Optimization of pharmacotherapy of chronic obstructive pulmonary disease complicated by bronhoectasis in patients with cardiovascular pathology

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Introduction.

Chronic obstructive pulmonary disease is a weighty social health and economic importance, and remains one of the major causes of morbidity and mortality worldwide. Presently, special attention is paid to comorbid conditions, when the patient has a combination of pathology respiratory and cardiovascular systems. This research has been devoted to finding ways to optimize the treatment of moderate acute exacerbations of chronic obstructive pulmonary disease with the complication of bronchoectasis on the background of coronary heart disease.

Keywords: obstructive bronchitis, bronchiectasis, coronary heart disease, glutoksim, L-arginine.

In the XX-XXI century there were accounts of sudden increase in the number of patients with chronic obstructive pulmonary disease (COPD). This pathology has now become of significant medical, social and economic importance, and remains one of the major causes of morbidity and mortality worldwide [7, 20]. Currently, according to WHO, COPD affects 0.8% of the world population, in different countries from 8 to 22% of the adult population aged 40 years and older are affected [9]. The prevalence of COPD in Europe is from 3.7 to 6.7% of the population and the number of relapses in patients with this disease varies from 1 to 4 times per year [5, 9, 20]. Morbidity and mortality rates are constantly rising. In Europe annually COPD is the cause of death of 200-300 thousand of people [9, 16]. In Ukraine, the death rate from COPD is 41.2 per 100 000 population, which is higher than the death rate from pneumonia and asthma [7, 8]. The high morbidity of COPD accounts for a significant economic burden on the economies of all countries. Thus, according to GOLD in EU annual direct costs of treating COPD constitute 38600000000 euro, the US, the figure is 21800000000 dollars, and indirect costs exceed 17 billion dollars [6, 7]. In recent decades, there is a constant increase in the incidence of COPD. This is due to environmental pollution, especially air, smoking and aging population worldwide [7, 9].

Distribution of underdiagnosis of COPD, inadequate antimicrobial therapy led to an increase in cases of COPD with complication of bronhoectasis. Among disadvantages, attention should also be given tobacco smoking, which is a common risk factor for the development of both cardiovascular and respiratory disease [2, 7]. Significant relevance acquires polymorbidity, which is typical for older age groups. It was in this group of patients older than 40 years have

seen the rapid progression of coronary artery disease (CHD). CHD is one of the leading places in the structure of morbidity and mortality in Ukraine. The country has about 6.8 million of patients with CHD. Over the past 10 years, the incidence and mortality from CHD are constantly increasing [1]. In view of the high prevalence of CHD and a high probability of serious complications that cause disability and high fatality this problem, other than medical, has a pronounced social character.

It is safe to assume that during exacerbations of COPD with complication of bronhoectasis unlike CHD, will require a more balanced prescription. And on conservative treatment of severe exacerbation of COPD with complication of bronhoectasis, unlike coronary heart disease in the literature has been given very little attention.

The pathogenesis is due to the activity of oxidant aggression on the mucosa of the respiratory tract by reactive oxygen species and other free radicals, resulting in lipid peroxidation and damage to biological membranes [19, 23], including immune cells. Today, more and more attention is paid to the immunological reactivity in patients with COPD [3]. It has been found that the development and exacerbation of COPD is accompanied by inhibition of a local immune defense against respiratory viruses and bacteria including systemic damage of cellular and humoral immunity [12]. There were installed systemic violations of cellular and humoral immunity in patients with acute exacerbation of COPD [13]. Violations of cellular immunity: inhibition of alveolar macrophage suppressor systems, reducing the number of T-helper cells, effector cytotoxic lymphocytes. With the most pronounced inhibition of T-suppressor lymphocytes exerted in patients receiving long-term antibiotic therapy [24]. Many infectious agents lead to an exacerbation of COPD, cause disturbances of mucous clearance, increased production of mucus thick bronchial secretions, local splitting of immunoglobulins, inhibition of phagocytic activity of neutrophils and alveolar macrophages, an increase in the release of histamine and other mediators of inflammation [3, 4]. Among the endogenous risk factors are the most important features of genetically caused immune reactivity. It is known that the greater propensity of man to infection with respiratory viruses and damage to ciliated epithelium determines selective IgA deficiency, and combined with a deficit of IgG [3].

Therefore, it is necessary to prescribe for patients with acute exacerbations of COPD medications, providing the activation of mechanisms of self-regulation, the adequacy of the immune response, improving the barrier function of the bronchial mucosa. The medication Glutoxim is an immunoreabilitator that has immunomodulatory, bronchodilator, desensitizing, anti-inflammatory and antimicrobial effect. [18]. Glutoxim (registration number 98 \ 279 \ 3) – is chemically synthesized biologically active compound – a hexapeptide with the stabilized disulfide bond. Glutoxim is a representative of a new class of drug – thiopentone that has a

modulating effect on intracellular processes, plays an important role in the regulation of metabolic processes in the tissues and organs, as well as in endogenous production of cytokines: interferons and interleukins. [10].

According to modern concepts, one of the leading roles in the onset and progression of cardiovascular diseases, (including coronary heart disease), hypertension plays the vascular endothelial dysfunction [25]. The vascular endothelium is the only body that regulates hemodynamics and perfusion according to the needs of each organ or tissue. The main role of the endothelium is the allocation of a number of biologically active substances. The proper functioning of the endothelium depends on the vascular tone (total vascular resistance, blood pressure), athrombogenic vascular wall, platelet activity, blood coagulation, inflammation, antioxidant resistance, as well as the preservation of the structural layers of the vessel wall and the manifestation of atherogenesis. It is likely that a violation of these regulatory actions leads to changes in the organs and systems that serve as the basis for the pathogenesis of many pathological processes, such as cardiovascular disease. Therefore, reducing damage, correction and maintenance of adequate functioning of the endothelium is one of the most urgent problems of modern therapy of vascular disease. Other drugs used in cardiology have varying degrees for normalizing the effect against endothelial dysfunction. One of such group of drugs is the donator NO, in particular L-arginine aspartate, which has positive effect in endothelial dysfunction. [14]. In addition, L-arginine aspartate has detoxifying, membrane stabilizing, anti-hypoxic, cytoprotective, antioxidant and antiradical activities. It also manifests itself as an active process controller of power supply and intermediary metabolism. L-arginine aspartate has a stimulating effect of on the activity of thymus which plays the leading role in differentiation and maturation of T-lymphocytes. And what is important that L-arginine aspartate promotes correction of acid-base balance. The accumulation of data about cardiovascular and respiratory pathology changes the paradigms to patient's treatment.

The purpose of this study was to determine ways to optimize the treatment of moderate COPD complicated bronhoectasis on the background of CHD.

Materials and methods.

The study included 63 patients with COPD complicated bronhoectasis on CHD in age from 40 to 65 years who were hospitalized in the pulmonary department of TH №1 with aggravation. The average age of the patients was $52,5 \pm 4,5$ years. COPD diagnosis was established on the basis of clinical, radiological, laboratory and functional examinations in accordance with the orders of the Ministry of Health of Ukraine from 27.06.2013year №555 all patients COPD complicated by bronchiectasis, confirmed by X-rays and computed tomography. Investigation of pulmonary ventilation with the registration curve "flow-volume" forced

expiratory and conduct standard bronchodilation by inhalation of salbutamol. Verify the diagnosis of CHD was performed according to the order of Ministry of Health of Ukraine №54 from 14.02.2002 year. The diagnosis of ischemic heart disease was confirmed on the basis of standard cardiac profiles of WHO (Rose questionnaire), the nature of the changes on the electrocardiogram at rest according to the recommendations of the VI National Congress of Cardiologists of Ukraine.

All patients were divided into 3 groups and clinical control 1 and 2 are similar in age and the clinical course of the disease. The control group consisted of 10 patients who received standard therapy with antibiotics, mucolytics within 10 days. Clinical group 1 (26 patients), which in addition to standard therapy was appointed Glutoxim 1ml 3% (30 mg) once a day intramuscular during 10 days (300 mg to 1 year), the clinical group 2 (27 patients), which in addition to standard therapy was appointed Glutoxim in combination with L-arginine aspartate 4.2%, which was used intravenously in 100 ml of 1 time per day for 10 days. The volume of the standard therapy for patients clinical groups was the same as that of the control group. In those cases where the prior ambulatory patients hospitalized both groups received clinical β2-agonists (salmeterol, formoterol) or anticholinergics (ipratropium, tiotropium), such treatment was continued for the entire period of observation in a dose corresponding to the severity. The observation period was 14 days.

Immunological examination of patients was carried out in the first 3 days after admission and after 10 days of treatment. To which included: quantitative evaluation of T and B components of immunity by immunofluorescence method, counting the cell phenotype CD3+, CD4+, CD8+, CD16 +, CD22+ and immunoregulatory index (IRI – the ratio of CD4+/CD8+) [21]; study the functional activity of T-lymphocyte blast transformation via reaction (RBTL) [15]; performance study serum IgG, IgA, IgM [17]; determining the concentration of circulating immune complexes (CIC) in the average size serum [11]; study of phagocytic activity of neutrophils with the calculation of phagocytic index (PI) Hamburg and phagocytic number (FF) Wright [21].

This study evaluated the dynamics of indicators of quality of life in COPD basic therapy and therapy with glutoxim connection. To study the quality of life in patients at different periods of exacerbation of COPD, treatment, rehabilitation using the version of the general questionnaire MOS SF-36 (MOS SF Item Short Form Health Survey). In order to evaluate the effect of treatment on quality of life of patients with COPD in addition to the questionnaire MOS SF-36 conducted tests global assessment of the quality of care the patient and the doctor. The test results are evaluated by the point system. Patients self-administered questionnaire SF -36 in the next phase of the disease:

1. In the beginning of the treatment at the time of admission, acute phase of the disease;
2. In the stationary end of treatment (days 12-14);
3. 2 months.

Statistical processing of the results was carried out on a personal computer using a standard package of functions «MS Excell» and «Statistica for Windous. Release 6.0».

Results and discussion.

Analysis of the initial results of immunological studies showed that the patients had significant disorders of the immune function in cellular and humoral. The common features of immunological disorders in patients with COPD were in violation of humoral immunity – a significant decrease in levels of IgG and IgA along with the increase in the number of B-lymphocytes (CD22+ lymphocyte population), as well as increasing the concentration of the CEC of medium size in the serum. Common signs of cellular immune disorders has been a significant decrease in the total number of subpopulations of lymphocytes and CD3+, CD4+, CD16+ lymphocytes. The analysis of baseline T-cell immunity in patients with COPD showed heterogeneity and multi-vector violations. Similar results were obtained by other researchers, and coincide with the literature data [13].

Most often in patients with COPD were observed multi-vectorviolations cellular immunity: some observed mainly T-helper immune deficiency with low immunoregulatory index, in other predominantly T-suppressor immunodeficiency high immunoregulatory index. What can explain the different orientation of the immune response depending on the adaptive-adaptive capabilities of a particular organism, the progression of bronchial obstruction and persistence of infectious and inflammatory process in the bronchial tree. Depending on these results all examined patients clinical groups were divided into two subgroups. The criteria for selection were the importance of the immunoregulatory index and type of immunodeficiency. Each clinical group was divided into subgroups: In subgroup A included patients with T-helper immune deficiency and low immunoregulatory index (in 95% of patients with IRI was within 0.8-1.3) A.1 – 13 patients, A.2 – 12 in the subgroup included patients with T-suppressor immunodeficiency and high immunoregulatory index (IRI 96% of the patients ranged from 2.1-2.6) B.1 – 13 patients B.2 – 15.

After a 10-day treatment in patients with both clinical groups positive dynamics of clinical symptoms with a decrease in the intensity of dyspnae and cough, reducing the volume and purulence of sputum, the normalization of body temperature, improvement in general well-being. This led to the restoration of health, or the return of health, which was before the escalation of the disease. Positive clinical dynamics was accompanied by improvements in pulmonary ventilation.

Analysis of immunological parameters in patients in the control group showed that despite the advent of standard treatment, improve the immune status were observed. The total number of lymphocytes increased from 1,70 ± 0,14 to 1,98 ± 0,76, CD4 + - lymphocyte 0,48 ± 0,11 to 0,46 ± 0,21, performance values were not reliable. There was a significant decrease in spontaneous RBTL with 0,055 ± 0,006 to 0,034 ± 0,008 (p≥0,05), although the change RBTL with PHA was not significant from 1,37 ± 0,11 to 1,49 ± 0,2. There was a trend to reduce the number of population with CD3 + 0,95 ± 0,18 to 0,84 ± 0,42, and CD8 + lymphocyte subpopulations with 0,41 ± 0,17 to 0,36 ± 0,22, immunoregulatory index with decreased from 1,76 ± 0,15 to 0,51 ± 0,85, amid tendency to increase the population of lymphocytes with CD16 + 0,26 ± 0,10 to 0,31 ± 0,12. In humoral immunity reduction of CD22 + - lymphocytes from 0,69 ± 0,08 to 0,66 ± 0,38, as well as the content of IgG, with 8,40 ± 0,19 to 7,97 ± 0,74, IgA from 1,31 ± 0,15 to 1,26 ± 0,22, IgM from 0,91 ± 0,06 to 0,83 ± 0,11, the number of CEC with 61,1 ± 2,71 to 62,47 ± 4,75, all indicators were not a valid value. Phagocytic activity of neutrophils remained at the same level of FI with 51,0 ± 3,6 to 50,32 ± 8,31, with the FF 4,4 ± 0,47 to 6,2 ± 3,51.

Patients in both groups were observed clinical improvement of immune parameters. Patients subgroups A.1 after treatment there was a statistically significant increase in the total number of lymphocytes with 1,69 ± 0,15 to 2,12 ± 0,12 (p≥0,05) populations: CD3 + lymphocytes with 1,02 ± 0,21 to 1,50 ± 0,09 (p≥0,05), CD4 + - cells to 0,44 ± 0,13 0,78 ± 0,09 (p≥0,05), CD16 + lymphocytes from 0,26 ± 0,05 to 0,41 ± 0,02 (p≥0,05), proliferative activity of lymphocytes with PHA RBTL with 1,45 ± 0,08 to 1,69 ± 0,04 (p≥ 0.05). Changes spontaneous RBTL with 0,055 ± 0,005 to 0,046 ± 0,004, the number of CD8 + - lymphocytes from 0,49 ± 0,08 to 0,50 ± 0,15, did not have a valid value. This is evidence of the positive effects of prescribed treatment on the immune response of the body. As a result, there was a decrease manifestations of T-cell immunodeficiency, which was accompanied by a statistically significant normalization of the immunoregulatory index from 1,13 ± 0,16 to 1,83 ± 0,22 (p≥0,05). Similar rates of immune status were obtained in the subgroup A2 so there was an increase of the total number of lymphocytes to 2,19 ± 0,09 (p≥0,05) populations: CD3 + lymphocytes to 1,51 ± 0,08 (p≥ 0,05), CD4 + - cells to 0,81 ± 0,10 (p≥0,05), CD16 + lymphocytes to 0,40 ± 0,04 (p≥0,05), proliferative lymphocyte activity with RBTL PHA to 1,67 ± 0,06 (p≥0,05). Changes spontaneous RBTL to 0,049 ± 0,006, the number of CD8 + - lymphocytes to 0,52 ± 0,11 did not have a valid value. This was accompanied by a statistically significant normalization of the immunoregulatory index to 1,83 ± 0,19 (p≥0,05).

Patients in the clinical group B showed improvement of quantitative and functional characteristics of the most affected T-suppressor/cytotoxic lymphocyte subpopulations. After

treatment in a subgroup B.1 noted a statistically significant increase in the number of CD3 + lymphocyte populations from 0,87 ± 0,15 to 1,27 ± 0,11 (p≥0,05) and a subset of CD8 + lymphocytes with 0,32 ± 0,05 to 0, 47 ± 0,03 (p≥0,05), CD16 + lymphocytes to 0,25 ± 0,06 0,40± 0,02 (p≥0,05) that a statistically reliable normalization of the immunoregulatory index 2, 39 ± 0,14 to 1,85 ± 0,13 (p≥0,05). Tended to improve the functional activity of lymphocytes activated with PHA RBTL increase from 1,28 ± 0,14 to 1,48 ± 0,11, spontaneous changes RBTL with 0,054 ± 0,006 to 0,038 ± 0,009, changing the total number of lymphocytes with 1,71 ± 0 12 to 2,04 ± 0,17, the amount CD4 + - lymphocyte 0,51 ± 0,15 to 0,73 ± 0,07, which did not have a valid value. A similar pattern was also observed in the subgroup B.2. There was a statistically significant increase in the number of CD3 + lymphocyte population to 1,26 ± 0,10 (p≥0,05) and a subset of CD8 + lymphocytes to 0, 49 ± 0,06 (p≥0,05), CD16 + lymphocytes to 0 41 ± 0,04 (p≥0,05), which was accompanied by a statistically significant normalization of the immunoregulatory index to 1,87 ± 0,16 (p≥0,05). Tended to improve the functional activity of lymphocytes with PHA RBTL increase to 1,47 ± 0,10, spontaneous changes RBTL to 0,039 ± 0,007, changes in the total number of lymphocytes to 2,06 ± 0,15, the number of CD4 + - lymphocytes to 0.76 ± 0,09, which did not have a valid value. Registered improve the phagocytic activity of neutrophils in both clinical groups - a statistically significant increase in the FI and FF. So in class A.1: FI with 52,1 ± 2,7 to 64,3 ± 3,3 (p≥0,05) FF with 4,6 ± 0,37 to 6,8 ± 0,9 (p≥0, 05), and the corresponding figures in the subgroup A2: PHI to 65,1 ± 3,1 (p≥0,05), the FF to 6,7 ± 0,7 (p≥0, 05) in the subgroup B.1: FI with 49,9 ± 4,54 to 62,9 ± 4,1 (p≥0,05) FF with 4,2 ± 0,56 to 5,5 ± 0,25 (p ≥0,05), a similar pattern was also observed in the subgroup B.2: PHI to 61,8 ± 3,22 (p≥0,05), the FF to 5,6 ± 0,31 (p ≥0,05).

Significantly less pronounced changes were observed in the humoral immunity of patients in both clinical groups. In the subgroup of A.1 tended to reduce the number of B cells: CD22 + lymphocyte population with 0,62 ± 0,06 to 0,53 ± 0,06, in the subgroup A2 to 0,54 ± 0,08, although in a subset of these results were statistically significant with 0,76 ± 0,09. In the subgroup of B.1 to 0,48 ± 0,07 (p≥0,05) in the subgroup B.2 to 0,47 ± 0,05 (p≥0,05). In both clinical groups showed a statistically significant increase in serum IgA: A.1 in the subgroup with 1,29 ± 0,14 to 1,76 ± 0,11 (p≥0,05) A.2 to 1,75 ± 0.09 (p≥0,05) in the subgroup with B.1 to 1,33 ± 0,15 1,69 ± 0,08 (p≥0,05) B.2 to 1,71 ± 0 09 (p≥0,05). Reduction of circulating immune complexes in the subgroup with A.1 62,8 ± 2,72 to 56,3 ± 1,49 (p≥0,05) A.2 - up to 55,4 ± 1,45 (p≥0, 05); B.1 in the subgroup with 59,4 ± 2,69 to 53,2 ± 1,22 (p≥0,05) B.2 - up to 52,5 ± 1,20 (p≥0,05). This is accompanied by a tendency to a decrease of IgM and IgG content. In the subgroup of A.1 IgG content increased from 7,83 ± 0,21 to 8,10 ± 0,29, A.2 – up to 8,32 ± 0,28, in the subgroup of B.1 with 8,96 ± 0, 18 to 9,56 ± 0,15, B.2 - up to 9,57 ± 0,14. In group A, the

content of IgM decreased from 0,88 ± 0,05 A.1 - up to 0,77 ± 0,03, A.2 – up to 0,76 ± 0,05, in Group B with 0,93 ± 0, 06 B.1 – up to 0,86 ± 0,04, B.2 – up to 0,87 ± 0,03, these figures were not reliable values. Such changes were quite expected result, given the short period of observation.

In the study of quality of life of patients in both clinical groups was obtained significant improvement in all parameters. In the control group, significant changes were observed only in the index of vitality (VT). In subgroups A.1 and B.1 when connected to glutoxim therapy improves vitality (VT), and role functioning (RP), and physical functioning (PF) and were significant. In the control group, these figures did not have a valid value. To a lesser extent in the treatment of positive changes related to indicators of general health (GH), a clinical groups, this figure had reliable value. In subgroups A.2 and B.2 connection to background therapy of glutoxim with L-arginine aspartate led not only to significant improvement in the general health (GH), vitality (VT), role functioning (RP), physical functioning (PF) and the restoration of mental health (MH), emotional functioning (RE), which eventually led to an increase in viability (VT) patients. It should be noted that the improvement in these indicators is beneficial not only to the quality of life of patients, but also to the establishment of Compliance. Long-term observation showed reduction in the number of exacerbations in subgroups A.2 and B.2, which is possible due to the improvement of stressresistance in patients.

Conclusions.

Among the major disorders of T-cell immunity in COPD patients with complication of bronhoectasis for CHD can distinguish T cell immunodeficiency, predominantly T-helper or T-suppressor of immune deficiency. Identified types of immunological disorders are the basis for immunological correction glutoxim. Use of glutoxim was effective and showed improve immunological parameters in patients with impaired cellular immunity.

In addition to standard therapy glutoxim in combination with L-arginine aspartate led not only to an improvement in the body's immunological defense, but also to a significant improvement of all the parameters of quality of life. Long-term follow-up in these patients showed a decrease in the number of exacerbations.

References:

1. Buch P., Friberg J., Scharling H. et al. (2003) Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur. Respir. J., 21 (6): 1012-1016.

2. Dankner R., Goldbourt U., Boyko V., Reicher-Reiss H. (2003) Predictors of cardiac and noncardiac mortality among 14,697 patients with coronary heart disease. Am. J. Cardiol., 91 (2): 121-127.

3. Dvoretskiy L.I. Infection and chronic obstructive pulmonary disease // Consilium Medicum. - 2001. - №3 (12). - P. 587-595.

4. Dzyublik A.Y., Pertseva T.A. Exacerbation of chronic obstructive pulmonary disease: state of the problem // Ukr. pulmonol Journal. - 2009. - №2. - P. 10.

5. Dyachenko V.V. Place of oral cephalosporins of the III generation in treatment of respiratory system infection // Terapia. Ukranian medical News. - 2010. - №10. - P. 40-42.

6. Feshenko Y.I. Control of chronic obstructive pulmonary disease – whether it is possible today? // Health Protection of Ukraine. - Topical number. - 2011. - №1. - P. 1-3.

7. Feshenko Y.I. The new edition of the Global Initiative to guide Obstructive Pulmonary Disease (GOLD) // Health Protection of Ukraine. - Topical number. - 2012. - №2 (18). - P. 10-11.

8. Feshenko Y.I., Yashina L.A., Polyanskaya A.M., et al. Obstructive pulmonary disease. - Singapore: 2004. - 287 p.

9. Global initiative for chronic obstructive lung gisease. WHO, updated 2011.

10. Gembitskaya T.E. Clinical features, diagnosis and treatment of certain genetically caused diseases of the respiratory system in adults: Thesis of Doctor. med. sciences: 14.00.43 / Proc. Institute of Pulmonology. - Leningrad, 1987. - 158 p.

11. Haskova V. Simple method of circulating immune complex defection in human sera be polyethylenglycol precipitation / V. Haskova // Immunol. Forsch. - 1977. - №4. - P. 399-486.

12. Herper-Owen R. Virus and chlamidia isolation in COPD exacerbation \\ Eur. Resp. J. - Vol. 14, Suppl. 30, Oct. 1999. \ abstracts. ERS. Annal. Congress. Madrid, Spain. October, 9-13, 1999. - P. 392 /

13. Ilnitsky R.I. Pecularities of imunological reactivity in patients with chronic obstructive pulmonary disease // Ukr. pulmonol. J. - 2007. - №2 (56). - P. 21-25.

14. Konopleva L.F., Kushnir L.V. Evaluating the effectiveness of L-arginine in pulmonary arterial hypertension of various origins. Ukrain. med. journal, - 2013. - №1 (93). - P. 115-119.

15. Kopelyan I.I., Grigorieva M.P. Micromodifications development of culturing blood cells / I.I. Kopelyan, M.P. Grigorieva // Bull. exp. biol. and med. - 1972. - №9. - 119-122 P.

16. Leshchenko I.V. The main directions of the treatment of chronic obstructive pulmonary disease // Ter. Archive. - 2007. - №5. - P. 75-84.

17. Mancini G., Carbonara A.O., Heremans J.F. Immunochemical quantitation of antigens by single radial immunodiffusion / G. Mancini, A.O. Carbonara, J.F. Heremans // Immunochemistry. - 1965. - Vol. 2. - P. 235-254.

18. Molodtsova A.V. Evaluating the effectiveness of Glutoxim immunomodulator in the treatment of patients with chronic obstructive pulmonary disease: Abstract of Cand. med. Sciences: 14.00.43 - St. Petersburg. - 2005. - 23 p.

19. Ozaras R., Tahan V., Talay F., Usun H., Getinkaya R. Changes in malondialdehyde levels in bronchoalveolar fluid and serum by the treatmentof asthma with inhaled steroid and beta 2 agonist // Respiratory/ - 2000. - Vol. 5, №3. - P. 289-292.

20. Ostrovsky M.M. Optimization of bronhial obstruction correction in acute period of chronic pulmonary disease // Health Protection of Ukraine. - Topical number. - 2011. - №4 (16). - P. 12-14.

21. Perederiy V.G., Zemskov A.M., Bychkov N.G., Zemskov V.M. // Immune status, the principles of evaluation and correction of immune disorders. - K.: Health Protection, 1995. - 211 p.

22. Rabe K.F. Roflumilast for the treatment of chronic obstructive pulmonary disease // Expert Rev Resp Med. - 2010. - Vol. 4. - P. 543-555.

23. Soodaeva S.K. Oxidant and antioxidant system in chronic obstructive pulmonary disease // chronic obstructive pulmonary disease. - SPb.: Nevsky dialekt, 1998. - P. 92-111.

24. Tager M., Biecyk A., Kohnelin T., Ansorge S., Welte T. Evidense of a defective thiol status of alveolar macrophages from COPD patients and smokers. COPD \\ Free Radic. Biol. Med. - 2000. - Vol. 29, №11. - P. 1160-1165.

25. Zinkovskiy M.F. Nitric oxide and pulmonary hypertension. // Health of Ukraine. - 2008. - № 13-14. - P. 62.