus enterotoxin and high IL-5 levels [44]. This study demonstrated the possible presence of the association of Th2/Th17 cells in bronchoalveolar lavage, which was characterized by a more severe course of the disease compared to the separate presence of these lymphocytes [44]. Patients with non-Th2 endotype are also characterized by late onset of the disease [45]. According to the literature, the neutrophil level in sputum is higher in elderly patients with BA than in young and middle-aged patients [45]. Poor response to inhaled and systemic GCs is a typical sign of patients with non-Th2-type inflammation. It is known that IGCs induce apoptosis of eosinophils. However, they have the opposite effect on neutrophils [40]. The main trigger factors in the group of patients with non-Th2-type inflammation include intense physical activity, weather conditions (in particular, exposure to cold), exposure to smoking, pollutants, and infectious agents. Colonization with microorganisms such as *Moraxella*, *Streptococcus*, and *Haemophilus* was associated with higher neutrophil and IL-8 levels in BA patients. Association with obesity was established for both Th2- and non-Th2 endotypes [40, 44].

Therefore, it becomes obvious that the patients with SBA need personalized treatment with consideration to the specific pathogenetic symptoms of the disease. To distinguish between Th2- and non-Th2-type inflammation, biomarkers that play a key role in a particular clinical case should be identified. A perfect biomarker is a parameter with high sensitivity and specificity that characterizes the symptoms of the disease, allows choosing targeted therapy, monitoring its effectiveness, predicting the response to treatment. At the same time, it should be non-invasive and available in clinical practice [50]. Established markers of Th2-type inflammation include blood and sputum eosinophilia, increased total IgE, and increased FeNO in exhaled air. However, all of them have certain limitations [49].

It is difficult to discuss the predominant role of a particular type of inflammation in SBA pathogenesis [43, 44]. It is noteworthy that the relationship between the severity of inflammation and the number of exacerbations, as well as the impact on the prognosis of BA, were demonstrated for both eosinophilic and neutrophilic inflammation [40, 44, 45, 49]. Both sputum eosinophilia and neutrophilia are associated with decreased FEV_1 before the bronchodilation test. However, only sputum neutrophilia was associated with post-bronchodilation FEV_1 [40]. This supports the impaired immune response as the basis for the severe course of BA. Molecular biology methods can help conduct a thorough analysis of existing impairments, which is required for the development of targeted therapy and improved management of patients with SBA.

Conclusion

SBA is definitely a serious medical and socio-economic issue. Non-drug factors and a multidisciplinary approach are of particular importance in the management of such patients. The heterogeneity of SBA includes the concepts of phenotype and endotype. Their determination in clinical practice is limited but is necessary for personalized treatment. A severe course of this disease is due to impaired regulatory mechanisms of innate and acquired immunity. Interpretation of mechanisms that cause airway remodeling with no severe inflammation presents a challenge. Further molecular biology studies are required in order to explain the pathogenetic mechanisms underlying the severe course of this disease, as well as the search for new biomarkers that will allow diagnosing pathological processes in clinical practice.

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