Насирова Азиза Акбаровна
PhD, Ассистент кафедры внутренних болезней
педиатрического факультета
Самаркандский государственный медицинский
университет
Самарканд, Узбекистан

КЛИНИЧЕСКИЙ ОПЫТ ПРИМЕНЕНИЯ ГЛИКОПИРРОНИЯ БРОМИДА У БОЛЬНЫХ С OVERLAP-СИНДРОМОМ

For citation: A.A.Nasirova. CLINICAL EXPERIENCE OF THE USE OF GLYCOPYRRONIUM BROMIDE IN PATIENTS WITH OVERLAP SYNDROME. Journal of cardiorespiratory research. 2023, vol 1.1, issue 69, pp.338-342.

АННОТАЦИЯ

Overlap-синдром (перекрёстный синдром) это две самостоятельные нозологические единицы включающие в себя хроническую обструктивную болезнь легких (ХОБЛ) и бронхиальную астму (БА), которое является крайне распространеным среди болезней органов дыхания и являются серьезными заболеваниями. В 2014 году экспертами GINA и GOLD был введень новый термин - ACOS (от английского слова Asthma-COPD Overlap Syndrome - перекрестный синдром бронхиальной астмы и ХОБЛ). Научными комитетами GINA и GOLD на основании обзора литературы и соглашения экспертов разработан документ «Диагностика заболеваний с хроническим ограничением воздушного потока: БА, ХОБЛ и СПБАХ», в котором дано определение СПБАХ, сформулированы критерии диагностики БА, ХОБЛ и СПБАХ и отражены подходы к тактике ведения больных.

Ключевые слова: Overlap-синдром, бронхиальная астма, хроническая обструктивная болезнь легких, глюкокортикостероиды.

Nasirova Aziza Akbarovna
PhD, Assistant of the Department of Internal
Diseases of the Faculty of Pediatrics
Samarkand State Medical University
Samarkand, Uzbekistan

CLINICAL EXPERIENCE OF THE USE OF GLYCOPYRRONIUM BROMIDE IN PATIENTS WITH OVERLAP SYNDROME

ANNOTATION

Overlap syndrome (cross syndrome) these are two independent nosological units that include chronic obstructive pulmonary disease (COPD) and bronchial asthma (BA), which is extremely common among respiratory diseases and are serious diseases. In 2014, GINA and GOLD experts introduced a new term - ACOS (from the English word Asthma-COPD Overlap Syndrome - a cross syndrome of bronchial asthma and COPD). The scientific Committees of GINA and GOLD, based on a review of the literature and an agreement of experts, developed a document “Diagnosis of diseases with chronic airflow restriction: BA, COPD and SPBAH”, which defines SPBAH, defines criteria for the diagnosis of BA, COPD and SPBAH and reflects approaches to patient management tactics.

Keywords: Overlap syndrome, bronchial asthma, chronic obstructive pulmonary disease, glucocorticosteroids.

Nasirova Aziza Akbarovna
PhD, pediatriya fakulteti ichki kasalliklar kafedrasi
assistenti
Samarqand davlat tibbiyot universiteti
Samarqand, O’zbekiston

OVERLAP SINDROMI BO’LGAN BEMORLARDA GLIKOPIRRONIY BROMIDNI QO’LLASHNING KLINIK TAJRIBASI

ANNOTASIYA

Overlap sindromi (o’zaro faoliyat sindrom) bu surunkali obstruktiv o’pka kasalligi (O’SOK) va bronxial astma (BA) ni o’z ichiga olgan ikkita mustaqil nozologik birlik bo’lib, ular nafas olish kasalliklari orasida juda keng tarqalgan va jiddiy kasalliklardir. 2014 yilda gina va GOLD mutaxassislari tomonidan yangi atama joriy etildi ACOS (Inglizcha astma - COPD Overlap Syndrome so’zidan-bronxial astma va O’SOKning o’zaro sindromi). Gina va GOLD ilmiy qo’mitalari adabiyotlarni ko’rib chiqish va ekspertlar kelishuvi asosida “havo oqimining surunkali cheklangan kasalliklari diagnostikasi: BA, O’SOK va Ba bilan O’SOKning birga kechishi” hujjatini ishlab chiqdilar, unda Ba bilan O’SOKning birga kechishi ta’rifi berilgan, BA, O’SOK va Ba bilan O’SOKning birga kechishi diagnostikasi mezonlari ishlab chiqilgan va bemorlarni boshqarish taktikasiga yondashuvlar aks ettirilgan.

Kalit so’zlar: Overlap sindromi, bronxial astma, surunkali obstruktiv o’pka kasalligi, glyukokortikosteroidlar.

Relevance. Overlap syndrome (cross syndrome) these are two independent nosological units that include chronic obstructive pulmonary disease (COPD) and bronchial asthma (BA), which is extremely common among respiratory diseases and are serious diseases. This term was officially included in 2014 in the International Recommendation Documents on the Diagnosis and Treatment of Asthma and COPD – GINA (The Global Initiative for Asthma) and GOLD (The Global Initiative for Chronic Obstructive Lung Disease) [11; 12]. Both pathologies are based on inflammation in the bronchial tree. It violates the integrity of the epithelial layer, and therefore provokes the development of irreversible bronchial obstruction. But these two nosological forms of the disease are fundamentally different.

There are several points of view of specialists regarding the choice of criteria for diagnosis. The Spanish Society of Pulmonologists and Thoracic Surgeons has made attempts to identify criteria for a combination of COPD and BA [3]. Experts suggest using basic and secondary criteria to confirm the diagnosis of a mixed COPD-BA phenotype. The main criteria include: a clearly positive result of evaluating the reaction to a bronchodilator, that is, an increase in the volume of forced exhalation per second of more than 15% and 400 ml compared to the initial value, eosinophilia in sputum, a history of asthma Secondary criteria are a high level of total immunoglobulin E, a history of atopy, more than two cases of positive evaluation of the reaction to a bronchodilator (an increase in the volume of forced exhalation per second of more than 12% and more than 200 ml compared to the baseline value). To confirm the diagnosis of the cross-syndrome of COPD-BA, it is necessary to have two main or one main and two secondary diagnostic criteria. The scientific committees GINA and GOLD [10] proposed an algorithm that allows you to suspect the overlap syndrome. The clinician needs to identify the signs that are most characteristic of COPD or BA, then compare the number of signs that indicate in favor of BA or COPD. If the number of signs characteristic of BA and COPD coincide, then a mixed phenotype of COPD and BA can be identified [4]. In our opinion, initially there is AD, then the effect of provoking, damaging factors, such as long-term smoking experience, chronic respiratory tract infections, contribute to the addition of COPD [6].

The basic treatment of AD primarily includes inhaled glucocorticosteroids (IGCS), and COPD – bronchodilators (long-acting anticholinergic drugs (LAAHD) and long-acting β2-agonists (LABA). More optimally, the therapy of overlap syndrome should include drugs that affect the pathogenetic mechanisms of both COPD and AD, and represent a combination of IGCS with combined bronchodilation therapy [7]. It is possible to use triple therapy (IGCS and LABA, and LAAHD) in patients with severe COPD and in patients with AD who do not respond to combined therapy with IGCS and LABA [13].

The issue of choosing a specific LAAHD is insufficiently covered. Tiotropium bromide is well known and studied. In patients with insufficiently controlled AD, despite the therapy of IGCS and LABA, the addition of LAAHD to therapy can significantly reduce the severity of bronchial obstruction and reduce the risk of severe asthma exacerbations [2]. One of the modern LAAHD is glycopyrronium bromide. The bronchodilatory effect of the drug is carried out by blocking the M-cholinergic receptors of the respiratory tract. Glycopyrronium bromide has a selective effect on M3-cholinergic receptors, having a minimal side effect on the cardiovascular system (tachycardia, arrhythmia) [9]. Also, another feature of the drug is the rapid onset of action [8]. A long half-life provides a prolonged bronchodilatory effect and the appointment of an inhaler once a day. This dosage regimen contributes to good compliance in treatment. The GLOW study (GLycopyrronium bromide in COPD airWays) showed that glycopyrronium bromide improves pulmonary function, reduces the severity of symptoms of the disease, increases the tolerance of patients to physical activity, reduces the frequency of severe and moderate exacerbations of COPD and improves the quality of life of patients [1]. The combination of IGCS, LABA and LAAHD should be considered as the therapy of choice in patients with a combination of COPD and BA phenotype [5].

The purpose of the study effectiveness of glycopyrronium bromide as part of triple therapy in patients with a combination of chronic obstructive pulmonary disease and bronchial asthma.

Material and methods. 31 patients (14 women, 17 men) with a combined diagnosis of COPD and BA were under observation. The diagnoses of "bronchial asthma" and "chronic obstructive pulmonary disease" were based on GINA documents from 2019 and GOLD from 2019.The criteria for excluding patients from the study were: severe and decompensated diseases of other organs and systems; tuberculosis of any localization in the active stage. The diagnosis of comorbidity pathology of BA + COPD was made on the basis of criteria (Gina and GOLD, 2019):

Presence of risk factors (bad habits, occupational or household hazards);

long-term history of asthma;

in a stable state of symptoms controlled by asthma, there is a low variability in the rate of exhalation (VRE) and the volume of forced exhalation decreases in 1 second (FED1);

progression of respiratory failure;

decrease in the effectiveness of corticosteroids, which was previously highly effective.

Inclusion criteria: patients with a combination of COPD and BA, the average age in patients with a combined course of BA with COPD is 64.4 ±2.5 years, long smoking experience, smoking index (IC) of more than 10 packs / years, moderate and severe, uncontrolled course of the disease against the background of high doses of IGCS. All patients included in the study received a fixed combination of formoterol fumarate dihydrate and budesonide at a daily dose of 24/800 mcg. Group 1 (combination of IGCS+LABA+LAAHD) - patients (n=16) who received glycopyrronium bromide (Sibri Brezhaler) in addition to basic therapy in a daily dose of 50 mcg once a day for 8 months. The 2nd group (combination of IGCS+ LABA drugs), the comparison group (n=15), received only double therapy. The evaluation of the function of external respiration (FVD) was performed on the spiroanalyzer ST-95 (Japan). Examination in the first half of the day, indicators of the functional state of the respiratory system were determined - VEL, FEV1, Tiffno index, PSV[11].Questionnaires were used: Asthma Control Test (AST), Chemis Obstructive Pulmonary Disease Assessment Test (SAT), questionnaire of St. George's Hospital (St. George's Respiratory Questionnaire (SGRQ)) was used to determine respiratory function for assessing quality of life, a modified questionnaire of the British Medical Research Council Assessment of Dyspnea (MMRs), the initial dyspnea index (BDI), including the following types of vital

activity (functional disorders, complexity of activity, degree of effort) and the transient dyspnea index (TDI), describing changes in the types of life activity during therapy (GINA 2019, GOLD 2019), before inclusion in the study and after 8 months of follow-up.

Data storage and primary processing were performed in the Microsoft Excel 2010 database using the Statistica 10 program. The data are expressed as follows: mean value (M) ± standard deviation (SD). Student's T-test (with parametric distribution) was used to determine the statistical significance of differences in continuous values depending on the type of distribution.

The importance of differences in group comparisons was evaluated; the reliability of differences in the frequency of propagation of the studied properties in groups was determined by a two-sided version of the exact Fisher criterion.

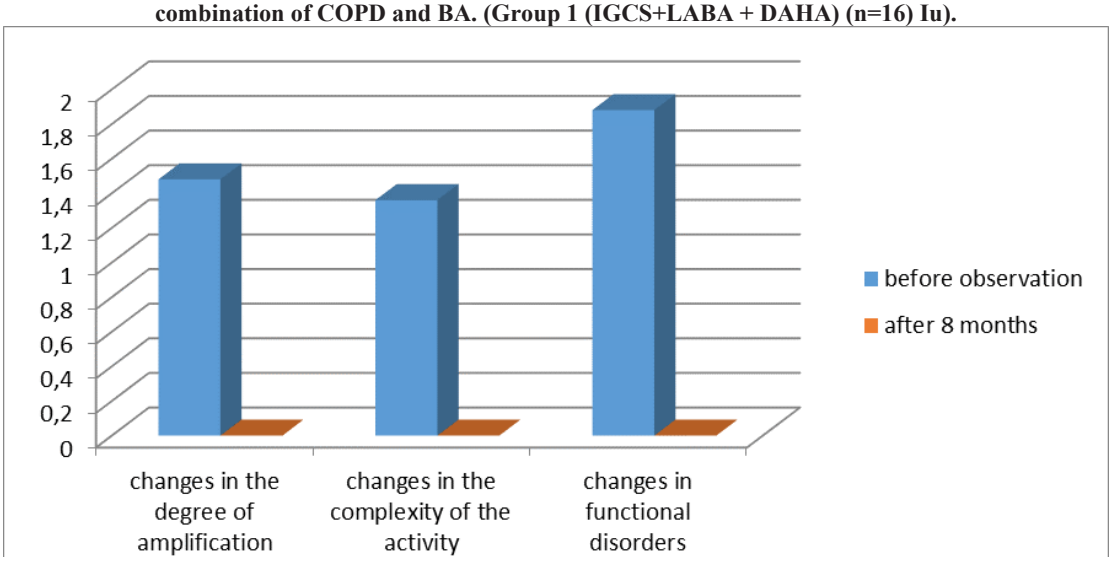
Research results. The clinical course in the observed patients with a combination of COPD and BA was characterized by: repeated acute and exacerbations of chronic lower respiratory tract infections requiring the appointment of antibacterial therapy, frequent exacerbations of the underlying pathology with the use of oral glucocorticosteroids, low levels of FEV1, leading to hospitalization [5]. Asthma had an uncontrolled course. All patients received high doses of IGCS. The average IR was 40.00 packs/years. COPD and BA had a significant impact on the quality of life of patients according to the BDI, ACT and CAT questionnaire.

A clinical, functional evaluation of the effectiveness of a triple combination of drugs for the course of the overlap syndrome was carried out. The degree of dyspnea, according to the mMRC questionnaire, decreased from 3.00 to 1.50 points ($p \leq 0.05$). In the comparison group, there were no significant differences before follow-up (3.00 points) and after 8 months (3.00 points) ($p \geq 0.05$).

The average TBI score increased from 1.45 to 1.98 during therapy ($p=0.05$), which is 3.5 times higher compared to the indicator in the second group. This concerned both functional disorders and the complexity of the activity, the degree of effort. There were no significant differences in the studied parameters in the comparison group before follow-up and after 6 months (Pic 1.2). Against the background of triple therapy, patients with a combination of COPD and BA began to walk a longer distance and it was easier to endure physical exertion.

Pic 1.

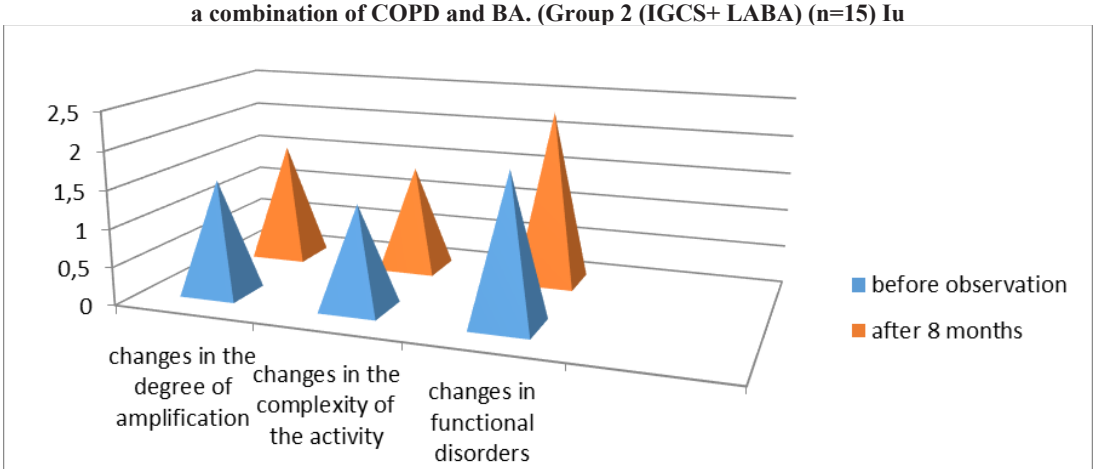
Indicators of TBI in various combinations of therapy in patients with a combination of COPD and BA. (Group 1 (IGCS+LABA + DAHA) (n=16) Iu).



Note:* - reliability of differences before observation and after 8 months

Pic 2.

TBI indicators for various combinations of therapy in patients with a combination of COPD and BA. (Group 2 (IGCS+ LABA) (n=15) Iu



Note:* - reliability of differences before observation and after 8 months.

Discussion. The results of the conducted studies indicated that the inclusion of glycopyrronium bromide in the therapy of patients with combined respiratory pathology was accompanied by a significant improvement in FVD indicators compared to those in the comparison group ($p<0.05$). FEV1 increased 1.5 times during 8 months of follow-up and by 68.00 ml compared with patients receiving therapy only with IGCS and LABA.

The evaluation of the AST test showed that the control of the course of asthma improved when glycopyrronium bromide was included in the treatment. The severity and severity of COPD symptoms decreased, according to the results of the SAT questionnaire, after 8 months, which indicated a positive effect of triple therapy in patients with a combination of COPD and BA. There were no significant changes in the results of the AST and SAT questionnaires in the comparison group ($p\geq0.05$).

In addition to functional indicators, patients had a decrease in the frequency of taking short-acting bronchodilators against the background of triple therapy. During the observation period, the number of exacerbations and hospitalizations due to severe exacerbations decreased. All patients of group 1 noted a rapid effect of therapy. When taking glycopyrronium bromide, 8 patients had undesirable side effects, such as dry mouth, sore throat, hoarseness of voice, 2 people had a dry cough when inhaling the drug, which was stopped independently. The listed side effects were of a short-term nature and did not require discontinuation of the drug. No serious adverse events were registered. To achieve an optimal effect in treatment, the proposed therapy should undoubtedly be long-lasting. It is planned to continue monitoring patients in groups with different therapy regimens to assess long-term results and assess the quality of life of patients.

Conclusions. The inclusion of glycopyrronium bromide in the complex therapy of patients with a combined diagnosis of COPD and BA showed significant clinical and functional efficacy of the drug. Triple combination therapy (IGCS, LABA, LAAHD) is optimal in patients with a combination of COPD and BA. Glycopyrronium bromide can be recommended as the drug of choice for LAAHD in patients with a combination of COPD and BA. In addition, a single dose of the drug improves patients' adherence to treatment.

References / Список литературы /Iqtiboslar

1. Трушина Е.Ю., Костина Е.М. КЛИНИЧЕСКИЙ ОПЫТ ПРИМЕНЕНИЯ ГЛИКОПИРРОНИЯ БРОМИДА У БОЛЬНЫХ С СОЧЕТАНИЕМ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ И БРОНХИАЛЬНОЙ АСТМЫ // Современные проблемы науки и образования. – 2017. – № 3.
2. Antoniu S.A. Targeting the TNF-alpha pathway in sarcoidosis. Expert Opin. Ther. Targets, 2010, Vol. 14, no 1, pp. 21-29.
3. Arkhipov V., Arkhipova D., Miravitlles M., Lazarev A., Stukalina E. Characteristics of COPD patients according to GOLD classification and clinical phenotypes in the Russian Federation: the SUPPORT trial. Int. J. Chron. Obstruct. Pulmon. Dis., 2017, Vol. 12, pp. 3255-3262.
4. Bade G., Khan M.A., Srivastava A.K., Khare P., Solaiappan K.K., Guleria R., Palaniyar N., Talwar A. Serum cytokine profiling and enrichment analysis reveal the involvement of immunological and inflammatory pathways in stable patients with chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis., 2014, Vol. 9, no. 1, pp. 759-773.
5. Burrows B., Fletcher C.M., Heard B.E., Jones N.L., Wootliff J.S. The emphysematous and bronchial types of chronic airways obstruction. A clinicopathological study of patients in London and Chicago. Lancet, 1966, Vol. 287, no. 7442, pp. 830-835.
6. Caramori G., Casolari P., Barczyk A., Durham A, Stefano A., Adcock Ia. COPD immunopathology. Semin. Immunopathol., 2014, Vol. 38, no. 4, pp. 497-515.
7. Cruz T., López-Giraldo A., Noell G., Casas-Recasens S., Garcia T., Molins L., Juan M., Fernandez M.A., Agustí A., Faner R. Multi-level immune response network in mild-moderate Chronic Obstructive Pulmonary Disease (COPD). Respir. Res., 2019, Vol. 20, 152. doi: 10.1186/s12931-019-1105-z.
8. Eltboli O., Bafadhel M., Hollins F., Wright A., Hargadon B., Kulkarni N., Brightling C. COPD exacerbation severity and frequency is associated with impaired macrophage efferocytosis of eosinophils. BMC Pulm. Med., 2014, Vol. 14, 112. doi: 10.1186/1471-2466-14-112.
9. Fraig M., Shreesha U., Savici D., Katzenstein A.L. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am. J. Surg. Pathol., 2002, Vol. 26, no. 5, pp. 647-653.
10. Ivanov S., Linden A. New drugs and targets for asthma and COPD. Progr. Respir. Res., 2010, no. 39, pp. 3-23. Chron. Obstruct. Pulmon. Dis., 2017, Vol. 12, pp. 1857-1865.
11. Koenderman L., Chilvers E. Future treatment in patients with chronic obstructive pulmonary disease: To reverse or not to reverse steroid resistance – that is the question. J. Allergy Clin. Immunol., 2014, Vol. 134, no. 2, pp. 314-322.
12. Le O., Pichavant R.M., Frealle E., Guillon A., Si-Tahar M., Gosset Ph., Th17 cytokines: novel potential therapeutic targets for COPD pathogenesis and exacerbations. Eur. Respir. J., 2017, Vol. 50, no. 4, 1602434. doi: 10.1183/13993003.02434-2016.
13. Li X.N., Pan X., Qiu D. Imbalances of Th17 and Treg cells and their respective cytokines in COPD patients by disease stage. Int. J. Clin. Exp. Med., 2014, Vol. 12, no. 7, pp. 5324-5329.
14. Morphological changes in the respiratory system in chronic obstructive pulmonary disease. Arkhiv patologii = Archives of Pathology, 2016, no. 1, pp. 42-50. (In Russ.)]№ 6. С. 657-672. [Nikonova A.A., Khaitov M.R., Khaitov R.M. Characteristics and role of different populations of macrophages in the pathogenesis of acute and chronic lung diseases. Meditsinskaya immunologiya = Medical Immunology (Russia), 2017, Vol. 19, no. 6, pp. 657-672. (In Russ.)] doi: 10.15789/1563-0625-2017-6-657-672.
15. Ponce-Gallegos M.A., Ramírez-Venegas A., Falfán-Valencia R. Th17 profile in COPD exacerbations. Int.
16. Pridgeon C., Bugeon L., Donnelly L., Straschil U., Tudhope S.J., Fenwick P., Lamb J.R., Barnes P.J., Dallman M.J. Regulation of IL-17 in chronic inflammation in the human lung. Clin. Sci., 2011, Vol. 120, no. 12, pp. 515-524.

17. Snoeck-Stroband J.B., Lapperre T.S., Gosman M.M.E., Boezen H.M., Timens W., ten Hacken N.H.T., Sont J.K., Sterk P.J., Hiemstra P.S.; Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) Study Group. Chronic bronchitis sub-phenotype within COPD: inflammation in sputum and biopsies. Eur. Respir. J., 2008, Vol. 31, pp. 70-77.Т. 18, № 3. С. 287-290.
18. Lobanova E.G., Kalinina E.P., Denisenko Yu.K. Peculiarities of the cytokine levels of Th1 and Th17 lymphocytes in patients with chronic obstructive pulmonary disease. Meditsinskaya immunologiya = Medical Immunology (Russia), 2016, Vol. 18, no. 3, pp. 287-290. (In Russ.)] doi: 10.15789/1563-0625-2016-3-287-290.
19. Бережная Н.М., Сепиашвили Р.И. Интерлейкины в патогенезе атопических аллергических заболеваний // Аллергология и иммунология, 2014. Т. 15, № 3. С. 169-176. [Berezhnaya N.M., Sepiashvili R.I. Interleukins in the pathogenesis of atopic allergic diseases. Allergologiya i immunologiya = Allergology and Immunology, 2014, Vol. 15, no. 3, pp. 169-176. (In Russ.)]
20. Долинина Л.Ю., Делиева А.Н., Богданова Е.О., Галкина О.В., Трофимов В.И. Особенности локально- го воспаления при хронической обструктивной болезни легких в зависимости от степени тяжести // Меди- цинская иммунология, 2013. Т. 15, № 2. С. 141-146. [Dolinina L.Yu., Delieva A.N., Bogdanova E.O., Galkina O.V., Trofimov V.I. Features of local inflammation in chronic obstructive pulmonary disease, depending on the severity. Meditsinskaya immunologiya = Medical Immunology (Russia). 2013, Vol. 15, no. 2, pp. 141-146. (In Russ.)] doi: 10.15789/1563-0625-2013-2-141-146.
21. Калинина Е.П., Лобанова Е.Г., Антонюк М.В. Иммунометаболические фенотипы хронической обструктивной болезни легких у мужчин // Медицинская иммунология, 2014. Т. 16, № 4. С. 375-380. [Kalinina E.P., Lobanova E.G., Antonyuk M.V. Immune and metabolic phenotypes of chronic obstructive pulmonary disease in men. Meditsinskaya immunologiya = Medical Immunology (Russia), 2014, Vol. 16, no. 4, pp. 375-380. (In Russ.)] doi: 10.15789/1563-0625-2014-4-375-380.
22. Лобанова Е.Г., Калинина Е.П., Денисенко Ю.К. Особенности содержания цитокинов Th1- и Th17- лимфоцитов у лиц с хронической обструктивной болезнью легких // Медицинская иммунология, 2016.
23. Малыхин Ф.Т., Косторная И.В. Морфологические изменения органов дыхания при хронической обструктивной болезни легких // Архив патологии, 2016. № 1. С. 42-50. [Malykhin F.T., Kostornaya I.V.
24. Насирова А. А. ХАРАКТЕРИСТИКИ КАЧЕСТВА ЖИЗНИ БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ, ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ И ИХ СОЧЕТАНИЕМ //Журнал кардиореспираторных исследований. – 2022. – Т. 3. – №. 3.
25. Насирова А. А., Бабамурадова З. Б., Базарова С. А. Особенности иммунологических показателей у больных хронической обструктивной болезнью легких и бронхиальной астмой //Журнал кардиореспираторных исследований. – 2020. – Т. 1. – №. 3.
26. Насирова А. А., Садикова Ш. Н., Курбанова З. П. Современные представления о роли поверхностного фенотипа лимфоцитов при хронической обструктивной болезни легких и бронхиальной астме и их лечение //Вестник науки и образования. – 2020. – №. 13-2 (91). – С. 49-53.
27. Насирова А. А., Садикова Ш. Н., Курбанова З. П. Современные представления о роли поверхностного фенотипа лимфоцитов при хронической обструктивной болезни легких и бронхиальной астме и их лечение //Вестник науки и образования. – 2020. – №. 13-2 (91). – С. 49-53.
28. Никонова А.А., Хаитов М.Р., Хаитов Р.М. Характеристика и роль различных популяций макро- фагов в патогенезе острых и хронических заболеваний легких // Медицинская иммунология, 2017. Т. 19