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**IMMUNOLOGICAL AND GENETIC APPROACHES
TO OPTIMIZE TREATMENT ASTHMA IN
ADOLESCENTS**

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ABSTRACT

of a dissertation on the scientific degree competition
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Work carried out in Samarkand state medical institute and Institute of Immunology, Academy of Sciences of Uzbekistan

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Dissertation can be reviewed at the Information-resource centre of Institute Immunology of the Academy of Sciences of the Republic of Uzbekistan.

Abstract sent out on _____

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GENERAL CHARACTERISTICS OF DISSERTATION

Topicality of the work. Adolescents in Uzbekistan - it is a significant and most important part of society, which serves as its reproductive, intellectual, moral, labor and defense reserve. Due to this Decree of the President of Uzbekistan and the resolution of the CM approved state programs, successfully implemented in the republic, "On complete solution of problems of improvement of the younger age group" (R CM Uzbekistan from 03.12.1993, N589) "On measures for implementation of priority directions of the medical culture in the family, women's health, birth and upbringing of healthy children" (R CM Uzbekistan from 05.07.2002, N242), "On additional measures to improve the health of women and younger generation" (R CM Uzbekistan from 26.07.2004, N358) which include increasing medical culture, the creation of conditions for the birth and upbringing of healthy children, the organization of the early detection of diseases and clinical examination of the younger generation in order to reduce the frequency of chronic illness and disability in children and young people.

Bronchial asthma (BA) is one of the most common and serious diseases, which in the world suffers from 3 to 12% of children have the world's population (Bridge Y.M., Demchuk A.V., 2005; Akdis S.L et al., 2009; Sullivan S.D., Bayern P.M., 2011). Proportion of adolescents with asthma is 36-40% of all children with this disease (Astafyeva N.G., 2005; Alexeev V.A., 2006; Andreev L.A., 2004; Mizernitsky J.L. et al., 2011). According to official statistics of the Republic of Uzbekistan incidence of asthma among children and adolescents from 2005 to 2010 increased by 26% (Ubaydullaev A.M. et al., 2010). High prevalence of asthma in the numbers of adolescents, characteristics of the disease, age-related aspects of the functioning of the endocrine and immune systems of teenagers that cause difficulties which arise in the course of the diagnostic process, highlight the need to find innovative approaches to diagnosis and treatment of this disease.

It is known that the key immune mechanisms in the pathogenesis of the vast majority of BA cases is real and indisputable fact (Gaymolenko I.N., 2004; Bogatyreva E.V., 2007; Kryvtsov A.V., et al., 2007; Kovalev V.L., et al. 2007; Cao J. et al., 2011). Currently, considerable interest to researchers involved in the pathogenesis of positions of allergic diseases, especially asthma, along with IL-4 and IL-13 causes a number of other (IL-6, IL-8, IL-10, IL-5, IFN- α and INF-g) immunoregulatory cytokines (Kuo P.L. et. al., 2011).

Genetic predisposition plays an important role in the development of allergic diseases. At present I present data have been obtained due to asthma and associated with the disease is recognized signs polymorphism approximately 150 genes (Baranov V.S., 2000; Vavilin V.A., 2003; Sokolova T.M., 2005; Freidin M.B., 2011). Significant contender for the role of major gene susceptibility to asthma is a gene code β -chain of high affinity receptor IgE. Interaction of elevated levels of antigen-specific IgE to Fc ϵ RI β plays a central role in the genesis of a stalemate allergic asthma (Balabolkin I.I. et al., 2000; Blank U., 1999). Particularly attractive candidate gene asthma is also one of the enzyme genes biotransformation - GST

$\pi 1$, encoding glutathione S-transferase $\pi 1$ expressing almost exclusively in the lung tissue in lung tissue. This gene is located at the locus 11q13, for which repeatedly shown clutch with atopic symptoms (Balabolkin I.I. et al., 2009; Ali - Osman F., 1997). Accumulated data in the literature say about the connection floor and gene polymorphisms Fc ϵ RI, GST $\pi 1$ with various allergic disorders (Koppelman G.H., 1998; Shirakawa T. et al., 1996; Sandford A.J., Malerba G., 2005).

From this perspective, the study of immunological and genetic mechanisms of the pathogenesis of this disease for the construction of rational treatment and prevention emphasizes the relevance of this thesis research.

Degree of study of problem. Despite the enormous attention paid to the problem of asthma, measures of effective diagnosis, treatment and prevention, and Professor of this pathology in adolescence and insufficiently developed accurately. Have not been studied sufficiently prevalence and clinical features of asthma in adolescents, as well as diagnostic capabilities of studies of lung ventilation function with carrying out various tests (Lyapunov E.V., 2007; Krasnorutskiy O.N., 2008). Quite controversial and you available data on changes in the immune status and activation markers involved in allergic inflammation in asthma adolescents (Kozlov O.S., 2007; Zlodeeva E.A., 2008). Not updated diagnostic and differential diagnostic value of the determination of cytokines, namely IL-6, IFN- γ , their regulatory actions on immunocompetent cells e by participating in the immune response in asthma. In domestic work is not surveyed genes Fc ϵ RI β , GST $\pi 1$, defining structure at hereditary predisposition to asthma.

All this is the basis for the work devoted to following bases and formation of asthma in adolescence and to the development of effective programs for early diagnosis, treatment and prevention of asthma that determines the relevance and priority of the post in the universe we problem.

Connection of dissertation work with state programmes or plans of Scientific-research works. The thesis work was carried out within the research department treatment plan number 2 for the preparation of GPs SamSMI, as well as in applied research project ITD - 1109-11.3-0-13801 "Development of new diagnostic technologies, differentiated treatment, prevention and immunorehabilitation n and consequently - caused forms asthma in adolescence" (2009-2011).

Purpose of research. Explore the immunological and genetic mechanisms and pathogenesis of asthma adolescents and form the basis of this plan rational diagnostic and therapeutic measures in this pathology.

Tasks research:

1. Set the clinical features of asthma population on d germs living in the Samarkand region, in the early stages of the pathological process in the bronchopulmonary system.

2. Examine the features of the state of cellular and humoral immunity, as well as activation markers in BA as a teenager in plants by determining the immunophenotype of lymphocytes in the peripheral blood.

3. Examine the level of production immunoregulatory cytokines interleukin-6 and interferon- γ and install them and inform the pathogenetic activity at BA among teens.

4. To characterize the distribution of allele and genotype frequencies of polymorphic variants of genes Fc ϵ RI β and GST π 1 in a population of Uzbek people with asthma, in comparison with the healthy part of population.

5. Explore the clinical and immunological aspects of the effectiveness of therapies using drugs and polioksidony cikloferon in patients with asthma in adolescence.

6. Based on these studies to develop a multivariate model of formation of bronchial asthma and develop an optimal algorithm for the diagnosis, treatment, prevention in adolescents with this pathological condition.

Object and subject of research. The object of the study were 4094 adolescents living in Samarkand region of Uzbekistan. The subject of the study were venous blood and serum for the quantitative determination of the main indicators of immune and cytokine status, genotyping of polymorphic variants of candidate genes that determine hereditary susceptibility to asthma, as well as clinical and immunological efficacy of drugs cikloferon and polioksidony patients.

Methods of research. Were used screening, clinical, functional, immunological, genetic and statistical methods.

Principial positions taken out to defense.

1. Clinical features of asthma in adolescents is the predominance of periodical exposure and lung persistent forms of asthma, as well as the high frequency of association with allergic processes in other organs and tissues, which necessitates a thorough investigation with the inclusion of biographical questionnaires and functional tests bronchomotor stages of early diagnosis of the disease in order to ensure timely adequate treatment of the pathological process in the bronchopulmonary system.

2. Features of the immune status of patients with asthma adolescents is conjugated immunodeficiency cellular and humoral immunity and imbalance products immunoregulatory cytokines IL-6, IFN- γ , while there are specific features of immune reactivity and cytokine status that characterize the clinical features of the pathological process in the bronchopulmonary system.

3. That polymorphic variants of genes Fc ϵ RI β , GST π 1, which is an important component of the genetic basis, make a significant contribution to the susceptibility to the development of asthma in the Uzbek population. Genes Fc ϵ RI β , GST π 1 play a role not only in the development of completely predisposed to asthma, but also in the formation of immunological disorders in the pathogenesis of the disease.

4. The expediency of incorporating the complex immuno therapy drugs and tsikloferon polioksidony in asthma in adolescents with clinical and functional recovery and parameters of immune reactivity, was more pronounced when using polyoxidonium.

Scientific novelty. Obtained information characterizing the true prevalence of asthma in adolescence among the population of Samarkand region. Based on the results of clinical and instrumental studies identified clinical features of the disease in adolescents with asthma and suggested the introduction to the work of doctors teen clinics layered approach testing, which significantly improves detection of asthma in adolescence and optimize preventive measures in high-risk groups. First defined the peculiar characteristics of the quantitative parameters of the immune status of patients with asthma in the cohort of adolescent age. Proposed regulations and the corresponding recommended mendatelnnye documents for a healthy adolescent population of the Samarkand region of Uzbekistan. World's first comprehensive assessment of the cytokine profile of blood serum in bronchial asthma in adolescents. Specific features of products immunoregulatory cytokines IL-6 and IFN- γ and their pathogenetic and regulatory information content in asthma among adolescents.

First analyzed the distribution of alleles and genotypes of polymorphic gene variants and gene Fc ϵ RI β GST π 1 among patients with different phenotypic variants of AD and healthy individuals of Uzbek nationality, which resulted in the identified markers of increased risk or, conversely, resistance to the development of asthma in adolescents Uzbek ethnicity.

On the basis of clinical, instrumental and laboratory research, a valid model of asthma, the algorithms of phase-diagnosis, treatment and prevention of asthma in adolescence in terms of disclosure of important moments of the pathogenesis of the disease, allowing to build a rational sequence of diagnostic search, aimed at verifying the diagnosis and expedient construction of preventive activities.

Scientific and practical value of results of research. The obtained data on the lack of diagnosis of asthma in adolescents allow a more rational organization of social and medical assistance to patients in this age group in the Samarkand region. Proposed use of questioning adolescents in primary care physicians in the periodic medical preventive examinations followed by functional testing aimed at detecting violations of pulmonary ventilation and, if necessary, study the reversibility of bronchial obstruction in the test with a bronchodilator.

Identified abnormalities in immune status in adolescents with asthma, characterized by a decrease in both cellular and humoral immunity, indicate a need to consider the diagnosis of immunodeficiency states and optimization of treatment - rehabilitation measures in adolescents with asthma.

Results of work are important for practical medicine by disclosing significant pathogenetic mechanisms of clinical and pathogenic forms of asthma in adolescents. The peculiarities of production of IL-6 and INF- γ in the pathogenesis of the disease, depending on the identified parameters are introduced into clinical

practice as additional differential diagnostic criteria focus pathogenetic process in asthma in adolescence.

Results of the thesis research 109C/T polymorphism of the gene variant FcεRIβ, Ile105Val polymorphic variant gene GSTπ1 contribute significantly to the overall view of the genetic basis of susceptibility to asthma. These dissertation can serve as a basis for further research to identify genetic risk factors for asthma and the development of adequate therapeutic measures. Results of the study can also be used in the educational process of medical and less widely biological universities. Material used in research practice physicians and adolescent clinic department of pulmonology allergy-CMA Samarkand, in the learning process for the preparation of therapy department GP SamSMI.

Realization of results and economic efficiency. Results of the study presented in the form of guidelines and innovations that are introduced into practice physicians adolescent clinic, allergy and pulmonology department of city medical association Samarkand named M.N. Khaitov and learning process for the preparation of therapy department GP SamSMI.

Approbation of work. The main provisions contained in the thesis presented and reported at scientific congresses, conferences, seminars, meetings during the 2008-2012 period.: 9th International Congress on Cell Biology & 20th Annual Conference of the Korean Society for Molecular and Cellular Biology (2008 - Seoul, Korea), the Republican Scientific-Practical Conference "Achievements and prospects for prevention, diagnosis, treatment and rehabilitation of internal diseases", dedicated to the 90th anniversary of the Scientific Research Institute of Balneology and Physiotherapy Semashko. (2009, Tashkent, Uzbekistan), 14th Congress of the Asian Pacific Society of Respiriology & 3rd Joint Congress of the APSR / ACCP (2009 - Seoul, Korea), the scientific-practical conference "Clinical Immunology, Immunogenetics - interdisciplinary problems" with international participation, perturbed devoted to the 25th anniversary of the Institute of Immunology, Uzbek Academy of Sciences, (2010, Tashkent, Uzbekistan), 12th Asian-Pacific Congress of Clinical Biochemistry (2010, Seoul, Korea), 13th Annual Congress Turkish Thoracic Society (2010, Istanbul, Turkish), VII Congress of Tuberculosis and Pulmonology of Uzbekistan (2010, Tashkent, Uzbekistan), European Respiratory Society Annual Congress (2010 - Barcelona, Spain), the scientific and practical conference with international participation "Actual issues of medicine," dedicated to the 80th anniversary SamGosMI (2010, Samarkand, Uzbekistan), VI scientific-practical conference of young scientists with international participation "Zavadsкая reading" dedicated to the 95th anniversary of the Department of Internal Medicine (2011, Rostov-on-Don, Russia), the international medical congress "Health of the Russian Federation, CIS countries and Europe "(2011, Moscow, Russia), scientific and practical conference with international participation "Medicine: new developments in theory and clinical practice "(2011, Sharja, UAE), Republican Scientific and Practical conference "Actual problems of medicine" (2012, Tashkent, Uzbekistan), XVII

International Congress of Rehabilitation Medicine and immunorehabilitation and V World Forum on asthma and respiratory allergies (2012, New York, USA).

Publication of results. On the topic of the dissertation is published 39 scientific papers, including one scientific manual, guidelines 3, 18 journal articles, 14 abstracts at conferences and congresses, 3 rationalization proposals.

Structure and volume of dissertation. The thesis consists of an introduction, literature review, research methods and material, five chapters of their own research findings, practical recommendations, a list of references consisting of bibliographic titles 419 (including 230 in Russian and other languages 189). The main text of the dissertation is set out on pages 189 typing, illustrated 6 tables 52 and drawings.

MAIN CONTENTS OF DISSERTATION

In the introduction the urgency of the thesis, formulated the goal and objectives of the study, the main points to be defended, given scientific novelty and scientific and practical significance of the results provides information about testing and publication of the results of work, scope and structure of the short dissertation.

The first chapter presents an overview of the literature, consisting of five sub-chapters, which provides information about the current state of the problem of asthma in the adolescent population; immunological mechanisms of pathogenesis and participation of cytokines in immune regulation in bronchial asthma in adolescents studying molecular genetic basis of several genes responsible for the development and predisposition to asthma; immunofarmakopreparatov use contemporary ideas in asthma.

The second chapter describes the materials and methods. In accordance with the objectives and tasks of the work carried out a comprehensive survey of 4094 adolescents from 2007 to 2011 Program of scientific research has been carried out on the basis of Samarkand city adolescent clinic and department of Allergology-Pulmonology Samarkand City Medical Association named after M.N. Khaitov. According to the scheme approved by the International Symposium on periodization age puberty, isolated adolescence (boys - from 13 to 16 years girls - from 12 to 15 years) and adolescence (boys - 17 to 21 years of girls - 16 to 20). Clinical diagnosis verification in the thesis was carried out in accordance with the international classification of WHO (X revision, ICD-10) diagnostic criteria and Global initiative for asthma (GINA, 2006).

The survey included a survey to identify the prevalence of asthma among adolescents, followed by a sample of adolescents to clinical and functional examination, together with specialists adolescent clinic. Among surveyed contingent boys in adolescence was - in 1224, in the youth - 766 girls in adolescence was - in 1318, in the youth - 729. The study population was Samarkand - 2326 Urgut district - 1711 persons puberty. If you suspect a common asthma conducted laboratory and instrumental methods of diagnosis, including the study of a general analysis of blood leukocyte count, total sputum examination,

chest radiography, electrocardiography, and the study of respiratory function (ERF).

Depth immunological studies were conducted in cohort of 237 patients with AD and healthy individuals adolescence, which in the course of research studied immunological (CD3⁺, CD4⁺, CD8⁺, CD16⁺, CD19⁺, CD23⁺, CD95⁺, IgA, IgM, IgG) and cytokine status (IL-6 and IFN- γ).

For molecular genetic testing used in the DNA samples of 204 patients BA Uzbek nationality aged 12 to 21 years, selected in the study. Control group consisted of 56 healthy individuals without clinical manifestations of allergic, autoimmune, and infectious and inflammatory diseases, matched by sex and age with patients and do not have family history of atopic diseases.

Among 57 patients with asthma in adolescents during their stay in hospital was conducted nonspecific immunotherapy drugs polioksidony tsikloferon and basic therapy in the complex. In accordance with Regulation GINA adolescents with asthma as basic therapy received cromolyn sodium - Intalum 5 mg, antihistamine (Zyrtec), inhaled corticosteroids - fluticasone propionate 50/100 or Beclason eco-light breathing 100/250, as a bronchodilator received β 2-agonist short steps (salbutamol or fenoterol). Prophylactic efficacy was assessed by clinical characteristics not earlier than one year after the course of therapies.

To study the prevalence of asthma in the thesis we used a questionnaire screening using a questionnaire European respiratory society. Specialized profile approved and recommended by researchers for the epidemiological screening of BA.

Ventilation lung function was studied alone for spirometer «SPIROSIFT SP-5000» (Fukuda DENSHI, Japan) with automatic processing parameters. Bronhodilyatatsionny test was performed by the standard technique. Reversibility of bronchial obstruction was considered positive for growth in FEV1 of 15% or more.

Analysis of polymorphic variants and GST π 1 Fc ϵ RI β gene carried by polymerase chain reaction of DNA synthesis (PCR) thermocycler for RFLP analysis with primers Forward - 5'-GTG GGG ACA ATT CCA GAA GA-3' Reverse - 5'-CCG AGC TGT CCA GGA ATA AA-3'; Forward - 5'-GTA GTT TGC CCA AGG TCA AG-3' Reverse - 5'-AGC CAC CTG AGG GGT AAG-3' and the subsequent detection of the restriction fragments by electrophoresis in a 6% polyacrylamide gel. HLA-phenotype to a standard mikrolimfocitotoxic test (Terasaki PI) c using a panel of HLA-antisera St. Petersburg Research Institute of Hematology and Blood Transfusion.

To test lymphocyte subpopulations and their monoclonal antibodies used and differentiation activation antigens CD3⁺, CD4⁺, CD8⁺, CD16⁺, CD19⁺, CD23⁺, CD95⁺. The concentration of serum immunoglobulins: IgG, IgM, IgA was determined by radial immunodiffusion according to Mancini gel (Mancini et al.).

Determining the level of INF-g and IL-6 in serum were determined by enzyme immunoassay using a test system for ELISA "IFA-INF-g - IL-6" (CJSC "Vector-Best", Russia, 2009).

Statistical analysis was performed on the programs developed in the package EXCEL using a library of statistical functions with the calculation of the arithmetic mean (M), the error of the arithmetic mean value (m), the Student test (t), the probability of error (p), the Pearson correlation coefficient (r). When genetic studies calculated criterion - χ^2 , RValue, RR-relative risk, EF-figure etiologic fraction and PF - figure preventive fraction.

The third chapter deals with the results of the survey students in high schools and colleges to determine the prevalence and clinical features of asthma in the adolescent population, which was conducted in two areas of Samarkand region: in Samarkand (4 Lyceum College 2) and Urgut district (3 colleges, 3 Lyceum). Based on analysis of questionnaire data was formed by a group of persons who had obstruction syndrome in the past 12 months. According to our data, such persons was 388, which accounted for 9.6% of all respondents. Girls accounted for 59.1% (229 people), 40 boys, 9% (159 people). As can be seen, asthma among girls living in the investigated region, met more often than boys - teenagers. As a young boy patients were also less than the girls - teenagers. The basis for the study of two areas of Samarkand was the fact that one of them (Urgut district) population is engaged tabakovodchestvom. In this regard, is of particular interest to compare the frequency of occurrence of symptoms astmopodobnyh adolescents living in different areas of the region.

Was interviewed in 1711 adolescent children - college students, high schools Urgut tobacco-growing areas. According to our data, the number of adolescent children with the presence of asthma among them was 185, which accounted for 10.8% of all surveyed. Number of teenagers college students involved in questioning of Samarkand - was 2326, and the results of a questionnaire on symptoms of asthma was observed in 203 adolescents, representing 8.7% of all surveyed teens.

In general, according to our results among the surveyed population of the Samarkand region rate of occurrence of asthma among adolescents in 2008 was 9.6% and was at a slightly higher level in the cohort of females, both in adolescence and in young adulthood.

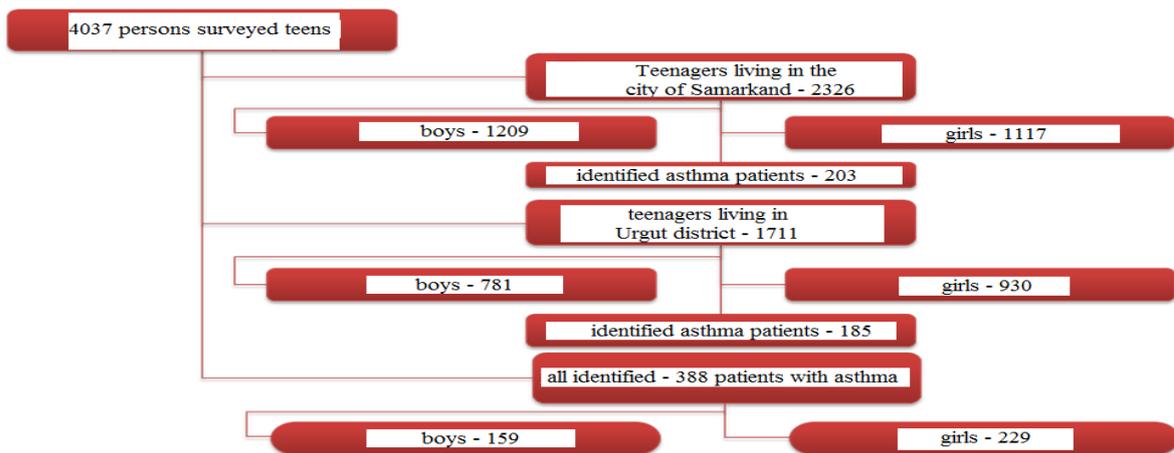


Fig. 1. Distribution of those surveyed teens

The second stage of examination (clinical and functional studies) was covered by a contingent of teenagers who indicated in the questionnaire at least one of astmopodobnyh symptoms in the last 12 months.

The examination of boys and adolescents with suspected asthma and intercept of oriented reduced FEV_1 , PEF, MEF_{25} , MEF_{50} , MEF_{75} , MEF_{25-75} at a relatively normal values of FVC, which corresponds violations obstructive pulmonary ventilation.

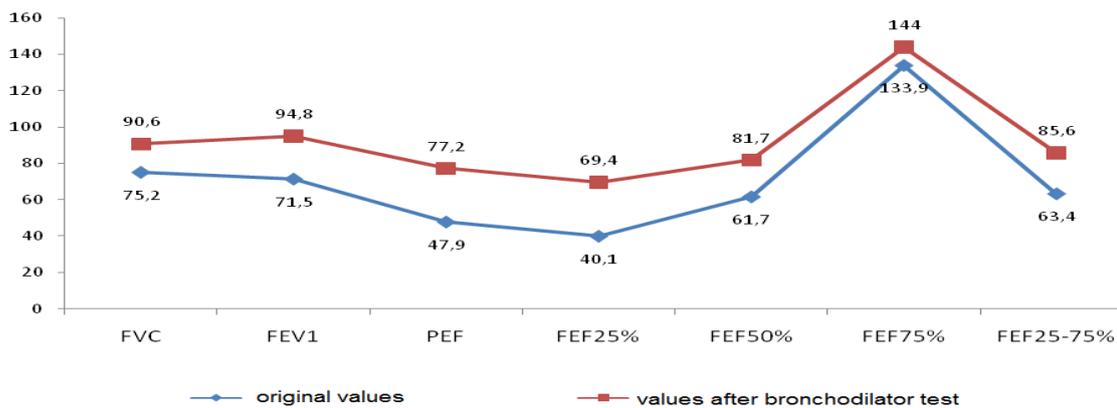


Fig. 2. Indicators ERF adolescent asthma bronchodilator test

Study of respiratory function after inhalation of a bronchodilator 15 minutes manifested increase in FEV1 and other indicators of pulmonary ventilation by more than 15% from baseline values corresponding to the normalization of all parameters of respiratory function to the level of standards. According to the results of our study revealed changes ERF, reversible test bronchodilator (salbutamol), allowed to confirm the diagnosis of asthma in 243 adolescents, representing 62.6% of the examined patients.

To study the clinical characteristics of the disease according to profiles to characterize the frequency of comorbid conditions. In our studies, 73.9% of the patients, asthma combined with allergic rhinitis, which is characterized by predominantly mild. In this mixed form of respiratory allergy, AR with asthma met in 88 teens surveyed, accounting for 44%. Most patients with adolescent asthma along with AR was associated with allergic diseases such as vnerespiratornymi -

atopic dermatitis, 16.6% of the adolescents, 53.7% of allergic conjunctivitis, urticaria / angioedema 14%. 7.6% of adolescents surveyed mentioned the presence of a food allergy, and 8.1% - about drug allergies.

Verification of the diagnosis of asthma according to the diagnostic criteria for Global initiative for asthma allowed to determine the features of clinical course severity. We examined adolescents for mild persistent observed in 8.8% of cases, periodical exposure for - BA reported among 91.2% of patients.

Thus, in a population of adolescents living in the Samarkand region, a study was conducted astmopodobnyh frequency of symptoms, which revealed the true prevalence of asthma among this category. Found that the majority of adolescent was stated periodical exposure for asthma, at least - for persistent disease. The patients were studied the structure of BA related allergic conditions, and also investigated the changes in functional performance characteristics at different severity of asthma, during which yielded important scientific and practical results.

The fourth chapter presents the results of the study of immune status features a healthy population and adolescent patients with asthma. Relative performance CD3⁺ cells in peripheral blood of healthy adolescent population amounted to 45,5±0,5%, CD19⁺ cells - 21,9±0,3%, the average values of the subpopulation of T-helper lymphocytes - 24,4±0,3%, T-suppressors - 21,1±0,3%, natural killer cells - 17,2±0,3%, and serum immunoglobulins major classes: IgA - 186,7±13,35mg%, IgM - 111,2±4,47mg%, IgG - 901,2±67,18mg%. A comparative study of the parameters of the immune status of healthy adolescent male and female differences in the mean values of these indicators have been identified.

In the study of the T cell immune contingent link to examinees identified significant decrease in the average relative content of CD3⁺ asthmatic patients adolescence (36,8±0,5% as compared to 45,5±0,5% in control, p<0.01). Characterized by a subpopulation of CD4⁺ levels 19,5±0,3% as compared to 24,4±0,3% in the controls (p <0.01). CD8⁺ content was also significantly reduced to 17,2±0,3% at 21,0±0,3% in controls (p<0.01). Results obtained in regard to NK-cells in asthma adolescence indicate a trend toward reduction of the indicator (16,0±0,3% as compared to 17,2±0,3% in control, p<0.02).

Serum IgA, IgM in the cohort of adolescents with asthma undergoing significant changes, characterized by a significant reduction in data immunoglobulins. IgG levels in patients with asthma was slightly elevated, not significantly different from the group of healthy adolescents. It should be noted that the cohort of patients tested was a significant decrease in the number of B-lymphocytes.

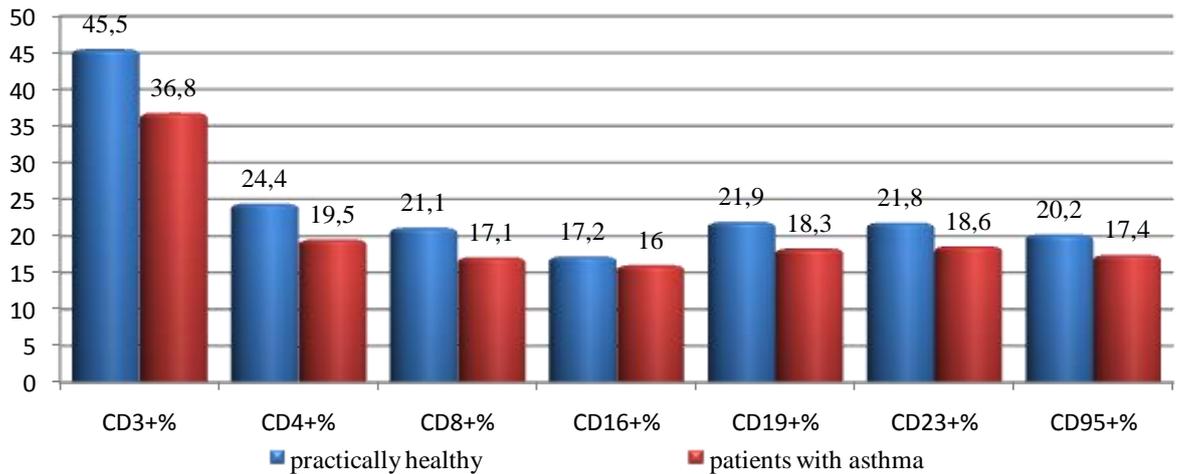


Fig. 3. Immune status of patients with asthma in adolescence in s plants

The results showed that patients with adolescents with asthma, there is a significant reduction of both CD23⁺- cells and the relative amount of CD95⁺- cells, which are markers of activation of T and B lymphocytes.

Improved knowledge about the functioning of the immune status of the links in the age periods in asthma is of practical importance, which will discuss the tactics of therapeutic and preventive aspects of immunomodulation. Intermediate CD3⁺- cells, reflecting a common pool of T-lymphocytes in patients with asthma and adolescent boys, was 35,4±1,1% and 39,6±0,59% respectively. It can be seen that the lowest level of this indicator registered patients adolescent age group. When analyzing immunoregulatory lymphocyte subpopulations minor differences detected level CD4⁺- cells in the age groups, but the level of CD8⁺- cells differed significantly increased in patients adolescence (17,2±0,32% compared to 11,2±0,6%, p<0.02), although in general not reached the level of control parameters (21,1±0,3%, p<0.05). When comparing the level of CD16⁺ in the target age groups revealed that if a group of patients with asthma boys this figure remains at healthy individuals, then the adolescent patients analyzed different figure as a significant decrease in relation to the performance of the control group (13,6±1,1% compared to 17,2±0,3%, p<0.01), and young patients with asthma group compared to 16,0±0,39%, (3,6±1,1%, p<0.05). Level of CD19⁺-cells was significantly reduced in the group of patients with asthma in adolescents compared with the control group (18,4±0,30% compared to 21,9±0,3%, p<0.02). Significant differences in the content of CD19⁺- cells in the comparison groups were found.

In general, the analysis of features mezhvoznrastnyh immune imbalance in the two groups studied individuals found deeper disorders of the immune status in the group of teens that require consideration inclusion of immunomodulatory drugs in complex basic therapy to restore quantitative indicators of immune status.

The fifth chapter, respectively, to the tasks of the thesis is devoted to the establishment of pathogenic and informative power of competing products cytokines serum IFN- γ and IL-6 in patients with asthma in adolescence.

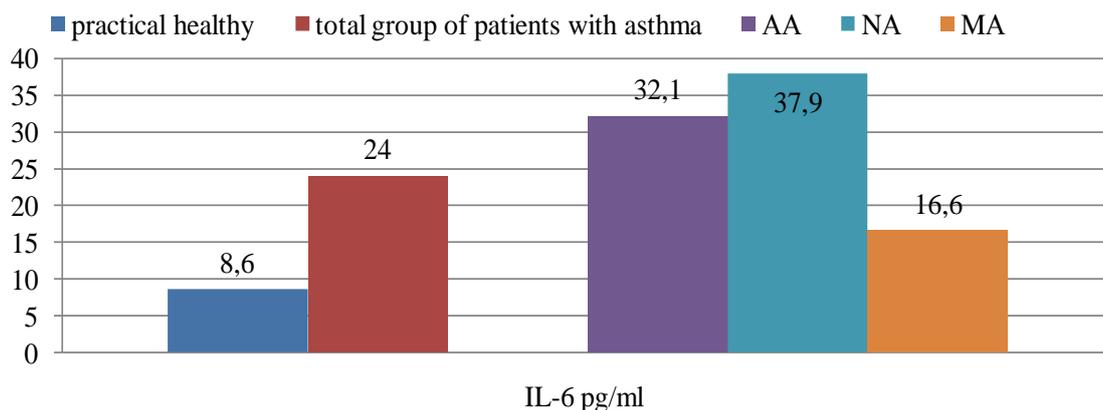


Fig. 4. Indicators IL-6 asthma patients in adolescence

Thus, the content of the cytokine IL-6 in peripheral blood serum of patients with asthma in adolescence was significantly increased up to $24,0 \pm 3,8$ pg/ml at $8,6 \pm 3,6$ pg/ml in controls ($p < 0.05$). To clarify the nature of communication and production of IL-6 with clinical and pathogenic forms of the disease was a comparative analysis with the study of pathology. Found that adolescents with asthma with predominantly infectious disease mechanisms, recorded the most elevated levels of IL-6 production, which averages, accounting for $37,9 \pm 1,3$ pg/ml in peripheral blood seems to reflect the severity and depth of inflammation of the bronchial tree in this group of patients. Patients with major mechanisms in the pathogenesis of allergic disease, in contrast, a marked decrease in production of IL-6 up to $32,1 \pm 1,1$ pg/ml. It is interesting to the finding of significant decrease of the level of IL-6 production in patients with mixed asthma.

Analysis of the parameters of interferon status in the subgroups of patients with asthma in adolescence found low IFN- γ production by immunocompetent cells. Thus, the content of the cytokine IFN- γ in peripheral blood serum in patients with asthma in adolescence was significantly reduced to $7,9 \pm 0,5$ pg/ml at $13,9 \pm 1,0$ pg/ml in controls ($p < 0.01$).

To clarify the nature of communication and IFN- γ production in the studied pathology with clinical and pathogenic forms of the disease, we conducted a comparative analysis.

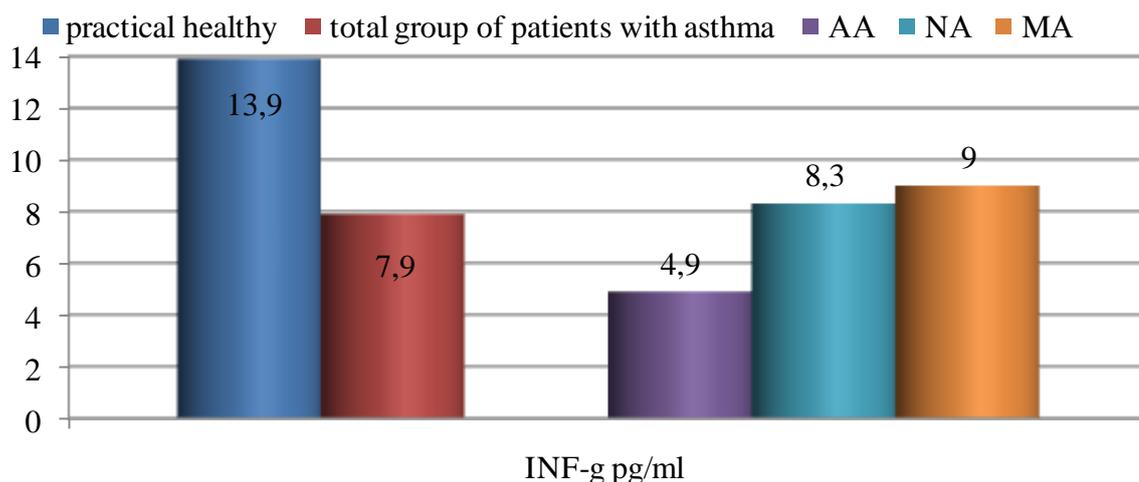


Fig. 5. Indicators of IFN- γ in patients with asthma adolescence.

As a result of statistical analysis, the lowest level of production IFN- γ ($4,9 \pm 0,2$ pg/ml; $p < 0,01$) was registered in the group of patients with asthma in adolescence with allergic clinical pathogenetic form of the disease. IFN- γ production by immunocompetent cells in mixed-dependent and infectious forms of asthma in adolescence was at almost the same low level, significantly different from the group of healthy adolescents.

These features production of IL-6 and IFN- γ may provide additional objective criteria and orientation of the inflammatory response in healthy and patients with various clinical and pathogenetic variants of BA, allowing differentiated approach to the choice of therapy and increase its effectiveness.

One of the main functions of IL-6 and IFN- γ is the regulation of the differentiation of immune cells. To clarify the nature of communication and immunological disorders with the level of production of IL-6 and IFN- γ in peripheral blood, we conducted a comparative analysis to examine the spectrum of immunological parameters in the study of pathology with the content of serum cytokine levels. There is an inverse relationship between the level of IL-6 and the content of CD3 $^{+}$ -cells ($r = -0,17$; $p < 0,05$), CD4 $^{+}$ -cells ($r = -0,15$; $p < 0,05$), CD8 $^{+}$ -cells ($r = -0,25$; $p < 0,05$) and found a positive correlation between IL-6 serum levels, and the pool of circulating CD16 $^{+}$ -cells ($r = 0,14$; $p < 0,05$). At the same time, there is a direct correlation between IL-6 and levels of CD16 $^{+}$ BA adolescent patients ($r = 0,20$; $p < 0,05$). The level of IL-6 and is weakly expressed in a negative correlation with the content of IgG, was positively correlated with the concentration of IgA and IgM.

Correlation analysis results of the study it was found that the content of indicators IFN- γ thoroughly negatively correlated with the mean values of all parameters of cellular immunity CD3 $^{+}$ ($r = -0,19$; $p < 0,05$), CD4 $^{+}$ ($r = -0,15$; $p < 0,05$), CD8 $^{+}$ ($r = -0,17$; $p < 0,05$), CD16 $^{+}$ ($r = -0,14$; $p < 0,05$). The results of correlation analysis of the concentration IFN- γ with indices of humoral immunity revealed pronounced negative correlation with indicators of CD19 $^{+}$ -cells and IgA, IgM. Here IgG is correlated positively with the level of IFN- γ ($r = 0,34$; $p < 0,05$).

Also studied the correlation dependence of IL-6, IFN- γ with activation markers of T and B-immunity. Indicators of IL-6 correlates positively with CD23+ ($r=0,39$; $p<0,02$), while the level of IL-6 in patients was pronounced negative correlation with the content of CD95+ ($r=-0,32$; $p<0,02$). It was also found that IFN- γ negatively correlated with the content of CD23+ ($r=-0,30$; $p<0,05$) and CD95+ ($r=-0,10$; $p<0,05$).

Set multiple interconnection levels indicate interdependence cytokine IL-6 and INF- γ content with impaired balance between the processes of activation (CD23+) and elimination (CD95+) in asthma in adolescents. The findings also suggest a possible regulatory role of the studied cytokines in the immune response characteristic phenotypic variants of BA.

In chapter six to clarify the mechanisms of the disease studied the significance of alleles genes Fc ϵ RI β , GST π 1 development and susceptibility to asthma.

In the study of 109C/T polymorphism Fc ϵ RI β of healthy individuals, the frequency of 109T-allele in a population of ethnic Uzbeks 46.8% 109C allele - 53.2%. For genotyping of patients with asthma 109T - allele was detected in 58.6% of cases, 109C allele - in 41.4% of cases ($\chi^2=3.59$, $p=0,058$, OR=1,24). In studying the frequency distribution of genotypes of polymorphic marker gene Fc ϵ RI β genotype 109T/T in healthy individuals is set to 32.6% of the heterozygous genotype 109C/T - 28.3%, and 109C/C - 39.1%. BA patients 109T/T-genotype detected in 45.4% of cases, 109C/C -genotip - 28%, 109C/T-genotype in 26,6% ($\chi^2=1,84$, $p=0,17$, OR=0,4). The analysis of distribution of allele and genotype frequencies of polymorphic variants - 109C/T gene Fc ϵ RI β revealed unreliable differences between the total group of patients with asthma and control subjects. Table 1 shows the results of the analysis of the frequency of alleles and genotypes of polymorphism 109C/T gene Fc ϵ RI β among patients depending on the clinical variants of the pathological process. As can be seen from the table, the analysis of allele frequencies at 109C/T polymorphism Fc ϵ RI β found that the 109T allele in patients ABA occurs significantly more frequently than in the healthy subjects (79,1% versus 46,7%, respectively, $\chi^2=26.0$, $p=0,000$, OR=3,12). The study of polymorphism genotypes shows that in patients with homozygous variant frequency ABA 109T/T gene significantly higher than the control group of healthy individuals (64.1% vs. 32.6%, respectively, $\chi^2=11,45$, $p=0.0007$, OR=3,68).

Table 1.

The distribution of alleles and genotypes 109C/T polymorphism of gene FcεRIβ in groups of patients with asthma and ah healthy individuals

109C/T polymorphism of gene FcεRIβ	Groups	N	allele		genotypes			χ ²	P _{Value}	OR
			109C	109T	109C/T	109C/C	109T/T			
	CG	46	49- 53,3%	43- 46,7%	13-28,3%	18-39,1%	15-32,6%	11,45	0,0007	3,68
	AA	103	43- 20,9%	153- 79,1%	31-30,1%	6-5,8%	66-64,1%			
	NA	19	26- 68,4%	12- 31,6%	8-42,2%	9-47,3%	2-10,5%	2,34	0,12	0,05
	MA	14	19- 67,8%	9-32,2%	3-21,4%	8-57,2%	3-21,4%	0,21	0,64	0,13

Thus the frequency of 109C/C in patients was significantly lower ABA level characteristic of the healthy part of the population studied persons (5.8% compared with 39.1%). Frequency of 109C/T gene FcεRIβ in this group of patients did not differ almost from the control group. The analysis features of the genotype groups in patients with MA and NA showed no significant differences in allele frequencies and genotype polymorphism 109C/T gene FcεRIβ compared with a control group of healthy individuals.

In order to evaluate the association of asthma by gender analyzes the frequency distribution of alleles and genotypes 109C/T polymorphism FcεRIβ: patients boys frequency-109T allele was 78,5% FcεRIβ, compared with asthma (67,2%) girls and was significantly higher than in males in the control group (56,2%) ($\chi^2=5,2$, $p=0.02$, $OR=4,71$).

Analysis of relationship between 109C/T polymorphism FcεRIβ level of T-lymphocytes and their subpopulations in asthma in adolescents found that in patients with genotype 109T/T recorded reduced performance relative to the amount of CD3+ 34,7±0,41% as compared with the in patients with the C/C and C/T genotype ($p<0.05$). The downward trend was also observed in patients with genotype 109T/T with respect to indicators of absolute values of CD4+ and CD8+, showing false differences. Indicators of CD16+ were not significantly different between treatment groups genotypes FcεRIβ in asthma in adolescents. The highest mean values of IgG were detected in the group is patients with genotype 109T/T. The lowest rate was registered IgA in patients with genotype 109T/T, which is significantly different from those with 109C/C genotype. The downward trend in IgM was also observed in patients with genotype 109T/T. Individuals with genotype 109T/T recorded a significant increase in the relative amount of CD23+ compared with a group of patients with 109C/C, C/T genotype ($p<0.05$, $p<0.01$, respectively), while dos tovernyh differences CD95+ - cells in combination of

genotypes in patients with asthma adolescents were observed. There was a significant difference between CD23+ homozygous genotype 109T/T and 109C/C ($p < 0.05$).

All the studies in the study and identification of functionally weakened combinations of genotypes and their relationship with the parameters of the immune status lead to the conclusion that to launch allergic reactions to adverse interaction gene combinations FcεRIβ with indicators of cellular and humoral immunity.

In the analysis of gene polymorphism Ile105Val GSTπ1 among healthy individuals, the frequency 105/Ile - allele in a population of Uzbek people is 65%, 105/Val - 35%. For genotyping of patients with asthma 105/Ile - allele was detected in 79,1% of cases, 105/Val - allele in 20,9% of cases. In studying the frequency distribution of genotypes of polymorphic marker gene GSTπ1 Ile-105/Ile-105 genotype in healthy individuals is set to 30% of cases, the heterozygote - 70%, and Val-105/Val-105 - not registered. BA patients Ile-105/Ile-105 - genotype was detected in 60.4% of cases, Val-105/Val-105 genotype - in 2,4%, Ile-105/Val-105 - genotype in 37,03% ($\chi^2 = 2,24$, $p = 0.13$).

The results obtained with respect to polymorphism gene GSTπ1 indicate the existence of the Association, c one hand, genotype Ile-105/Ile-105, and on the other allele carriers Ile-105 in patients with asthma in the Uzbek population in terms of statistically insignificant χ^2 and P_{value} . The study of gene polymorphism Ile-105/Val-105 GSTπ1 an allergic form of asthma found that is relatively significant ($\chi^2 = 3,49$, $p = 0,06$) accumulation of unfavorable genotype Ile105Ile (62%) compared with the same genotype in Control (30%). The analysis features of genotype distribution in groups of patients NBA and MBA showed no statistically significant differences in the frequencies of genotypes and alleles of the gene polymorphism Ile-105/Val-105 GSTπ1 compared with the control group of healthy individuals.

Thus, the specificity of gene polymorphism Ile-105/Val-105 GSTπ1, manifested Association Ile105Ile genotype combination with allergic form of the disease in the Uzbek population.

Studies of gene polymorphism GSTπ1 by gender persons surveyed indicate that girls frequency Ile105 - GSTπ1 allele was 87%, compared with asthma (65%) boys and was not significantly higher than that of girls in the control group (13%) ($\chi^2 = 3,216$, $p = 0,073$). The combination of genotypes shows that patients homozygous variant frequency girls genotype Ile105Ile gene GSTπ1 significantly higher than the control group of healthy individuals ($\chi^2 = 3,936$, $p = 0,047$). In studies of variation in levels of T-lymphocytes and their subpopulations in asthma in adolescents depending on the gene polymorphism genotypes Ile-105/Val-105 GSTπ1 revealed that in patients with genotype I/I recorded reduced performance CD3⁺, CD8⁺ and CD16⁺ to 33,6±0,45%, 15,6±0,88% and 15,6±0,88%, respectively, compared to a group of persons who did not have this genotype. Significant differences were calculated with respect to the relative

amount of CD3⁺ as compared with the Val-105/Val-105, Ile-105/Val-105 genotype and between genotypes and Val-105/Val-105 Ile-105/Val-105 ($p < 0.01$, $p < 0.02$, $p < 0.05$, respectively), CD4⁺-cells compared with Ile-105/Val-105 ($p < 0.02$), CD8⁺-cells as compared with the Val-105/Val-105 and also between genotypes and Val-105/Val-105 Ile-105/Val-105 ($p < 0.02$ in both cases) and CD16⁺ in comparison with the genotype Val-105/Val-105 Ile-105/Val-105 gene polymorphism GST π 1. Reduction in the absolute measure CD3⁺-cells in the patients had asthma genotype Ile-105/Ile-105, and CD4⁺ - genotype Val-105/Val-105, which revealed statistically insignificant differences.

In the study of differences in the relative number CD19⁺-cells between the compared groups of patients was found between the accuracy of the performance groups and genotypes Ile-105/Val-105 Val-105/Val-105 ($p < 0.02$). Registered a significant increase in the level of IgG in patients with asthma, adolescents with homozygous genotype and heterozygous genotype Ile-105/Ile-105 Ile-105/Val-105 compared with homozygous genotype Val-105/Val-105 ($p < 0.01$ in both cases). Expressed a reduced level of IgA was associated with the presence of genotype I/I BA patients against patients with asthma adolescents with genotype Val-105/Val-105 ($p < 0.05$). Significant difference in the level of IgM concentration between genotypes were not available.

Found that adolescents with asthma genotype Val-105/Val-105 relative and absolute levels of CD23⁺ than in groups Ile-105/Ile-105, Ile-105/Val-105. Thus, the average value of the relative content of the activation marker CD23⁺ genotype Val-105/Val-105 significantly different from the group of patients with genotype Ile-105/Val-105 ($p < 0.05$), and the level of the absolute content of CD23⁺ in the group of individuals with Val -105/Val-105 genotype was equal to $558,5 \pm 32,3$, which was significantly higher compared to $415,15 \pm 26,3$ group genotype Ile-105/Ile-105 gene GST π 1 ($p < 0.05$). Significant differences were manifested decrease CD95⁺ content depending on Ile-105/Val-105 gene polymorphism GST π 1 studied patients reported in individuals with genotype Ile-105/Ile-105, compared with the group having genotype Ile-105/Val-105 ($p < 0.05$).

Thus, the identified association Ile-105/Val-105 GST π 1 gene polymorphism with the disease itself and the immune status in asthma suggest that genes metabolizing enzymes play an important role in the development of direct hereditary predisposition to asthma, and the indirect formation of immune system disorders in the pathogenesis of the disease.

Chapter seven presents the results of evaluating the effectiveness of the use of immunomodulators and polioksidony tsikloferon in asthma in adolescents with "unfavorable genotypes" 109T/T gene and Fc ϵ RI β Ile-105/Ile-105 gene GST π 1.

The data on the results of complex treatment of adolescents with asthma to include polyoxidonium indicate marked recovery from the immune system in this scheme of therapeutic treatment. Especially notable was the increase in the relative (with $36,9 \pm 0,59\%$ to $44.2 \pm 0,7\%$, $p < 0.01$) the amount of CD3⁺. In respect of T-lymphocyte subpopulations for the used method of treatment characteristic was a

significant increase in the relative content of CD4⁺, CD8⁺-cells. In particular, the CD4⁺ count increased to 19,6±0,23% to 27,6±0,3% (p<0.01) increase substantially the total number of CD8⁺-cells (c 17,2±0,32% to 23,1±0,4%, p<0.01). Number of B-lymphocytes increased from 18,4±0,20% to 21,6±0,9%. Significantly increases the content of CD95⁺ (from 17,3±0,43% to 23,2±0,5%, p<0.01). Complex therapy polyoxidonium also accompanied by a significant increase in the concentration of IgA, which is one of the leading factors of antimicrobial and antitoxic protection in the lumen of the airway (from 17,2±0,32% to 23,1±0,4%, p<0.01) and a trend to higher levels of IgM and IgG.

To achieve the objectives of the study evaluated the clinical and immunological efficacy of the use of synthetic interferon inducer - tsikloferon in complex treatment of patients with asthma in adolescence.

After applying tsikloferona marked improvement in immune status. Thus, in the complex treatment of adolescents with asthma, further cycloferon noted a significant increase in the relative (with 36,9±0,59% to 41,7±0,4%) number of CD3⁺-cells compared with the original data. Immunoregulatory lymphocyte CD4⁺ (a 19,6±0,3% to 24,2±0,3%) and CD8⁺-cells (with 17,2±0,32% to 20,12±0,3%) increased, almost reaching the average values of the control group. Showed a slight increase of activated lymphocytes bearing markers of T-cell activation CD95⁺, a marker of B lymphocytes activate CD23⁺. There was a trend to increased concentrations of immunoglobulins IgA, IgG and IgM.

Thus, in patients with asthma adolescents with genotypes 109T/T gene and FcεRIβ Ile-105/Ile-105 gene GSTπ1, receiving complex treatment with immunomodulatory drugs - and polioksidony cikloferon, noted the reopening of most clinical and functional parameters and immunoreactivity, the onset of clinical remission disease.

Effectiveness of prevention of asthma using immunomodulatory drugs and interferon inducer polioksidony tsikloferona also evaluated the results of observation of patients treated with "unfavorable genotypes" within 12 months. The monitoring of clinical indicators led to the conclusion that if basic hyposensitization therapy changes do not present fairly the average duration and number of exacerbations per year, the clinical data of patients disinfected cycloferon-tion, compared with the initial data indicate a significant decrease in the frequency of exacerbations in during the year. After treatment cycloferon statistically significant decrease in the frequency of exacerbations with 6,9±0,4 times to 4,3±0,5 per year.

In the study of patients treated polioksidony also showed a significant decrease in the number of exacerbations. Reduction of asthma exacerbations during the year in patients receiving treatment course with the drug polioksidony, manifested in the average 3-4 exacerbations per year, whereas prior to the current treatment of acute illness were recorded, on average, up to 7 times during the year (p<0,05). The average duration of an exacerbation in patients treated polioksidony

has significant differences from the index, calculated prior to the application of immunomodulators in treatment of asthma in adolescents.

Severity and duration of symptoms (temperature reaction, symptoms of intoxication, rhinorrhea, cough, and changes in the lung determined physical signs) in the groups treated with drugs and polioksidony cikloferon in a complex of basic therapy differed significantly. For adolescent patients with asthma who received polioksidony these phenomena, respectively, lasted an average of $2,21 \pm 1,12$, $2,6 \pm 1,11$, $3,81 \pm 1,20$, $4,6 \pm 1,19$, $3,8 \pm 1,25$ days, whereas in patients with asthma treated with teenagers cikloferon these phenomem lasted an average of $3,2 \pm 1,14$, $3,4 \pm 1,16$, $4,2 \pm 1,31$, $7,8 \pm 2,22$, $4,9 \pm 1,13$ days. Consequently, the inclusion complex Polyoxidonium basic treatment contributes to more rapid elimination of all forms of acute pulmonary involvement.

Thus, the results indicate that the courses of nonspecific immunotherapy drugs and polioksidony cikloferon BA patients with genotypes 109T/T and Ile-105/Ile-105 genes FcεRIβ, GSTπ1 2-3 times reduces the frequency of exacerbations. According to the calculations positive indicators prevalent in patients treated polioksidony advantage and reflect the inclusion of the drug in the treatment of BA integrated circuits.

On the basis of detailed studies, we developed a model of multi-factor of BA (Fig. 6).

It should be noted that this development has enabled a new way to consider the pathological phenotype positions nonrandom combinations studied genes involved in dysregulation of the immune response, impaired detoxification processes of xenobiotics and receptor mechanisms of initiation of allergic inflammation, which emphasize the importance of these processes in the development of allergic disease in particular asthma.

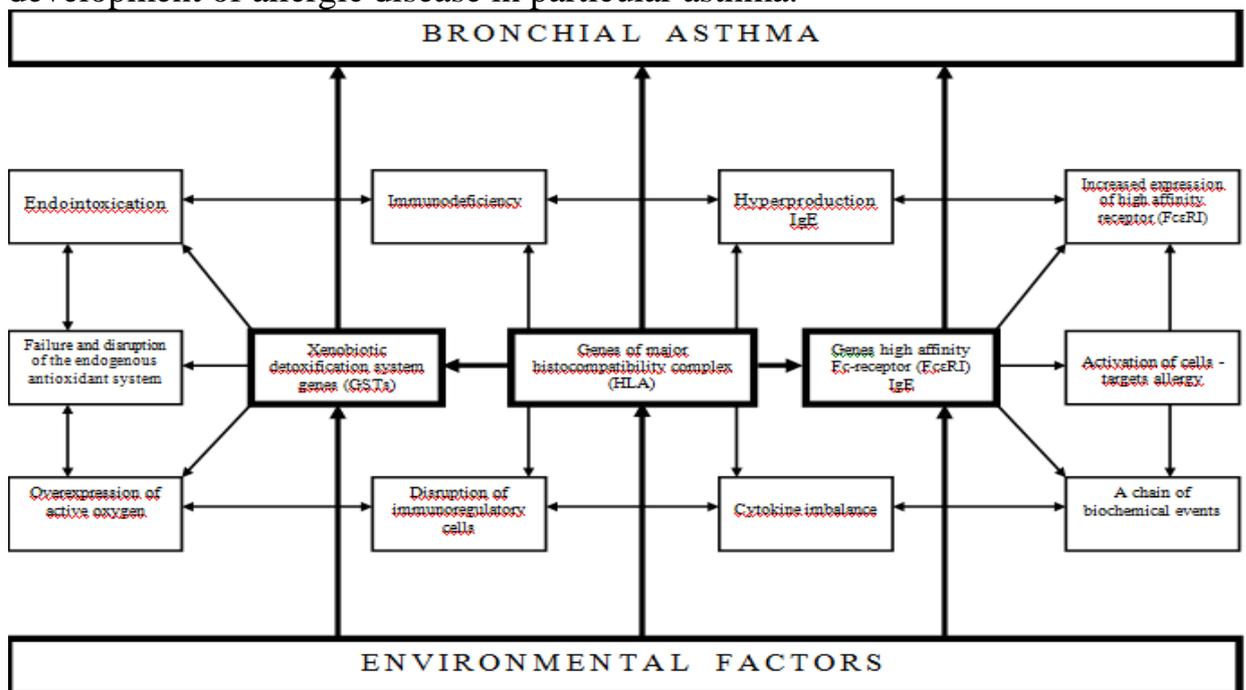


Fig. 6. Multivariate model of asthma

On the basis of clinical and functional , immunological and genetic studies to verify the diagnosis of asthma, we developed an algorithm for diagnostic procedures, according to which at allergic examination should follow a three-tier approach of their performance (Fig.7).

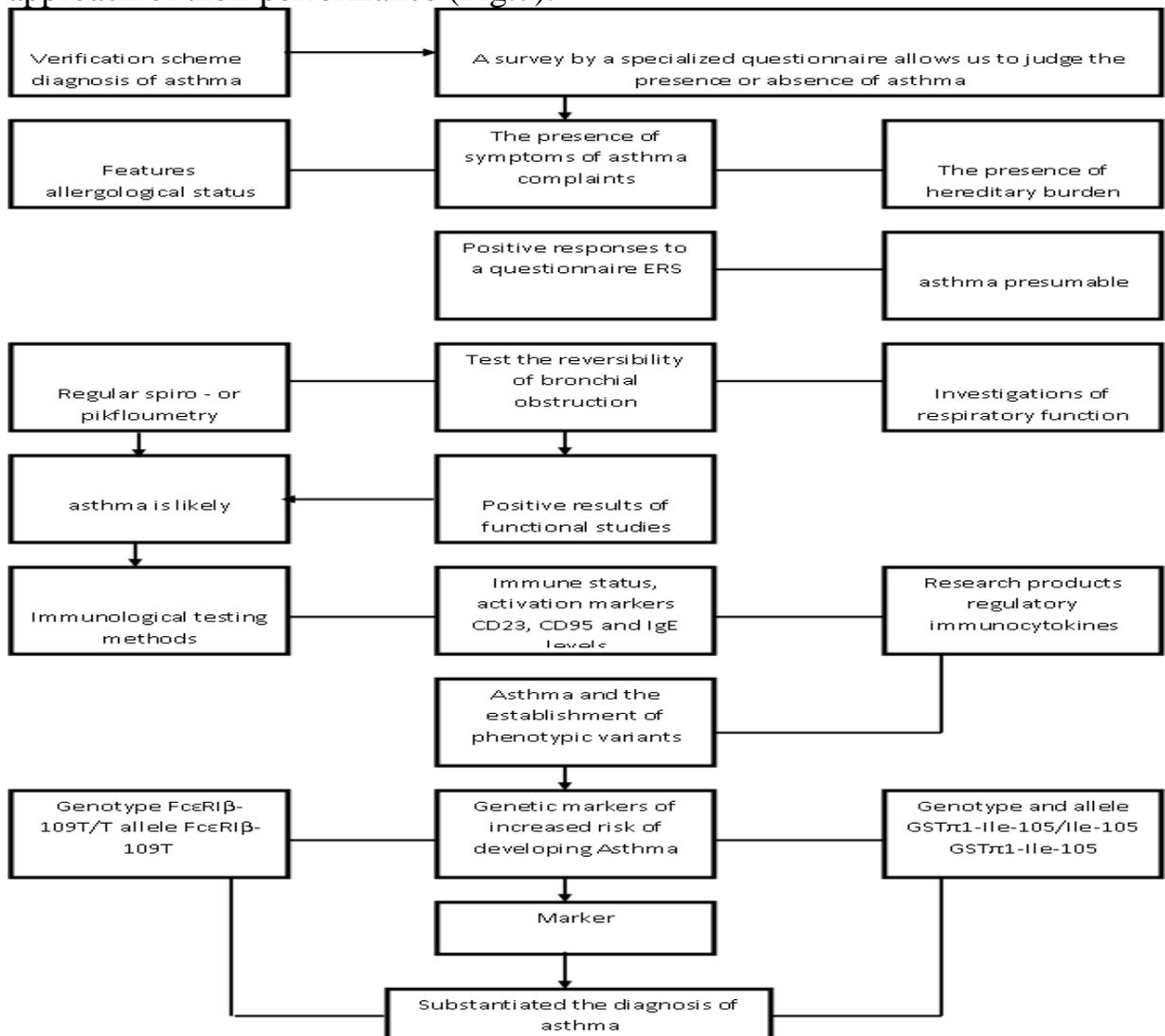


Figure 7. Algorithm level approach to diagnostic measures asthma

At the first stage it is recommended primarily by questionnaire and interview to conclude expectation of asthma in a given individual. Then selected from cohort to investigate ventilation lung function with holding bronchodilation test. With positive results at this stage we can restrict the probability of having asthma. At the second level of diagnostic measures , the detection of immunological disorders documented changes in both cellular and humoral parts of the immune system and the definition of the level of IL-6, IFN- γ and a diagnosis of asthma defined pathogenic form of the disease. Third level tests can detect adverse genotypes, which confirms the certainty of the diagnosis of asthma.

Conducted screening, clinical and functional, immunological and genetic studies have allowed to define approaches to preventive measures of asthma in adolescents. Description compiled from the survey program of activities for primary, secondary and tertiary prevention is given in Table 3.

Table 3.

Programme of activities for the prevention of asthma in adolescents

Primary prevention	Secondary prevention	Tertiary prevention
<p>Purpose: presymptomatic diagnosis of hereditary predisposition to respiratory allergies and asthma.</p> <p>Population: newborns, children, adolescents from families with a high risk of developing allergies and asthma.</p> <p>Research: Molecular genetic studies aimed at identifying genetic markers of increased risk of asthma (the genetic marker HLA-B40, genotype FcεRIβ-109T/T allele FcεRIβ-109T, the genotype and allele GSTπ1-Ile-105/Ile-105 GSTπ1-Ile-105)</p> <p>Action plan: reduced antigenic load on the body, including the hypoallergenic diet, hypoallergenic life, prevention of recurrent respiratory infections and excretion of antigens/allergens from the body through the appointment of sorbents and treatment of chronic foci of infection</p> <p>Expected result: the gates will allow preventing the development of allergic diseases</p>	<p>Purpose: To prevent the manifestation of asthma in children and adolescents with severe manifestations of atopy</p> <p>Population: children and adolescents with minor forms of respiratory allergy and scarce, difficult to diagnose asthma symptoms</p> <p>Research: study of respiratory function with carrying out provocative tests and test the reversibility of bronchial obstruction and the study of the immune status and activation markers; research products regulatory im munotsitokinov; research and serum specific IgE</p> <p>Action plan: An elimination of work fixed on separation with the allergen after anamnestic or clinical his identification, preseason or preventive specific and nonspecific (immuno-therapy) desensitization of the body as the small forms of respiratory allergy and asthma in adolescents.</p> <p>Expected result: will help to identify patients with a low degree of severity of asthma symptoms characteristic of adolescence and the timely appointment of an adequate treatment of the disease</p>	<p>Purpose: a set of measures for the effective treatment and achieve long-term, long-term remission</p> <p>Population: children and adolescents with asthma patients with genotypes 109T/T gene FcεRIβ and Ile/Ile105 gene GSTπ1</p> <p>Research: monitoring the immune status, monitor pulmonary ventilation or regular pikfloumetry</p> <p>Action plan: annual conducting courses nonspecific immunotherapy drugs cikloferon and polioksidony to prevent being the main trigger nonspecific disease patient education control symptoms of asthma</p> <p>Expected result: solve the problem of frequent exacerbations thereby prevent the development of serious complications and disability of patients with asthma</p>

CONCLUSION

1. Set the frequency of occurrence of the disease and the structure of "asthma" in the arid zone among teens. Said pathology is recorded in 9,6% of the population surveyed adolescents, while the disease is more common among females. In the structure of the disease prevails periodical exposure and mild persistent form.

2. Identified by clinical features of asthma among adolescents living in the arid zone, indicate a high frequency of lesions of the bronchial tree association with allergic processes in other organs and tissues: in 73,9% of the AR, 53,7% with AK 16,6% with BA and 14% with urticaria/angioedema.

3. Found that in the study population of patients with asthma adolescence occur expressed disturbances of the immune status, manifested deficit indicators as cell (CD3⁺, CD4⁺, CD8⁺, CD16⁺), and humoral immunity (CD19⁺, IgA, IgG, IgM) and activation markers (CD23⁺, CD95⁺). The immune status of patients with asthma in young people, adolescence has distinctive features, the depth of detected violations immunoreactivity was most pronounced in the younger age group.

4. In patients with bronchial asthma in adolescence revealed distinct changes in cell-cell interactions in the immune system: a significant increase in the content of Th2-cells secreted IL-6 is a regulator of maturation of antibodies and immunoglobulin production it self, and vice versa reducing regulator activity of Th1-cell cytokine INF- γ .

5. It was found that the contents of cytokines IL-6, INF-g and in the peripheral blood is in communication with one pathogenic disease. It is shown that the lowest level of INF-g production in the serum is characteristic of allergic clinical pathogenic variant asthma in adolescence. Adolescents suffering from predominantly infectious form of asthma, there is a sharp trend towards increased production of IL-6 in peripheral blood.

6. Revealed that markers of increased risk of allergic forms of asthma in adolescents Uzbek ethnicity are genotype Fc ϵ RI β -109T/T allele Fc ϵ RI β -109T, low-risk markers - Fc ϵ RI β -109C/C and allele Fc ϵ RI β -109C. A high degree of cohesion genotype Fc ϵ RI β -109T/T allele and Fc ϵ RI β -109T with hereditary burden of asthma in the Uzbek population.

7. Among females ethnic Uzbek Association revealed Ile-105 allele and genotype Ile-105/Ile-105 polymorphic gene locus GST π 1 at high risk for asthma. Revealed that the genotype associated with the development Ile-105/Ile-105 allergic form of asthma in adolescents Uzbek population.

8. Complex therapy with adolescents and patients with asthma cikloferon polyoxidonium, providing immunocorrective effect, enhances the clinical efficacy of basic therapy. In the study of prophylactic efficacy of immunomodulators positive indicators prevailed in the group of patients receiving polioksidony, necessitating its inclusion in the priority scheme of integrated treatment and prevention of asthma in adolescents.

PRACTICAL ADVICE

1. In the diagnosis of asthma in adolescents is advisable to use the developed algorithm, assuming a 3-tiered approach to the diagnostic process, including the use of modern biographical questionnaires and tests aimed at identifying reversible bronchial obstruction syndrome, in-depth immunological study assessing the most important products and research of genetic immunocytokines markers of increased risk of developing asthma.

2. Obtained immunological data: dual immunodeficiency cellular and humoral in adolescents with asthma - to consider when developing prevention and treatment programs for the appointment of immunomodulatory drugs in the basal complex therapy of bronchial asthma.

3. As additional differential - diagnostic criteria for clinical and pathogenic nature of the disease in adolescents with asthma may use indicators The cytokine IL-6, IFN- γ in serum.

4. The obtained results of genetic testing, in which the identified markers of increased risk of asthma (the genetic marker HLA-B40 genotype Fc ϵ RI β -109T/T allele Fc ϵ RI β -109T, the genotype and allele GST π 1-Ile-105/Ile-105 GST π 1-Ile-105) should be considered as evidence of clinical feasibility predictive genetic testing, allowing for the presymptomatic diagnosis of hereditary predisposition to asthma and organize effective prevention of this disease.

5. High therapeutic and prophylactic efficacy of immunomodulators polioksidony and cikloferon, absence of complications and adverse reactions when used can recommend into practice allergist appointment combined immunomodulatory therapy in patients with asthma adolescents.

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