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Modern Methods of Diagnosis and Treatment of Severe Bronchial Asthma (Systematic Review)

Yudina E.O., Melenteva A.P., Shevelev I.Yu., Ogorodova L.M., Fedorova O.S.

Siberian State Medical University (SibSMU)
2 Moscovsky trakt, 634050 Tomsk, Russian Federation

ABSTRACT

Currently, the prevalence of bronchial asthma (BA) is steadily increasing worldwide. Official statistics show that severe BA accounts for 5–10% of cases in the severity profile of this disease, and when treated with high doses of corticosteroids, uncontrolled symptoms persist in most people, which significantly reduces their quality of life. This supports the relevance of finding new strategies for the treatment of severe BA. The aim of the review was to analyze and summarize published data on modern approaches to the diagnosis and treatment of severe BA.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 3,177 sources were found. Excluding publications that were unavailable for viewing allowed us to leave 578 sources, of which 120 papers were relevant to the study topic to some extent. Of these, 63 sources were selected that contained the information necessary for the study and met the selection criteria for the studies: 28 of them were review articles and 35 were original studies (randomized controlled, cohort, and case-control studies). The work presents a description of phenotypes and endotypes, as well as characteristics of modern biomarkers of severe BA.

Particular attention is paid to a new approach to the treatment of severe BA. The conducted studies, systematized in this article, indicate that a detailed description of asthma phenotypes and endotypes can help identify new biomarkers and therapeutic targets specific to each endotype. Profound knowledge of the patient's phenotype and endotype can determine a personalized approach to the treatment of severe BA.

Keywords: severe bronchial asthma, biological therapy, phenotype, endotype, biomarkers

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Современные методы диагностики и лечения бронхиальной астмы (систематический обзор)

Юдина Е.О., Мелентьева А.П., Шевелев И.Ю., Огородова Л.М., Федорова О.С.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

В настоящее время распространенность бронхиальной астмы (БА) во всем мире неуклонно растет. Данные официальной статистики свидетельствуют, что от 5 до 10% случаев в структуре тяжести данного заболевания составляет тяжелая БА и при ее лечении высокими дозами ингаляционными кортикостероидов (ИКС)

✉ *Melenteva Anastasya P.,* anastasiaymelenteva@gmail.com

сохраняются неконтролируемые симптомы у большинства людей, что значительно снижает качество их жизни. Это поддерживает актуальность поиска новых стратегий лечения тяжелой БА. Цель обзора заключалась в проведении анализа и обобщении опубликованных данных о современных подходах диагностики и лечения тяжелой БА.

Используя рекомендации «Предпочтительные элементы отчетности для систематических обзоров и мета-анализов» (PRISMA), были обнаружены 3177 источников. Исключение публикаций, недоступных для просмотра, позволило оставить 578 источников, из которых теме исследования в той или иной степени соответствовали 120 работ. Из них отобраны 63 источника, содержащие необходимую информацию и соответствующие критериям отбора исследования. Из них 28 обзорных и 35 оригинальных исследований (рандомизированные контролируемые, когортные и исследования «случай – контроль»). Представлено описание фенотипов и эндотипов, а также характеристика современных биомаркеров тяжелой БА. Особое внимание уделяется новым подходом лечения тяжелой БА.

Проведенные исследования, систематизированные в данной статье, свидетельствуют о том, что подробное описание фенотипов и эндотипов БА может помочь выявить новые биомаркеры и терапевтические мишени, специфичные для каждого эндотипа. Глубокое знание фенотипа и эндотипа пациента может определить персонализированный подход к терапии тяжелой БА.

Ключевые слова: тяжелая бронхиальная астма, таргетная терапия, фенотипы, эндотипы, биомаркеры

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INTRODUCTION

Bronchial asthma (BA) is a chronic inflammatory disease of the airways, the mechanisms of which are associated with the influence of many factors, including genetic predisposition, environmental exposure, and regulation of the immune system [1]. The prevalence of BA increased sharply in the late 20th century, and despite the advent of biological drugs, in 2019, the WHO recorded that the incidence of BA reached 260 million cases, and the mortality rate was 450 thousand per year [2]. Allergic BA is associated with increased sensitivity to allergens, and their repeated exposure to the airways leads to the activation of antigen-presenting cells [3]. The developing inflammation can be characterized by a T2 or non-T2 immune response (endotype) [4], and each of them can lead to a severe uncontrolled course of the disease. However, the non-T2 endotype is more often associated with uncontrolled asthma [5] and ineffectiveness of step-down therapy with glucocorticoids (GSs) [6, 7]. It is necessary to develop new therapeutic strategies for severe BA based on modern scientific data on inflammation and biotargets.

The aim of the work was to present modern data on the study of biotargets to improve the effectiveness of targeted therapy based on the analysis of scientific publications, including recommendations for the use of biomarkers for the diagnosis of phenotypes and endotypes of bronchial asthma.

MATERIALS AND METHODS

The study material included publications in scientific journals that to some extent touched upon the topic of the study. The search was carried out in the scientific electronic library Elibrary.ru. In the advanced search, using the keyword combination “severe bronchial asthma”, 3,177 sources were found. Further limitation by the writing time from 2015 to present and exclusion of any forms of manuscripts except for articles in scientific journals narrowed the search to 2,269 sources. Exclusion of publications unavailable for viewing allowed us to leave 578 sources. A search was also carried out in the PubMed database, where 1,094 sources were found in the advanced search using the keyword combination “severe bronchial asthma”. The keywords for selecting articles were: biological therapy or targeted

therapy or asthma biomarkers or asthma biotargets. Of these, 120 works corresponded to the research topic to one degree or another, of which 63 sources were selected containing the information necessary for the study and meeting the study selection criteria. Twenty-eight of them were review studies and 35 – original articles (randomized controlled, cohort and case-control studies). References of the found articles also contained less than 10% of sources published in 1998–2014.

PHENOTYPES AND ENDOTYPES OF BRONCHIAL ASTHMA

The 2024 Clinical Guidelines for Bronchial Asthma contain a section devoted to the characteristics of clinical phenotypes. In particular, allergic (atopic) and non-allergic (including aspirin-induced, including occupational) asthma are distinguished, as well as late-onset asthma, asthma with fixed airflow obstruction, and asthma in obese patients. This approach to diagnosis is widely used in clinical practice when determining a treatment program for most patients [8].

However, patients with severe BA symptoms require personalized treatment using biological / targeted therapy, when it is necessary to determine a specific biotarget and diagnose it using biomarkers. In this regard, a classification of BA is currently proposed based on information on the molecular and cellular mechanisms of inflammation, which makes it possible to distinguish endotypes and inflammatory phenotypes of the disease. This is a fairly new area for clinical science, where data are rapidly accumulating, allowing for more accurate selection of targeted drugs and development of new medications, but many questions remain unanswered [9, 10].

Currently, two endotypes of BA are recognized based on the type of immune response – T2 and non-T2. The T2 endotype is based on the dominance of the CD4+ T cell response, providing eosinophilic inflammation. However, evidence has recently been obtained about type 2 innate lymphoid cells (ILC-2) as the primary regulators of the type 2 immune response. ILC-2 express the main transcription factor GATA 3, which, in turn, regulates the production of type 2 cytokines. Thus, biomarkers of the T2 endotype include eosinophilia, high levels of IL-4, IL-5, and IL-13 in the blood and sputum, the presence of ILC2 in the blood and respiratory tissues, high levels of total immunoglobulin E (IgE) in the blood, increased levels of fractional exhaled nitric oxide (FeNO), and a good response to inhaled corticosteroids (ICS) and biological therapy [11, 15].

The non-T2 endotype is not clearly defined. This is an endotype without signs of T2 inflammation: there is no eosinophilia. Severe symptoms of the disease and resistance to ICS are more often recorded, and IL-6, IL-1b, IL-8, and IL-17A are involved in the immune response [16, 17]. Along with endotypes, four inflammatory phenotypes of BA are distinguished: eosinophilic (EA), neutrophilic (NA), mixed granulocytic (MG), and paucigranulocytic (PG). The gold standard for diagnosing phenotypes is the results of an induced sputum analysis of patients [18].

In the work by A. Plavsic et al., based on the study of induced sputum in 80 patients, 17 of whom received biological therapy, it was shown that EA and MG phenotypes were more common than others [13]. In the same work, the characteristics of phenotypes were presented with and without biological therapy. Thus, patients with NA were characterized by the highest level of IL-8 compared to patients with EA, MG, and PG phenotypes ($p = 0.002$, $p = 0.031$, $p = 0.021$, respectively).

Patients with an EA phenotype have significantly higher IL-17A levels in the blood compared to others ($p = 0.004$). During biological therapy, these patients have lower IL-5 levels compared to untreated patients ($p = 0.043$).

Patients with a MG phenotype after targeted therapy are characterized by lower lymphocyte and neutrophil counts than before treatment ($p = 0.003$). In contrast, IL-5, IL-6, and IL-8 levels after treatment are higher than baseline values ($p = 0.012$, $p = 0.032$, $p = 0.038$, respectively).

The lack of reduction in some inflammation indices during targeted therapy in the MG phenotype in this study, according to the author's comment, indicates the need for search for another biological target in such patients.

BIOMARKERS OF SEVERE BRONCHIAL ASTHMA

The use of biological markers for the selection of targeted drugs depending on the nature of inflammation (phenotype/endotype of BA) has significantly expanded the possibilities of achieving control over BA symptoms. Along with this, the effectiveness of severe BA treatment still remains a therapeutic problem. Therefore, the search for biotargets for the treatment of severe BA is an urgent research and clinical task [11–15].

The results of studies in recent years indicate possible expansion of a list of new biotargets, as well as biomarkers of already known biotargets. In particular, the following are discussed [11, 12, 20]: eosinophil peroxidase (EP) in the respiratory tract (sputum) [12–21], eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) [11], exhaled breath condensate (EBC), urine metabolites, microRNA, Charcot – Leyden crystals, dipeptidyl peptidase, osteopontin [11, 12, 21].

In general, the analysis of biomarkers is regularly updated in publications. In this article, we will focus on those that are valid for severe BA.

1. Blood / serum biomarkers.

1.1. Eosinophilia.

Eosinophils play a key role in the development of type T2 BA [14–16]. Currently, the determination of the number of eosinophils in the blood is used as a biomarker for BA and the choice of targeted therapy. The most important in the context of inflammation are activated eosinophils. They release mediators that damage bronchial epithelium, cause overproduction of mucus, edema, and bronchospasm, which leads to frequent exacerbations in patients [17].

1.2. Eosinophil-derived neurotoxin and eosinophil cationic protein.

The results of the study of EDN and ECP were published in the work of by T. Tsuda et al. It was shown that their level increased after the activation of eosinophils by cytokines (including IL-5, IL-1b, and IL-33), and the level of EDN in the blood serum of patients with severe BA was significantly higher [11, 12, 20, 26, 27]. Probably, the determination of the level of EDN in the blood serum can help in assessing the severity of the disease [12].

1.3. Eosinophil peroxidase.

Eosinophils have a unique set of enzymes that allow them to produce reactive oxidants that damage the respiratory tract [13]. One of these oxidants is EP, the level of which was higher in patients with severe BA than in the control group. It is proposed to use EP as a biomarker of eosinophilic inflammation in severe BA with the EA phenotype [14, 15, 28].

1.4. Periostin.

Periostin is a matricellular protein that is produced by epithelial cells and fibroblasts in response to stimulation by IL-4, -5, -13. The association of periostin levels with eosinophilic inflammation of the airways has been shown in a large number of studies. The relationship between periostin levels and lung function parameters and asthma characteristics (severity, exacerbation frequency) indicates the potential applicability of this biomarker to identify patients with severe forms of the disease [15, 28–33]. However, there are limitations to using periostin as a prognostic biomarker in children due to bone growth and its constant high levels [34].

2. Sputum biomarkers.

The number of eosinophils in sputum reflects the degree of inflammation in the airways and, therefore, is a sensitive and specific non-invasive diagnostic biomarker [35–38], which is used as the gold standard for diagnosing asthma phenotypes [39]. The eosinophilic inflammatory phenotype is the most common. It is diagnosed when 3% or more eosinophils are detected in sputum.

Normalization of sputum eosinophils is associated with better asthma control, reduced hospitalizations, and exacerbations.

4. Exhaled breath condensate.

EBC is a noninvasive method for studying the respiratory tract. In adult patients with BA, the concentration of hydrogen ions in exhaled air, nitric oxide breakdown products, hydrogen peroxide, and 8-isoprostanoids is increased and is associated with poorer lung function compared to healthy individuals [40]. Recently, there has been growing interest in metabolomic analysis of EBC [41–51].

5. Urine biomarkers.

The composition of urine metabolites changes significantly during different periods of BA. Research results indicate an increase in the content of alkanes, aldehydes, and amino acids in urine during an exacerbation episode [41]. The most studied metabolite is the amino acid bromotyrosine, high levels of which are associated with the eosinophilic phenotype of BA. In the work by A. Tiotiu et al., it was shown that its content decreased during the use of GCs in severe BA. The author suggested using bromotyrosine as a biomarker of the response to steroid treatment [42–44].

6.OMICS technologies.

Based on the analysis of the sputum transcriptome in patients with BA, three molecular phenotypes are distinguished. The first (TAC1) is associated with the T2 endotype and is characterized by eosinophilia and high levels of IL-13 and ILC2. The second (TAC2) and third (TAC3) are not associated with the T2 endotype. TAC2 is characterized by high levels of INFγ, TNFα, as well as increased expression of the *NLRP3*, caspase-1, and IL-1b genes in sputum macrophages in patients with NA phenotype of BA.

TAC3 is characterized by increased expression of genes associated with paucigranulocytic inflammation [45–49].

7.MicroRNA (miRNA).

MicroRNAs are short sequences of single-stranded RNA (19–24 nucleotides) that, by complementary binding to the 3'-untranslated end of messenger RNA (miRNA), can interfere with the proper function of a particular gene. Recent studies have shown that miR-28-3p, -16-2-3p, -210-3p, -185, -125b, -338-3p, and -125b are markers of severe BA [49–51]. MicroRNAs can also be used to predict the response to targeted therapy. Thus, in a study by J.A. Cañaset et al., miR-1246, miR-5100, and miR-338-3p were shown to be potential biomarkers for predicting the response to benralizumab [53]. In the study by M. Gil-Martínezet et al. [54], which examined changes in microRNA expression in patients with severe BA depending on systemic GC therapy, significant differences were found in the expression of eight microRNAs: hsa-miR-148b-3p, -221-5p, -618, -941, -769-5p, -144-3p, -144-5p, and -451a (the first five were determined in serum, the last three – in lung tissue). MicroRNA profiling can be used to search for new biomarkers of severe BA and predict the effectiveness of biological therapy [51].

MODERN METHODS FOR TREATING SEVERE BRONCHIAL ASTHMA

The strategy of modern asthma therapy is based on achieving and maintaining control over symptoms of the disease and reducing the risk of exacerbations. For this purpose, a stepwise approach is used, which involves the possibility of increasing or decreasing the volume of therapy in the patient. Genetically engineered biological drugs are currently used to achieve control over severe BA symptoms.

According to the 2024 clinical guidelines, monoclonal antibodies against T2 cytokines are used to treat patients with severe BA: omalizumab is a monoclonal body against IgE, mepolizumab and reslizumab – against IL-5, benralizumab – against the IL-5 receptor, dupilumab – against IL-4Rα, and tezepelumab – against thymic stromal lymphopoietin [55, 56].

Despite the obvious clinical effect in patients with severe BA taking biological drugs, questions remain open regarding the insufficiency of biomarkers for the selection and prognosis of the effectiveness of biological therapy and phenotype variability during the natural course of the disease. In some patients, there is no association between the clinical effect and the positive dynamics of biomarkers [8, 57–62].

Publications of recent years contain a large number of studies devoted to the analysis of biomarkers and their suitability for use in the process of biological therapy for BA [8, 57–62].

Thus, in a retrospective study, M. Lampalo et al. compared the effect of therapy with omalizumab, reslizumab, benralizumab, and mepolizumab in patients with severe BA (n = 74). The patients were followed up for 24 months. The response to therapy was assessed using the asthma control test (AST), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FeNO, the number of eosinophils and IgE in the blood, the number of exacerbations, and the need for GCs. The results showed that treatment with both anti-IgE and anti-IL-5 monoclonal antibodies can reduce the frequency of exacerbations and the volume of GC therapy and increase AST values. At the same time, the authors point out the insufficient information on the dynamics of inflammation against the background of the applied therapy and associate this with the lack of prognostic biomarkers of an individual response to treatment [57].

N. Contreras et al. published the results of an 18-month follow-up of adult patients with severe BA (n = 67) during treatment with omalizumab (n = 20) and mepolizumab (n = 36). The clinical effect is confirmed by an increase in AST and FEV1 after therapy and a decrease in the number of eosinophils in the blood and the frequency of exacerbations. Proteomic and metabolomic analysis revealed a group of metabolites (arachidonic, oleic, palmitoleic, lactic acids, propionyl L-carnitine, bilirubin, CCL11, and TNFSF10) that changed in response to therapy with mepolizumab alone, in association with a clinical improvement. These results indicate different effects of omalizumab and mepolizumab on the metabolomic kinetics of inflammation in severe BA. Thus, the study confirms the need to search for multiple biomarkers of inflammation for biological therapy of BA [58].

R. Djukanović conducted a cross-sectional open study, where the clinical efficacy of omalizumab was assessed in patients with severe BA (n = 216) over 16 weeks. Using omics technologies, they studied 1,408 parameters of a number of eicosanoids and volatile organic compounds in exhaled breath, as well as proteins in sputum and urine. Following the use of covariance or quantile regression models, the authors established a list of biomarkers of volatile organic compounds and blood lipids, the use of which is able

to predict a decrease in the frequency of exacerbations by more than 50% during treatment with omalizumab ($p < 0.05$). The inclusion of such markers as eosinophil count in the blood and sputum, nitric oxide in exhaled breath, and serum IgE in the regression model did not confirm their prognostic value in this study [60].

The search for biotargets for adequate therapy for severe BA is also carried out using genomic technologies. Thus, the results of a 12-month retrospective observational cohort study, including patients with severe eosinophilic asthma (n = 72), revealed that after treatment with mepolizumab and benralizumab, the volume of GC therapy and the frequency of exacerbations decreased, and FEV1 increased. An association was established between the alleles ZNF415 rs1054485-T, IL1RL1 rs1420101-T, and FCER1B rs569108-AA with severe BA.

At the same time, carriers of the ZNF415 rs1054485-T allele showed a decrease in the frequency of exacerbations after completion of treatment with mepolizumab ($p = 0.042$), and carriers of the IL1RL1 rs1420101-T allele exhibited an improvement in FEV1 ($p = 0.023$).

The use of benralizumab led to a decrease in the number of exacerbations in patients who were carriers of the ZNF415 rs1054485-T allele (p = 0.073) and FCER1B rs569108-AA ($p = 0.050$) [61].

The publication by S. Harada et al. is devoted to the study of changes in single nucleotide polymorphisms when using benralizumab in patients with severe BA (n = 72). The results of the work show that after 12 months of treatment with benralizumab, patients showed positive clinical dynamics: FEV1 increased, the volume of GC therapy and the frequency of exacerbations decreased, and the expression of key genes involved in non-T2 inflammation (IL-8, IL-17RA, CXCR1, and CXCR2) decreased. An important conclusion of the work was that benralizumab affects T2 and non-T2 endotypes of BA. However, further research in this area is needed to confirm the role of pharmacogenetics in the search for prognostic biomarkers of severe BA [62].

Biological therapy is widely used in severe BA in pediatric practice, although the list of drugs for children has age restrictions. According to the 2024 clinical guidelines, drugs such as omalizumab and mepolizumab are approved for use in children aged 6 years, dupilumab – for children aged 12 years, and reslizumab and benralizumab – for children aged 18 years [8]. Given the lack of research on prognostic biomarkers in children, it is currently difficult to assess the effectiveness of biological therapy in a pediatric cohort [8, 34].

CONCLUSION

Biological therapy is an expensive treatment strategy, so there is a high demand for personalized approaches when prescribing targeted therapy for BA. In this regard, new data on prognostic biomarkers and disease biotargets are needed, which are an important part of scientific research in pulmonology.

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Author Information

Yudina Ekaterina O. – Postgraduate Student, Division of Intermediate-Level Pediatrics with a Course in Pediatric Diseases of the General Medicine Department, Siberian State Medical University, Tomsk, yudina.eo@ssmu.ru, https://orcid.org/0009-0006-1761-553X

Melenteva Anastasya P. – Postgraduate Student, Division of Intermediate-Level Pediatrics with a Course in Pediatric Diseases of the General Medicine Department, Siberian State Medical University, Tomsk, anastasiaymelenteva@gmail.com, https://orcid.org/0009-0009-5600-5760

Ogorodova Ludmila M. – Dr. Sci. (Med.), Professor, Corresponding Member of RAS, Honored Scientist of the Russian Federation, Professor of the Division of Intermediate-Level Pediatrics with a Course in Pediatric Diseases of the General Medicine Department, Siberian State Medical University, Tomsk, edu@tomsk.gov.ru, https://orcid.org/0000-0002-2962-1076

Fedorova Olga S. – Dr. Sci. (Med.), Professor, Vice-Rector for Science and Postgraduate Training, Head of the Division of Intermediate-Level Pediatrics with a Course in Pediatric Diseases of the General Medicine Department, Siberian State Medical University, Tomsk, olga.sergeevna.fedorova@gmail.com, https://orcid.org/0000-0002-7130-9609

(✉) **Melenteva Anastasya P.,** anastasiaymelenteva@gmail.com

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