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Diagnostics and forecasting of non-controlled bronchial asthma

Key words: *bronchial asthma, controllability, diagnosis, forecasting.*

The rapid development of molecular biology, genetics and genetic engineering, in particular hybridoma technology that occurred in the last decades of the last century, and in the beginning of this century, has led to remarkable progress in understanding pathophysiological and immunopathological mechanisms of occurrence of bronchial asthma (asthma), and determining the characteristics of its progress, as well as revolutionary advances of pharmacotherapy of this disease. Currently, a wide range of drugs used in the treatment of asthma, in addition to glucocorticosteroids (GCS), β_2-agonists short and long acting, cromona, theophyllines, statins and anticholinergic drugs include the so-called biological molecules – a new class of drugs, dominated by monoclonal antibodies (MCAB): leukotriene receptor antagonists, monoclonal antibodies against immunoglobulin E (IgE), blockers of some interleukins (IL-2, IL-4, IL-5, IL-9, IL-13), inhibitors of tumor necrosis factor alpha (TNF-α), and the like. Today, they form the basis of so-called targeted therapies aimed at specific biological target involved in the pathogenesis of asthma [12], [49], [50], [56], [57], [58]. However, the use of the latest developments in the treatment of asthma in a significant proportion of patients still does not provide sufficient control of the disease, which involves the following (GINA 2014 [55]):

– achieving and maintaining adequate controllability of asthma symptoms for a long time;
– minimizing fixed airway obstruction;
– minimizing undesirable side effects of therapy;
– minimizing the risk of future asthma exacerbations.

According to expert estimates among patients with asthma, its non-controlled progress in industrialized countries is 40% – 67% of cases (in the USA and Western Europe), and 80% – 90% in the Russian Federation, Ukraine and other countries of the former Soviet Union. Among them, only 8.0% – 20.0% of patients show true treatment resistance to anti-asthma drugs, while in others non-controlled asthma is caused by inadequate treatment (due to violation by the patient of inhalation technique, doses and regimens of drugs, incorrect assessment of the severity of the disease by the physician), by the presence of comorbide pathology and triggers (Smoking, presence of allergens, etc.) [10], [14], [51], [60].

It is known that non-controlled asthma presents various clinical, functional and pathophysiological phenotypes and endotypes (brittle or fragile, nocturnal asthma, steroid-sensitive and steroid-resistant asthma, asthma with fixed bronchial obstruction, premenstrual, acute severe asthma, status asthmaticus, fatal asthma, etc.). It is caused by different mechanisms of its formation [5], [14], [45], [59], [62] and therefore requires different approaches to diagnosis and forecasting.

Based on the components of asthma controllability stated by GINA, in order to determine the controllability, it is necessary to evaluate asthma symptoms and airway obstruction, as well as the risk of unwanted side effects of therapy and future exacerbations of the disease (i.e., forecasting).

As a rule, for evaluation of asthma symptoms, standard questionnaires are usually used: c-ACT in children aged from 4 to 11 years, c-ACT in children aged from 12 years and adults, a questionnaire on asthma controllanility – ACQ-5 (table). To assess the risk of asthma exacerbations, an analysis of independent risk factors is used, such as intubation or asthma treatment in the ICU, or one or more exacerbations of the disease during the last 12 months. Among the risk factors for asthma exacerbations they distinguish those that are potentially modifiable, namely:

• the presence of symptoms of non-controlled asthma,
• excessive use of β_2-agonists short-term acting (more than 1 inhaler of 200 doses for a month),
• inadequate therapy with inhaled GCS, where there was an improper technique of inhalation, or poor compliance of the patient, or when these drugs were not prescribed for the patient because of any reason,
• low rate of FEV_1, especially if it is less than 60,0% of reference value,
• significant psychological or socio-economic problems

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• action of triggers (contact with allergens, smoking and the like),

• the presence of comorbide disease (allergic rhinitis, sinusitis, non-controlled chronic gastroesophagal reflux disease, hormonal disorders, atopic dermatitis, obesity, etc.)

• pregnancy

• sputum and/or blood eosinophilia.

The presence of at least one of these factors increases the risk of asthma exacerbations even if symptoms are well controlled.

Risk factors of the development of fixed airway obstruction are:

• lack of or inadequate treatment with inhaled corticosteroids,

• exposure to tobacco smoke, noxious chemicals or professional agents

• low baseline of FEV_1,

• chronic hypersecretion of mucus,

• sputum and/or blood eosinophilia.

Risk factors for the development of unwanted side effects of drugs are:

• frequent use of systemic GCS,

• long-term use of high doses or potent inhaled corticosteroids,

• the use of P450 inhibitors,

• poor inhalation technique.

It shall be noted that even a week with fever should be regarded as a week with non-controlled asthma, and requires an assessment of the adequacy of maintenance therapy and its adjustment [11], [48].

Numerous studies have shown that validated questionnaires such as c-ACT questionnaire and ACQ-5 test provide standardized quantitative assessment of controllability of asthma, correlated with the GINA criteria, instrumental methods of examination of patients with markers of inflammation: clinical test for the assessment of controllability of asthma ACQ-5 provides best results in short term (weeks), and ACT – in long term (a month or more) [4], [5], [7], [11], [16], [49].

Other anamnestic data are also used extensively for diagnosis and forecasting of non-controlled progress of asthma both independently, and in combination with other parameters. V.T. Burlachuk, A.V. Budnevsky and L.V. Tribuntsova predict non-controlled asthma by evaluating the following history data: age, sex of the patient, the frequency of routine and emergency hospital admissions, ambulance calls (EMS), frequency of doctor visits. Thus, the age is established as the completed years at the time of examination, the sex is determined in the following way: 0 – female, 1 – male, planned hospitalizations – the number of planned admissions in the previous year, emergency hospitalizations – the number of emergency hospitalizations in the previous year, visits to the doctor – the number of outpatient doctor visits in the previous year, EMS calls – the number of EMS calls in the previous year. Controllability of asthma (CBA) shall be calculated according to the formula:

(CBA) = 24,434–0,0672748 × age –1,72615 × sex – 0,87602 × planned hospitalization– 0,414709 × emergency hospitalization – 0,340425 × visits to the doctor – 0,61832 × EMS calls,

and, if CBA is equal to 19 or less, non-controlled progress of asthma is predicted [27].

The airway obstruction shall be detected by carrying out spirometry, peakflowmetry and pneumotachography with the identification of indicators of external respiration function and their changes after physical load, provocation tests, and after bronchodilatatory test (β2-agonists short acting) or tests with other pharmacological agents.

Spirography is a graphic method of registering the volume of the lungs during breathing. Spirography characteristic signs of disturbances of bronchial patency in patients with asthma are: decrease in forced expiratory volume in first second (FEV_1), forced vital capacity (FVL), as well as the decline in Tiffeneau index (the ratio of forced expiratory volume in 1 second to forced vital capacity – FEV_1/FVC).

Peakflowmetry is a method of measurement of maximum (peak) flow rate of air during forced exhalation after a full breath (peak expiratory flow rate – PEFR). It shall be carried out several times a day, before and after application of bronchodilators, and the results shall be registered by the patients into the diary for self-assessment of asthma symptoms.

Pneumotachography is a measurement in twocoordinate system of a loop «flow-volume» the rate of expiratory air flow in the area of 25–75% FVL, that is in the middle of exhalation. By using this method, it is possible to calculate the peak flow rate (PFR), maximum flow rate at 25, 50, 75% FVC (MFR25, MFR50, MFR75) and average flow rate 25–75 AFR. According to pneumotachography, it is possible to diagnose bronchial obstruction at the level of large, medium or small bronchi.

The definition of these parameters is widely used for diagnostics and forecasting of non-controlled progress of asthma. N.S. Bezrukov et al. define the parameters of daily peakflowmetry (morning and evening peak expiratory flow, its variability during the day, reaction to bronchial spasmolytic in the morning and evening, and entering these data by authors in the software (sub-system) for forecasting non-controlled progress of asthma within the package «Medical Toolbox», which automatically detects the prognostic risk factors of non-controlled progress of the disease and determines their reliability [15].

Ya.I. Zhakov et al. monitor the child patient with asthma by keeping by their parents a diary of symptoms, periodic study of indicators of external respiration function, particularly, peak expiratory flow (with the help of peakflowmeter), and carry out pharmacological tests with bronchodilators. Peakflowmetry data taken before and after each pharmacological effects are reflected graphically; they carry out computer processing of obtained curves, and represent the area between them in a numerical form for the visualization of «area of inadequate control of asthma». It helps to identify possible triggers of acute asthma, and to assess the degree of their influence on the severity and duration of broncho-obstructive syndrome [35].

D. L. in patients with persistent light or moderate progress of the disease, D.L. Nachamchen et al. determine

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the standard deviation (SD) of duration of respiratory cycle during quiet breathing for 3 minutes, and the degree of change (%) in instantaneous flow rate of forced expiration at 50% of vital capacity of lungs (MFR50%) in response to the introduction of β_2-agonist short acting (200 μg of Salbutamol or 200 μg of Fenoterolum), and calculate a discrimante equation:

$$D = 0{,}923 \times MFR50\% + 68{,}766 \times CKB,$$

where D is discriminant function, boundary value of which is 77,0, and when D is equal to or exceeds boundary values (77,0), the authors predict a failure of asthma controllability after 6 months of standard therapy [38].

O.K. Koloskova et al. assess syptoms in school-age children with early-onset asthma according «ACT» questionnaire, and carry out a study of spirographic indices, and then calculate the coefficient of controllability of the disease as the ratio of bronchial lability, which is characterized by their hypersensitivity, against the sum of the scores of the questionnaire «ACT» questionnaire; and non-controlled progress of asthma is diagnosed at the coefficient of 0.7 RU and more [21]. A.A. Savysko, M.M. Batushyn and A.A. Lebedenko in children with bronchial asthma define the parameters of external respiration function, the amount of treatment, the spectrum of sensitization of the child, individual anthropometric characteristics of the patient and their parents, the presence of concomitant atopic diseases, assess the factors of heredity, etc. The above is followed by a discriminant analysis with the calculation of K coefficient; and if its value exceeds 0.8, non-controlled progress of the disease is predicted [31].

Some experts, in order to determine the level of asthma controllability and/or forecast its loss, assess respiratory function and carry out additionally other non-invasive methods of research. Thus, in order to predict controllability of asthma after the childbirth, Russian scientists L. G Nachamchen, Yu.M. Perelman and I.M. Gorykov propose to carry out zonal rheography of the lungs in pregnant women suffering from this disease, in addition to spirography with the definition of peak expiratory flow rate (PEFR, l/s) and to evaluate the breathing capacity of the lower zone of the right lung (Dor, Ohm), and then calculate discrimante equation according to the obtained results:

$$D = -5{,}999 \times MFRpeak - 7{,}491 \times DOr,,$$

where D is discriminant function, boundary value is –48,39. Non-controlled progress of asthma is forecast by these authors when D is less –48,39. According to their reports, the indicator of the sensitivity of this forecasting amounts to 87.8%, specificity – to 83,3%, and accuracy – to 84.7% [37].

Yu.M. Perelman et al. determine by method of spirography the forced expiratory volume in first second (FEV_1) in% of the proper value, the change of forced expiratory volume in first second (ΔFEV_1) after bronchial provocation test with 3-minute isocapnic hyperventilation with cold air in% from the initial value, determine the coefficient of variation (υ) between densitometric indices of six lung regions in inspiratory phase of respiration, the total difference (RSO) between densitometric indicators in the middle zones of both lungs on the inhale and the exhale up to densitometric increased inspiratory indice (expressed in percentage), by means of computer tomography of lung with inspiratory-expiratory test, and then solve a discrimante equation:

$$D = 1287\ \upsilon + 213\ RSO + FEV_1 + 1{,}25\ \Delta FEV_1,$$

and if the value of D is less 139.2, non-controllability of asthme rogress shall be predicted in remote (12–14 months) period of time [1], [39].

Noteworthy is the fact that «routine» monitoring of controllability of asthma is mainly based on the assessment of clinical symptoms and indicators of external respiration function, and that studies of these parameters are regulated by international and national guidelines for the management of patients with asthma. At the same time, these documents do not provide for definition of the characteristics of inflammatory process in airways, their remodeling and hyperresponsiveness, although they characterize the most important pathogenetic mechanisms in asthma, and are important in the development of its non-controlled progress. It was proved the importance of atopy in the pathogenesis of severe non-controlled asthma, but its different phenotypes, the role of this mechanism in the development of treatment resistance was mixed: the most important occurred in patients with unstable asthma; the least – in the case of chronic asthma with persistent bronchial obstruction. It was also revealed that regardless of clinical phenotype of severe asthma, low sensitivity to therapy is associated with progressive persisting inflammation in the respiratory tract. Given this, studies of various biomarkers of inflammatory process such as effector cells of allergic inflammation, cytokine profile, metabolism of nitric oxide, oxidative stress, acidification of airway are widely used in the diagnosis and forecasting of non-controlled asthma [14].

O.K. Koloskova et al. determine in school-age childrenthe risk of loss of controllability of asthma according to the nature of the inflammatory response of bronchi, namely, they calculate the absolute content of eosinophilic and neutrophilic granulocytic cells in peripheral blood; and at its values for eosinophilic granulocytic cells of 250 cells/mm^3 and/or neutrophilic cells of 5000 cells/mm^3 or more they diagnose hypergranulocytic pattern of inflammatory response associated with a significant risk of loss of controllability of asthma [22]. J. Casciano et al. suggest using the definition of the content of eosinophils in peripheral blood and comorbidity index of Charlson for predicting non-controlled progress of severe asthma (Charlson Comorbidity Index – CCI [51]). These authors developed a new scale of assessing the risk of development of non-controlled asthma based on readily available medical information and routine laboratory data: a high risk of non-controlled progress of the disease is forecast by the authors at higher levels of eosinophils in the blood ≥ 400 cells / μl, and the result of assessment of CCI > 0 [61].

Yu.V. Zakharov et al. carry out diagnosis of non-controlled progress of asthma in patients receiving baseline anti-inflammatory therapy with combination inhaled corticosteroids and β_2-agonists long acting by GINA 2006 criteria

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and quantitative levels of the various lymphocyte subpopulations in the peripheral blood, which are determined by them by means of indirect immunofluorescence: CD4+lymphocytes (T-helper cells), CD20+lymphocytes (B-cells) and CD25+lymphocytes (regulatory T-cells). The authors consider the progress of asthma as non-controlled if the relative number of CD4+lymphocytes exceeds 44%, CD20+lymphocytes exceeds16%, CD25+lymphocytes exceeds 11% [9], [28], [32], [29].

To assess the efficiency of standard basic therapy in patients with bronchial asthma, Russian inventors L.M. Ogorodova define the generally accepted clinical and functional parameters before and after treatment, and examine the levels of IL-5 and IL-4 in blood serum, and in the absence of dynamics or increase in these indicators compared to the initial values assess the standard basic therapy as ineffective [36]. At the same time, I.A. Solovyova and co-authors forecast the effectiveness of therapy of severe asthma by integrated cytokine index defined by them as the sum of the arithmetic mean value of indexes of proinflammatory cytokines and the arithmetic mean value of indexes of anti-inflammatory cytokines; cytokine concentration is examined twice: during exacerbation of severe asthma and after its elimination. For allergic steroid-dependent severe asthma Pro-inflammatory cytokines IL-2, IL-4, IL-6, IL-8, TNF-α, INF-γ and anti-inflammatory IL-10 are determined; for non-allergic asthma the levels of proinflammatory cytokines IL-2, IL-6, IL-8, TNF-α, INF-γ and anti-inflammatory IL-4 and IL-10 are determined. They compare integral cytokine indexes calculated at exacerbation of severe asthma and after its elimination, and if the difference between them is less 1 RU, they forecast low efficiency of the basic anti-inflammatory therapy for severe asthma, that is non-controlled progress of the disease [45].

G.P. Pobedionna et al. propose also to determine before and after treatment the content of proinflammatory cytokines IL-1b, TNF-α and IL-8 for monitoring the effectiveness of treatment of patients with severe asthma and asthma of moderate severity; however not in serum, but in condensate of exhaled air [23].

One of indirect methods of assessment of inflammation in the bronchi in asthma is identification of bronchial hyperresponsiveness in metacholine (or histamine) test. On this basis, L.O. Bezrukov et al. carried out tests with dosed physical load in school-age children with asthma, according to the results of which they determine the index of bronchospasm. Also they carry out bronchoprovocation test with histamine (PC20H), in order to create dose-dependent curve reflecting the hyper-reactivity of respiratory tract. While the index of bronchospasm exceeds 7.0%, and dose-dependent curve exceeds 2.4 RU – they diagnose non-controlled progress of asthma [20].

Numerous studies have shown involvement of non-immune mechanisms in the etiopathogenesis of asthma, in particular those due to the functioning of the vascular endothelium. This is the basis of the use of parameters characterizing the state of endothelial cells for diagnosis of non-controlled progress of the disease [17]. N.A. Orlova et al. patented two methods of assessment of the efficiency of basic anti-inflammatory therapy of bronchial asthma in children, in which in the absence of normalization of indicators of peakflowmetry an additional criterion of non-controlled progress of the disease shall be a negative dynamics of endothelemia (that is, the number of circulating endothelial cells in peripheral blood) [34], as well as negative dynamics of the level of serum endothelin-1 in the patient after three months of treatment with inhaled corticosteroids [33].

O.K. Koloskova et al. perform diagnosics of the condition of the bronchi for predicting non-controlled progress of asthma in schoolchildren, given the markers of their remodeling, namely in terms of lability of bronchial tubes, and vascular endothelial growth factor (VEGF) of sputum in supernatant fluid, a mitogenic peptide playing a key role in neovascularization of the bronchial mucosa. Non-controlled progress of bronchial asthma in schoolchildren is predicted by these authors when the VEGF concentration of exceeds 120 PG/ml, and index of lability of the bronchial tubes in FEV_1 is less than 10% [24].

M.T. Lutsenko et al use radioaerosol method for forecasting of non-controlled asthma by which they determine the rate of bronchial mucociliary clearance (MCC) of radiotracer in% per 1 hour, and then they solve a discrimante equation:

$$D = -0{,}6 \ldots MCC,$$

and when the value D exceeds15,51, they predict unstable progress of asthma [41].

Many scientists have demonstrated that chronic inflammation in the respiratory tract of patients with asthma led to significant changes in the composition of exhaled air. Therefore, these parameters are also used for diagnosis and forecasting non-controlled progress of the disease. Russian scientists L.O. Krasnobaeva et al. use laser spectroscopy of exhaled air as an additional criterion for the assessment of effectiveness of therapy in patients with severe asthma [8]. While P.A. Selivanova et al. predict non-controlled progress of severe asthma according to the results of ACT, parameters of external respiration function (PFR, FVL, MFR25, MFR50, MFR75, FEV_1 and FEV_1 after the salbutamol test and ΔFEV_1) and concentrations of gases in exhaled air (CO, NO, NO_2); based on these data, with certain mathematical formulas, the authors calculate the likelihood of assigning the patient to a group with high (R1) and low (R2) risk of non-controlled progress of severe asthma; and if R1 > R2 they predict a high risk of the development of non-controlled progress of the disease, which gives the opportunity to develop the best management plan for each patient [40].

Tsyplenkova S.C. and Myzernytsky Yu. L. study in children patients with bronchial asthma the level of nitric oxide in the condensate of exhaled air (NOex), determine the levels of total IgE, circulating immune complexes (CIC) and precipitating serum antibodies; and at the detection of NOex within the normal range, or slightly elevated at normal levels of total IgE, high CEC and precipitating serum antibodies they suggest that the effectiveness of basic therapy is low, indicating inability to control the

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progress of asthma and a low informative monitoring of Noex level [44].

At the same time, T.I. Eliseeva et al. developed and published in an open access computer program (http://clma.nnov.ru/files/-badiagnostics2013.xls), which allows to securely verify the level of controllability of asthma on the basis of the analysis of objective studies (spirometry parameters, and results of the assessment of bronchial patency variability), organspecific inflammatory markers (pH and total content of metabolites of nitric oxide in the condensate of exhaled air), and oxidative stress (parameters of chemiluminescent saliva) [13, [18], [7]. These authors have convincingly demonstrated that combined (comprehensive) methods of assessment of controllability of asthma based on functional and biometric approaches, surpass the information content of isolated techniques and demonstrate a higher level of statistical significance [9].

L.L. Gurieva et al. predict non-controlled progress of atopic asthma in children according to the level of nitric oxide in the blood serum, the sex and the age of the child: the probability (P) of non-controlled progress of the disease is calculated by the authors according to the formula developed by them and, if P exceeds 0.60 in children with mild asthma, and asthma of moderate severity, they predict the probability of non-controlled progress of the disease and the lack of efficacy of low-dose inhaled corticosteroids. High informative value of this forecast, according to the authors, allows to differentially predict non-controlled progress of atopic asthma, and to choose an individual program of basic therapy and the schedule of monitoring the patients [40].

S.V. Kovalenko and O.I. Fediv, in the period between attacks in moderate and severe asthma, use cytochemical method for determining the number of catecholamines in an ordinary erythrocyte, and with the growth of catecholamines compared with the age norm they predict semicontrolled asthma [23].

Unstable progress of bronchial asthma, according to Yu.O. Krylov et al., is predicted by integral assessment of the functional state of the pulmonary microcirculation, pressure in the pulmonary artery and reactivity of the respiratory tract. For this purpose they explore the original value of the functional reserve capacity of pulmonary capillary blood flow in%, average pressure in the pulmonary artery (AvPPA) in mm Hg. St. and daily variability of peak volumetric expiration rate (ΔPFR) in%, and solve a discrimante equation:

Δ = + 1,376 • FEV-2,087 • AvPPA-1,023 • ΔPFRex.

And when the value D exceeds 25,71, they predict unstable bronchial asthma and the lack of control of the disease [42].

O. Yu. Pozdnyakova, V.A. Baturin and A.P. Bayda proposed a method for forecasting non-controlled asthma, which involves performing spirometry, peakflowmetry, additional collection of medical history, laboratory studies, analysis of obtained data and identification of risk factors: family history, comorbid disease, the presence of bacterial and fungal infection, sensitization, smoking, treatment with glucocorticoids for more than 10 years, exposure to adverse environmental factors – poor living conditions and hazardous work, the presence of pets, age older than 50 years, the use of β_2-agonists short acting up to 6 times per day, the level of material income less than 20 thousand per month, and indicators of external respiration function (ERF) – FIL, FEV_1, PFR under 60% ofnormal value, SARS, bronchitis more often 5 times a year. The authors assign 1 point to each of these factors, tabulate the total points, and at the total points from 9 to 12 predict a very high risk of non-controlled asthma, at 6 to 8 – high risk, at 3 to 5 – mild risk, and at 0 to 2 – low risk [43].

Currently, the most promising direction of research that expand the understanding of pathogenetic mechanisms of the development of therapeutic resistance in asthma, and are used for the development of new diagnostic tests with high sensitivity and specificity, are considered genetic research. Asthma is one of the first diseases for which the genom-wide analysis of genetic associations was carried out. Now, over twelve genom-wide studies confirmed association of asthma with the loci where genes-candidates of this disease are localized, such as (5q23–31, 5p15, 5q31.1–33, 6p12–21.2, 11p13, llql2–13, 12ql4–24.1, 13qll-14, 13q21.3, 14qll.2–13, 16pl2.1–11.2, 17pl 1.1-ql 1.2, 19ql3, 21q2) and others. They have allowed to determine 15 loci on 10 different chromosomes associated with the risk of asthma, and features of its progress. According to experts, it is the genetic determinism that causes 60% – 80% of variations in the response of patients to asthma medications [2], [3], [10], [14], [46], [49], [54]. In this regard, the study of polymorphism of target genes for drug is of particular urgency – pharmacogenetic studies. During their conduct, genes encoding the «target molecules» of drugs (receptors, enzymes of metabolism and transport of drugs, johnny channels) are examined, as well as genes whose products are involved into pathogenetic processes in asthma: cytokines, transcription factors and others. In recent years, the relationship between pharmacokinetics and pharmacodynamics of drugs with gene polymorphism of transporters of organic anions (OATP-C, OAT-1, OAT-3) and cations (OCT-1) are actively explored, as well as gene of transport protein Pgp-170, which is encoded by the MDR1 gene. Also, a group of genes encoding enzymes of biotransformation of drugs is actively studied, in particular, isozymes of cytochrome P-450 (CYP2E1, CYP1A1, CYP2C19) and enzymes of the phase II of biotransformation (N-acetyltransferase, glutathione SH-S-transferase and others). GSTP1 gene, encoding glutathione S-transferase, is considered the most attractive gene candidate for asthma and atopy, because it is more highly expressed in the lung tissue and located in the locus llql3 for which traction with atopic symptoms has been proven [2], [3], [10], [14], [46]. Enzymes controlled by these genes are responsible for the metabolism of all xenobiotics, including a variety of pharmacological agents. Genes associated with resistance to GCS in asthma include the cluster identified

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in 5q31–32-chromosome, which among other includes glucocorticoide receptor gene (NR3C1), and the genes of receptors for IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF (32-blockers (ADRB2) for biosynthesis of of leukotrienes [2].

It is demonstrated that mutations leading to the replacement of one amino acid in β_2-adrenoreceptor (ADRB2) predetermine severe progress of asthma, reduce therapeutic response and accelerate processes of desensitisation of receptors. Currently, the most studied and the most common is polymorphism with Gln27Glu amino acid replacement, which is associated with a reduction in the number of receptors on the cell surface of the bronchial tubes after the interaction with β_2-agonists, and contributes to the development of bronchial hyperreactivity (BHR). It is established that carriers of Glu27Glu genotype of ADRB2 gene show more likely a non-controlled progress of asthma, a more pronounced bronchial obstruction and often use beta-blockers short acting, when compared to carriers of Gln27Gln and Gln27Glu genotypes [2], [3] [10], [14], [47], [49], [59], [62].

Pharmacogenetic studies have been increasingly included in clinical practice of an allergist, including for the diagnosis and forecasting of progress of asthma. O.K. Koloskova et al. predict non-controlled bronchial asthma in schoolchildren in the presence of deleted polymorphism in glutathione-S-transferase T1 and M1, defined by them by the method of multiplex polymerase chain reaction, and index of controllability according to GINA clinical-scale – 17 points or more [26]; in the presence of deleted polymorphism in glutathione-S-transferase T1 and M1 and lysis of azo-albumin in the condensate of exhaled air exceeding 1.56 ml/h. [20]. These authors argue that the identification of deletions in the genes of glutathione-S-transferase T1 and M1 in asthma in schoolchildren can also be used to predict the lack of effectiveness of standard maintaining therapy [25].

L.M. Ogorodova et al., 3 months after the start of treatment of patients with asthma, determine the levels of INC2, INC3, GJA8, SV2 gene expression in DNA of blood lymphocytes by using Affymetrix microarrays. After conducting genotyping, they expect the probability of assigning an individual to the group with high (R1) and low (R2) risk of treatment resistance by the formula:

$$R1 = -351{,}966 - 48{,}274 \times INC2 + 46{,}608 \times INC3 + 129{,}530 \times GLA8 + 105{,}438 \times SV2A$$

where: 48,274; 46,608; 129,530; 105,438 are numerical values being coefficients; (–351,966) is a constant for patients with asthma with a high risk of treatment resistance; INC2, INC3, GJA8, SV2 are genotypes.

$$R2 = -403{,}217 - 64{,}874 \times INC2 + 55{,}603 \times INC3 + 141{,}648 \times GJA8 + 116{,}342 \times SV2A$$

where: 64,874; 55,603; 141,648; 116,342 are numerical values being coefficients; (–403,217) constant for individuals with high risk of the development of asthma and if R1 > R2 they predict high risk, while if R1 < R2 they predict low risk of therapeutic resistance in the patient with bronchial asthma [43].

Korean scientists use polymorphism of eotaxin genes that contains the EOT2+1265A>G as a criterion for the diagnosis and prediction of non-controlled asthma, which is associated with the occurrence of asthma, and EOT1+123A1a>Thr, which is associated with high IgE levels. Researchers from the United States D. Gudbjartsson, U. Bjornsdottir and P. Sulem invented a method in which they use polymorphic variants of genes containing rs1420101, rs3939286, rs2416257 and rs9494145h for diagnosing asthma and predicting its progress, the genes are associated with high levels of eosinophils in asthma, myocardial infarction and hypertension. The authors believe that such polymorphic genetic markers can be used to predict and evaluate an individual's probable response to therapy [55].

In fact, modern research has formed a new direction of strategy of diagnosis and prediction of non-controlled progress of asthma, based on the determination of genetic factors. Their study forms the future of medicine;

Table 1. Controllability of bronchial asthma (GINA, 2016)

Control of symptoms of the disease	Response controlled		Controllability		
			Semicontrolled	Non-controlled	
In the progress of 4 last weeks, the patient showed:					
Daytime symptoms more often 2 times a week	YES		Nothing of listed	1–2 of listed	3–4 of listed
	NO				
Night waking due to the asthma	YES				
	NO				
The need for drugs to relieve symptoms more than twice a week	YES				
	NO				
Any limitation of activity due to asthma	YES				
	NO				

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a personalized medicines that takes into account specific component in the forecast of the tendency to the disease and its phenotypic manifestations. But molecular-genetic and pharmacogenetic studies require a significant financial outlay (expensive equipment and reagents, software), highly qualified specialists, and are not available neither for medical, nor for patients. There are certain methodological limitations. Thus, the value of pharmacogenetic information may vary considerably and this is due to many factors, in particular, the prevalence of alleles in the population, the expressiveness of association between the polymorphism and pharmacogenetics effect. As well, many associations determine only a small part of the variability of response to drugs. For example, CRHR1 gene variability is less than 3%. Pharmacogenetics regulation depends on several or many loci acting together via complex intragenic interaction [10], [14].

A separate issue is the use of pharmacogenetic information for combined preparations, for example, if the patient is a carrier of alleles that determine a reduced response to β_2-agonists, and at the same time, of CRHR1 gene polymorphism associated with better response to IGCS, it will be difficult to predict response to a combination of β_2-agonist long-acting and IGCS. It is also necessary to consider the characteristics of the patient population with asthma involved in the study (severity, level of control, the severity of clinical manifestations, etc.), on the basis which effects were identified. For example, pharmacogenetic information obtained from a cohort of severe asthma, is not always suitable for patients with moderate severity and patients with mild forms of the pathology [14].

Thus, monitoring and predicting of controllability of asthma remain one of central problems in the management of patients. For this purpose, validated and customized questionnaires are used, as well as data of spirography, peakflowmetry, pneumotachography and other functional tests, definition of subpopulation composition of lymphocytes is carried out, pro- and anti-inflammatory cytokines and other inflammatory markers in blood, sputum, or condensation of exhaled air and study of its gas composition and content of certain substances are performed, as well as genotyping. Each of these methods has its advantages and disadvantages, but none of them is multifunctional, due to the heterogeneity of pathogenetic mechanisms in asthma and the diversity of the pheno- and endotypes. This requires the use of complex (combined) methods as diagnosis and predicting of non-controlled progress of the disease, and also dictates the necessity of its improvement [4]. Further development and use in practice of methods of individual long-term prediction of non-controlled progress of asthma will contribute to the improvement of providing patients with this disease with medical care and improvement of their quality of life.

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ДИАГНОСТИКА И ПРОГНОЗИРОВАНИЕ НЕКОНТРОЛИРУЕМОЙ БРОНХИАЛЬНОЙ АСТМЫ

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Резюме

Осуществление мониторинга и прогнозирования контролируемости бронхиальной астмы остается одной из центральных проблем ведения пациентов. Неконтролируемая бронхиальная астма представлена различными клиническими, функциональными и патофизиологическими фенотипами и эндотипами, что обусловлено различными механизмами ее формирования и потому требует различных подходов к ее диагностике и прогнозированию.

Для определения контролируемости бронхиальной астмы нужно провести оценку ее симптомов, обструкции дыхательных путей, риска нежелательных побочных эффектов терапии и будущих обострений болезни. Для этого используются валидизованные и авторские опросники, данные спирографии, пикфлоуметрии, пневмотахографии и других функциональных тестов, проводится определение субпопуляционного состава лимфоцитов, про- и противовоспалительных цитокинов и других маркеров воспаления в крови, мокроте или конденсате выдыхаемого воздуха, исследуется его газовый состав и содержание определенных веществ. Также проводится генотипирование больных бронхиальной астмой.

В статье представлено краткое описание этих подходов. Каждый из них имеет свои преимущества и недостатки, но ни один не является универсальным. Это обусловливает целесообразность применения комплексных (комбинированных) методов как диагностики, так и прогнозирования неконтролируемого течения бронхиальной астмы, а также диктует необходимость их дальнейшего совершенствования и внедрения в практическую деятельность медицинских учреждений пульмонологического и аллергологического профиля. Это будет способствовать улучшению предоставления этой категории пациентов медицинской помощи и улучшению качества их жизни.

Ключевые слова: бронхиальная астма, контролируемость, диагностика, прогнозирование.

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ДЕЯКІ ПІДХОДИ ДО ДІАГНОСТИКИ ТА ПРОГНОЗУВАННЯ НЕКОНТРОЛЬОВАНОЇ БРОНХІАЛЬНОЇ АСТМИ

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Резюме

Здійснення моніторингу та прогнозування контрольованості бронхіальної астми залишається однією з центральних проблем ведення пацієнтів. Неконтрольована бронхіальна астма представлена різними клінічними, функціональними та патофізіологічними фенотипами і ендотипами, що обумовлено різними механізмами її формування і тому потребує різних підходів до її діагностики та прогнозування.

Для визначення контрольованості бронхіальної астми потрібно провести оцінку її симптомів, обструкції дихальних шляхів, ризику небажаних побічних ефектів терапії і майбутніх загострень хвороби. Для цієї мети використовують валідизовані і авторські опитувальники, дані спірографії, пікфлоуметрії, пневмотахографії та інших функціональних тестів, проводиться визначення субпопуляційного складу лімфоцитів, про- і протизапальних цитокінів та інших маркерів запалення в крові, мокротинні або конденсаті повітря, що видихається, досліджується його газовий склад і вміст визначених речовин. Також проводиться генотипування хворих на бронхіальну астму.

У статті подано короткий опис цих підходів. Кожен з них має свої переваги і недоліки, але жоден з них не є універсальним. Це обумовлює доцільність застосування комплексних (комбінованих) методів як діагностики, так і прогнозування неконтрольованого перебігу бронхіальної астми, а також диктує необхідність їх наступного вдосконалення і впровадження в практичну діяльність медичних установ пульмонологічного та алергологічного профілю, що сприятиме поліпшенню надання медичної допомоги цій категорії пацієнтів і поліпшення якості їхнього життя.

Ключові слова: бронхіальна астма, контрольованість, діагностика, прогнозування.

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