ARTICLE

IMMUNE AND METABOLIC PARAMETERS OF BLOOD PLASMA AND ERYTHROCYTES AS QUALITY FACTORS OF ANTIBACTERIAL THERAPY IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRACT

Community-acquired pneumonia (CAP) holds a dominate position in the structure of infections mortality factors in the world. Immune and metabolic disorders were studied before and after standard medical therapy in patients with community-acquired pneumonia. Laboratory criteria indicating immune inflammation, oxidative stress, endothelial dysfunction, and activation of lipid peroxidation were detected in the patients included in the study. Standard treatment does not normalize most of the altered parameters of the immune and metabolic status, which stipulates the necessity to search for the methods to correct the disorders by administering various combinations of preparations with immunomodulatory and antioxidant action in complex pharmacotherapy.

KEY WORDS
community-acquired pneumonia, immune inflammation, oxidative stress, endothelial dysfunction, lipid peroxidation

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INTRODUCTION

Diseases of the respiratory system (DRS) consistently occupy a leading position in the structure of the overall morbidity among the population of the Russian Federation, accounting in 2014 29 455 225 cases (54.2% of all diseases) in children, 3 403 (33.2%) in adolescents, 23 394 842 (13.6%) - in adults [1- 3]. According to the World Health Organization report, in 2012 due to the development of lower respiratory tract infection (LRTI) 3.1 million people died [4]. Severe LRTIs rank third among the leading causes of death, conceding only to coronary heart disease, stroke, and other cerebrovascular diseases. Besides, the findings of the research show a change in the nature of the course, frequent development of complications and an increase in mortality in CAP [5].

Community-acquired pneumonias (CAPs) are one of the most common infectious diseases in the world and the Russian Federation [2]. M. Rosenbaum et al. provide data on the epidemiology of pneumonia in Europe and North America. Among adults, pneumonia occurs in 5-10 people per 1,000 population [3]. CAP morbidity in the developed countries varies from 1 to 11.6‰ among young and middle age and from 25 to 44‰ in people aged 65 and older [2]. According to Federal Oversight Service for Consumers' Right and Human Welfare, the incidence of CAP in Russia in 2014 accounted 337,77 cases per 100 thousand adult population [4]. About 400 thousand people are administered to hospitals of the country; in 2014 a little more than 40 thousand people died from pneumonia [3].

Medical statistics data over the country lay emphasis on the immediacy of the problem in Russian healthcare system. If we summarize and compare them with international epidemiological studies, we can state the following: approximately 1 million people are not timely diagnosed with pneumonia, and mortality from severe forms of pneumonia has reached 10% [3].

Immune mechanisms are known to have an important role in the development and resolution of almost all pathological conditions, especially those with an infectious etiology, upon that the relationship between metabolic and immunological changes is well described. A mass and virulent infection, a decrease in nonspecific resistance of the organism, an imbalance of local and systemic immunity, a disturbance of free-radical oxidation processes play a leading role in CAP pathogenesis [5]. It is obvious that the timely and adequate administration of antimicrobial drugs, as the indicators of medical care quality, is the fundamental factor in the management of CAP patients. The immune system dysfunctions are manifested by hypo- and/or hyperactive processes and are one of the causes of the disease development [6, 7]. In this case, hypoactivation is associated with either a quantitative and functional insufficiency of the immune system components, or with the absence of full activation to a specific pathogen. The development of hyperactive conditions is associated with an increase in the quantitative and functional characteristics of the immune system effector components and/or insufficiency of suppressor factors [8]. It is such dysfunctional features or their combinations that underlie the development of infectious diseases [9, 10]. In this regard, immunological assessment of standard antibiotic therapy effectiveness is a general indicator of the therapy. Nevertheless, there are very few comprehensive researches devoted to the study of the immune and metabolic status not only prior, but also after the standard treatment [11- 16].

The aim of the study is to detect immune and metabolic disorders before and after standard treatment in patients with community-acquired bacterial pneumonia.

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MATERIALS AND METHODS

Based on the conducted screening, 46 patients with community-acquired bacterial pneumonia were enrolled in the examination in the pulmonary department of the non-governmental healthcare institution "Department Hospital at the station Kursk "Russian Railways". Clinical observations were of controlled prospective open randomized study in nature. The general characteristics of the patients examined and the representation of concomitant pathology are shown in [Table 1]. Written consent from the subjects was taken and the study was approved by the Kursk State Medical University ethical committee.

Inclusion criteria: the patients under 18 are not included, CAP diagnosis made on the basis of epidemiological, clinical-radiological and laboratory data typical for this disease [17-19]. CAP diagnosis was made according to Russian National Recommendations for CAP and the recommendations of American Thoracic Society/Infectious Diseases Society of America [20- 22].

Patients with aspiration pneumonia, atypical pneumonia, viral pneumonia, nosocomial pneumonia, pulmonary tuberculosis, primary or metastatic lung cancer, cystic fibrosis, hepatic and/or renal failure, with severe concomitant diseases, with acute respiratory disorders, and those taking immunomodulatory agents for the preceding year were excluded from the study.

The control group consisted of practically healthy individuals (n = 18), consistent with the patients by sex and age.

Table 1: General characteristic of the patients examined

Clinical-anatomical characteristics		Patients included in the study
Sex (number of patients / percent)	Males	21 / 45,7
	Females	25 / 54,3
Mean age (years)		47,03±3,2 (from 20 to 77)
Disease duration (days) at out-patient treatment stage		8,23±1,05
Antibacterial therapy used at out-patient treatment stage (number of patients / percent)		20 / 43,4
First hospital admission with CAP diagnosis (number of patients / percent)		46 / 100
Smoking (number of patients / percent)		18 / 39,1
Smoking index (for smoking patients)		15,7
Comorbid conditions (number of patients / percent)		34 / 73,9
Upper respiratory tract diseases (number of patients / percent)		11 / 23,9
Characteristic of egocentric and objective status on admission (number of patients / percent)	Chest pain	37 /80,4
	Cough	46 /100
	Dyspnea (scores)	3,47±0,47
	Body temperature	38±0,12
	Respiratory rate	21,97±0,92

Table 2: Characteristic of patients concerning CAP severity

Indicants	Patients included in the study
CRB-65 (scores)	0,53±0,13
SMRT-CO (scores)	0,53±0,12

According CAP severity was determined in accordance with clinical guidelines [23]. To collect clinical and laboratory data, we used specially designed case registration forms which included demographic data, diagnosis, medical history, physical findings, results of laboratory and instrumental research methods. Mortality prediction estimation was made by CRB-65 scale [24]. Identification of patients requiring intensive respiratory support and vasoconstrictors infusion was carried out by SMRT-CO scale [23]. To interpret these scales data, the assessment of the following parameters was involved: age, impairment of consciousness, respiratory rate, systolic and diastolic blood pressure, chest X-ray findings, heart rate. Prognosis and severity of the disease assessment was performed upon the patient's admission, on the 3rd, 7th day of ward treatment and at time of hospital discharge. Characteristics of the study group in relation to the underlying pathology severity are presented in [Table 2].

Assessment of clinical laboratory data in the main groups was carried out on the 1st and 10th day of therapy. Erythrocytes and plasma were obtained from 10 ml of heparinized blood, for this purpose plasma was separated after its centrifugation, and packed erythrocytes were twice precipitated in 20 ml of 10 mM Na-phosphate buffer (pH = 7.4) containing 0.9% sodium chloride and 3% dextran T-500 for 30 minutes at 37°C.

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After centrifugation, the supernatant fluid was removed by aspiration, and the packed erythrocytes were subjected to additional purification by chromatographic column through HBS-cellulose.

The intensity of lipid peroxidation (LPO) processes was assessed by acyl hydroperoxides (AHP) and malondialdehyde (MDA) content in blood plasma and erythrocytes, which form a colored butanol-extractable iodine complex with thiobarbituric acid. To determine MDA and AHP, TBK-Agat kit (Agat-Med Russia), Apel-330 spectrophotometer (Japan) at the wavelength 535 nm and 570 nm were used. To assess the antioxidant system status, we used the method of direct/ competitive heterogeneous enzyme-linked immunosorbent assay (ELISA) with the detection of resultants in 405-630 wavelength range by ready-made commercial kits: superoxide dismutase (SOD) activity "Bender Medsystems" (Austria) and catalase activity "Cayman Chemical" (USA). Total antioxidant status (TAS) was determined by a method based on the inhibition degree of ascorbate- and ferro-induced tween-80 oxidation to MDA. The level of stable metabolites of nitric oxide (SMON) was detected by two analytical operations: measurement of endogenous nitrite and conversion of nitrate into nitrite using nitrite-reductase, followed by total nitrite measurement by absorption of azo dye in Griess reaction at the wavelength 540 nm using ELISA kit "R&D" (England). In addition, the levels of C-reactive protein (CRP) "Vector-Best" (Russia), neopterin "IBL" (Germany), erythropoetin "Biomerica" (USA) were determined in blood plasma. Ceruleoplasmin was determined by immune turbidimetry method using "Sentinel" kit (Spain).

The content of cytokines, complement components and their inhibitors was determined in the blood plasma. Interleukin 1β (IL-1β), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 17 (IL-17), interleukin 18 (IL-18), gamma-interferon (IFNγ), interleukin 10 (IL-10), tumor necrosis factor (TNFα), interleukin-1 receptor antagonist (IL-1RA), granulocyte-macrophage colony-stimulating factor (G-CSF), complement components (C3, C3a, C4, C5, C5a) and immunoglobulins M, G, A (IgM, G, A) were detected by ELISA method using ZAO "Vector-Best" and OOO "Tsitokin" (Russia) sets. When determining inhibitors of the complement system, factor H concentration was established by OOO "Tsitokin" (Russia) diagnostic kit through two principles: hemolytic method for CS activation accounting and ELISA method to detect a terminal complex by specific antibodies, and C1-inhibitor activity (C1-inh.) was detected by the ability to inhibit C1-esterase. ELISA results registration was carried out by means of microplate photometer "Sunrise", Tecan (Austria).

Phagocytic activity of poly morphonucleocytes after their isolation from the blood on velocity sedimentation gradient ficoll-urografin (d = 1.077) was assessed determining the phagocytic index (PI), phagocytic number (FN) and phagocytosis activity index (PAI) [24]. The activity of oxygen-dependent neutrophil systems was assessed by PD 303 SApel (Japan) spectrophotometer through the reduction reaction of nitro-blue tetrazolium (NBT-test), spontaneous (NBT-sp.) and stimulated (NBT-st.), by zymosan, stimulation index (STI) and neutrophils functional reserve (NFR) [25].

In addition, immunological and metabolic parameters in plasma samples and peripheral blood erythrocytes of 18 healthy donors (38.2 ± 4.5 years old) that formed the control group were studied; the obtained results were taken for conditional norm.

Statistical processing of the research results was performed in accordance with generally accepted principles of statistical analysis. When comparing the quality parameters, we used the criterion $\chi 2$ (chi-square). To assess the polygenic character relationship to the type of distribution, we used Shapiro-Wilk statistics. To compare normally distributed values we used Student t-test. The estimation of statistical significance of differences for quantitative values with abnormal distribution was performed by means of Wilcoxon-Mann-Whitney test (when comparing dependent groups). Values of normally distributed quantitative parameters are presented by arithmetic mean (M) with mean deviation (m), and abnormally distributed – by median (Me) with interquartile interval (P25; P75). The relationships were established on the basis of factor analysis, cluster analysis and Spearman rank correlation. Statistically significant differences were considered at $p<0.05$.

RESULTS AND DISCUSSION

For correct interpretation of changes in egocentric and objective status of patients, prior to the analysis of immune and metabolic changes, indicators of routine prognostic scales were evaluated (Table 3). According to CRB-65 scale, a significant ($p <0.05$) reduction in the risk of adverse outcome occurs to the 7th day and the end of therapy. The results of SMRT-CO scale illustrate a significant reduction in the need for intensive respiratory support and vasoconstrictors infusion in order to maintain an adequate level of blood pressure to the 3d day of therapy ($p<0.05$) and an increase in positive changes to the 7th day ($p <0,01$) and the end of treatment ($p <0.001$).

In blood plasma of patients with CAP, prior to treatment, we established an increase in pro-inflammatory cytokines: TNFα, IL-1β, IL-6, IL-8, IL-17 and IL-18 by 4.8; 2.2; 2.9; 4.0; 1.5 and 2.3 times respectively, a decrease in anti-inflammatory cytokines: IL-4, IL-10 and IL-1RA by 1.8, 2.4 and 2.3 times respectively. The content of IFNγ, IL-2 and G-CSF growth factor turned out to be higher than those of healthy donors by 2.1; 25.7 and 7.0 times respectively. After conducted treatment, the concentrations of IL-4 and IL-10 returned to normal, the levels of IL-17 and IFNγ did not change, and the content of the other cytokines studied was corrected towards the values of healthy donors, but not to their values [Table 4].

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Table 3: Shift table for CRB-65 and SMRT-CO scales in CAP patients

Indicants	Curation days				Statistical significance of differences
	I. 1st	II. 3d	III. 7th	IV. on hospital discharge	
CRB-65 (scores)	0,53±0,13	0,33±0,11	0,23±0,08	0,2±0,07	P I-II>0,05 P I-III<0,05 P I-IV<0,05 P II-III>0,05 P II-IV>0,05 P III-IV>0,05
SMRT-CO (scores)	0,53±0,12	0,27±0,09	0,13±0,06	0,03±0,03	P I-II<0,05 P I-III<0,01 P I-IV<0,001 P II-III>0,05 P II-IV<0,05 P III-IV>0,05

Table 4: Cytokine spectrum of blood plasma in patients with community-acquired pneumonia before and after standard treatment (M±m)

Indicants	Unit of measure	1 Healthy	2 Before therapy	3 Post-treatment period
TNFα	pkg/ml	3,81±0,92	18,23±1,08*1	7,11±0,63*1,2
IL-1β	pkg/ml	1,9±0,09	4,13±0,22*1	3,6±0,08*1,2
IL-6	pkg/ml	2,8±0,11	8,13±0,23*1	6,43±0,32*1,2
IL-8	pkg/ml	4,7±0,9	18,7±2,1*1	10,3±1,41*1,2
IL-17	pkg/ml	8,1±0,32	11,9±1,1*1	10,02±1,02*1
IL-18	pkg/ml	291,4±12,3	656,2±17,1*1	585,5±14,7*1,2
IL-4	pkg/ml	3,8±0,31	2,12±0,24*1	4,3±0,23*2
IL-10	pkg/ml	10,53±0,76	4,45±0,56*1	11,3±0,55*2
IL-1RA	pkg/ml	420,9±10,4	181,2±11,3*1	220,3±9,72*1,2
IFNγ	pkg/ml	4,65±0,41	9,87±2,13*1	10,2±1,4*1
IL-2	pkg/ml	0,21±0,01	5,4±0,32*1	4,3±0,17*1,2
G-CSF	pkg/ml	12,1±1,0	84,33±8,71*1	65,3±4,4*1,2

Note: here and in the tables below, an asterisk (*) indicates significant differences in arithmetic means (p <0.05); the figures next to the asterisk - in relation to which group indicators these differences are given

Table 5: Immune status parameters of blood in patients with community-acquired pneumonia before and after standard treatment (M±m)

Indicants	Unit of measure	1 Healthy	2 Before therapy	3 Post-treatment period
C_3	mg/dL	15,0±2,0	0,45±0,04*1	0,42±0,02*1
C_{3a}	ng/ml	50,1±4,3	21,52±0,71*1	26,2±0,5*1,2
C_4	mg/dL	12,1±2,7	0,27±0,01*1	0,45±0,03*1,2
C_5	mg/dL	8,3±0,9	0,69±0,04*1	0,72±0,02*1
C_{5a}	ng/ml	4,0±0,6	7,77±0,21*1	5,83±0,55*1,2
C_1-inh.	ng/ml	220,1±12,3	425,1±17,5*1	245,0±20,2*2
Factor H	ng/ml	78,3±10,4	80,5±12,31	69,67±13,7
IgM	mg/dL	26,04±3,92	29,94±3,95	19,8±3,84*1,2
IgG	mg/dL	658,73±24,3	626,81±32,5	583,7±24,3*1,2
IgA	mg/dL	177,68±38,16	332,29±26,99*1	238,4±48,4*1, 2
PI	%	74,3±2,3	66,8±1,93*1	73,7±1,6*2
PN	abs.	4,64±0,23	4,07±0,15*1	4,88±0,2*2
PAI	-	3,43±0,11	2,72±0,13*1	3,6±0,2*2
NBT-sp.	%	9,4±0,5	13,7±1,1*1	11,4±0,72*1,2
NBT-st.	%	22,3±2,04	27,8±2,0*1	24,1±1,7
NFR	%	12,9±1,3	14,1±1,2	12,7±1,1
STI	-	2,37±0,12	2,03±0,1*1	2,11±0,24

Upon hospital admission, among other paramours of immune status in CAP patients a decrease in the content of C3, C3a, C4, C5-complement components and C1-inhibitor by 33.3, 2.3, 44.8, 12.0 and 1.9 times respectively, an increase in C5a and IgA by 1.9 times were revealed, the level of factor H inhibitor remained within normal range. After the standard treatment, the C1-inhibitor concentrations returned to normal, C3a, C4, C5a and IgA levels were corrected in the direction of healthy donors, C3, C5-complement components and factor H level did not change, but the concentration of IgM and IgG decreased below the donor levels [Table 5].

When studying functional metabolic activity of peripheral blood neutrophils at the beginning of treatment, the following results were obtained: a decrease in indicators of phagocytosis activity and intensity (PI, PN and PAI) in comparison with healthy donors, an increase in activity parameters of polymorphonucleocytes oxygen-

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dependent systems (NBT-sp., NBT-st.), in the absence of NFR changes and a decrease in STI. On treatment completion most of the studied parameters of neutrophils functional metabolic activity normalized, to the exclusion of corrected NBT-sp. test [Table 5].

In CAP patients, activation of peroxidation processes in blood plasma and erythrocytes was established prior to treatment (increased concentration of MDA by 5.5 and 10.4 times respectively and AHP by 7.7 and 10.5 times in blood plasma and erythrocytes), a decrease in antioxidant defense factors (TAS in plasma and erythrocytes by 1.2 times, ceruleoplasmin concentration in plasma by 1.3 times, SOD activity by 1.3 and 1.5 times, respectively, and catalase activity by 1.7 and 1.4 times) as well. In blood plasma and erythrocytes the level of SMON increased by 3.5 and 3.9 times, respectively. Besides, an increase in the concentration of erythropoietin by 2 times and inflammatory markers: neopterin by 1.5 times and CRP by 2.6 times was detected in blood plasma. After the treatment conducted, catalase activity in blood plasma and erythrocytes, ceruloplasmin level and SOD activity in the plasma normalized. Erythrocytes TAS remained unchanged, the other metabolic parameters studied shifted towards the level of healthy donors, without reaching their level [Tables 6, 7].

Thus, upon clinical admission of patients with CAP, 41 (91.1%) values were changed from the values of healthy donors out of 45 studied parameters of the immune and metabolic status. We can conclude that there are deep immune metabolic disorders that might be considered as immune inflammation, oxidative stress, endothelial dysfunction and activation of lipid peroxidation.

It is important to note that the course of conducted standard treatment, consisting of 10 days, did not normalize 70.7% of the studied laboratory immune metabolic parameters that had been changed before treatment and additionally reduced IgM and IgG content below the donors level in CAP patients cohort, which requires the administration of combined immunomodulatory and antioxidant therapy.

The presence of immune inflammation in the patients studied is confirmed by the increased level of TNFα, IL-1β, IFNγ, IL-17, activation marker of cellular immunity neopterin, and an increase in the level of C5a fragment-active chemotactic and vasodilator factor released by complement activation, that is anaphylactogenic in its activity.

Table 6: Metabolic parameters of blood plasma in patients with community-acquired pneumonia before and after standard treatment (M ± m)

Indicants	Unit of measure	1 Healthy	2 Before therapy	3 Post-treatment period
MDA	mcmol/l	0,92±0,03	5,1±0,28^{*1}	3,5±0,12^{*1,2}
AHP	c.u.	0,21±0,04	1,61±0,11^{*1}	0,71±0,05^{*1,2}
Catalase	mcat/l	21,7±0,27	12,86±0,48^{*1}	21,95±0,47^{*2}
SOD	c.u.	16,97±0,34	13,35±0,59^{*1}	20,37±0,67^{*1,2}
TAS	%	37,95±0,8	31,78±0,58^{*1}	39,19±0,45^{*2}
Ceruleoplasmin	g/l	0,32±0,04	0,24±0,03^{*1}	0,34±0,03^{*2}
Neopterin	pg/ml	6,02±0,15	4,06±0,11^{*1}	5,12±0,2^{*1,2}
CRP	mg/dL	3,7±0,27	9,54±0,69^{*1}	6,7±0,13^{*1,2}
SM_{NO}	mcmol/l	1,68±0,14	5,82±0,27^{*1}	3,93±0,1^{*1,2}
Erythropoetin	me/l	3,72±1,41	7,6±1,24^{*1}	2,6±0,29^{*1,2}

Table 7: Indicators of erythrocytes metabolism in patients with community-acquired pneumonia before and after standard treatment (M ± m)

Indicants	Unit of measure	1 Healthy	2 Before therapy	3 Post-treatment period
MDA	mcmol/l	0,32±0,03	3,34±0,1^{*1}	2,14±0,09^{*1,2}
AHP	c.u.	0,14±0,02	1,47±0,09^{*1}	0,87±0,06^{*1,2}
TAS	%	33,4±1,4	27,4±1,5^{*1}	28,5±1,32^{*1}
SOD	c.u.	19,23±1,62	12,41±1,02^{*1}	16,7±0,89^{*1,2}
Catalase	mcat/l	11,5±1,31	8,4±0,56^{*1}	10,3±1,2^{*2}
SM_{NO}	mcmol/l	1,12±0,04	4,34±0,12^{*1}	3,02±0,2^{*1,2}

and takes part in inflammation and hypersensitivity reactions with the absence of compensatory inhibitor increase (factor H) or even its decrease (C1-inh.) [13, 30, 31].

Oxidative stress development (imbalance between prooxidants and antioxidants, in which prooxidants predominate) is suggested in our studies by an increased concentration of LPO (MDA, AHP), SMON and CRP products (a marker of systemic inflammatory response) in plasma and erythrocytes, a significant decrease in antioxidant defense (TAS, SOD, catalase activity) [26, 27].

An increase in vasodilatory (ON) factor, an increased level of proinflammatory cytokines (TNFα, IL-1, IL-17), neopterin and CRP are indicative of endothelial dysfunction in patients with CAP [28- 30].

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The obtained results show that laboratory immune metabolic disorders have been revealed in patients with CAP which is indicative of immune inflammation, oxidative stress, endothelial dysfunction, activation of lipid peroxidation. This establishes the necessity to intervene in the pathological process, to restore normal pulmonary tissue functioning and to reduce disabling effects. Conducted standard treatment does not normalize most of the altered parameters of the immune and metabolic status, which necessitates the search for agents able to correct the disorders by combined administration of various drugs with immunomodulatory and antioxidant effects in complex pharmacotherapy [3, 12].

CONFLICT OF INTEREST

There is no conflict of interest.

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None.

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