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INFLAMMATION ROLE IN FORMATION OF EARLY DISTURBANCES OF A FUNCTIONAL CONDITION OF A LIVER AT COMMUNITY — ACQUIRED PNEUMONIA (LITERATURE REVIEW)

Abstract

Community-acquired pneumonia (CAP) is a topic issue of medicine nowadays due to its high incidence, the severity of its course, the increasing antibiotic resistance, a large number of complications and high mortality rate. Now in the pneumonia pathogenesis the leading role belongs to various changes of metabolism, including the induction of lipid peroxidation and oxidative stress. The importance is attached to the liver function impairment in patients with pneumonia. The pathogenetic mechanisms of this impairment are diverse and include vascular endothelium dysfunction. At the same time, among the therapeutic approaches to normalize the metabolism of body cells, the priority role is given to peroxidation substrates. It is shown that the succinate-containing drugs have various pharmacological effects, generally providing the cytoprotective action that allows considering them the perspective compounds with hepatoprotective activity, which are essential in complex treatment of community-acquired pneumonia (CAP).

Key words: *Community-Acquired Pneumonia (CAP), endothelium dysfunction, liver dysfunction, succinate-containing drugs*

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ATP — adenosine triphosphate; ROS — reactive oxygen species; CAP — community-acquired pneumonia

Today, community-acquired pneumonia (CAP) ranks fourth among causes of death after cardiovascular, cerebrovascular diseases and cancer [3, 25].

Despite the great progress made in understanding the etiology, pathogenesis and treatment of this pathology, there is an increase in the number of patients worldwide, and, consequently, mortality [4, 6]. Specifically, the average annual incidence of community-acquired pneumonia among adults in recent years in Europe was 1.07–1.2 per 1,000 inhabitants per year, and in older age groups it was 14 per 1,000 person-years [9]. Primary morbidity rates in the CIS generally indicate a significant increase in the incidence of respiratory diseases [8]. In the Russian Federation, the primary morbidity of respiratory diseases increased by 1.3% in 2015, accounting for 338 cases per

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1,000 people [7]. It is believed that one of the reasons for the increase in mortality from CAP is the lack of treatment efficacy at early stages of the development of the disease [8].

During the past decades, the so-called "metabolic" trend has been rapidly developing in medicine. Ideas about the role of cellular energy metabolism disorders in a variety of pathological processes are emerging very rapidly [10].

Being the physiological component of the body's response to infectious inflammation, changes in metabolism are pathological in nature, leading to irreversible damage to cellular structures and failure of individual organs and systems. At the same time, biochemical markers of inflammation are often ahead of morphological changes in tissues and therefore can be considered as early criteria for the development and resolution of the pathological process in various diseases [6, 2].

Inflammation that occurs in community-acquired pneumonia, along with hypoxia, is among the most common typical pathological processes [14]. It should be noted that the protective role of inflammation is indisputable. However, this reaction is also of a pathological nature, since the mechanisms of inflammation lead to secondary self-injury of tissues. The severity of inflammation along with other factors determines the severity and prognosis of the disease in CAP [22]. Therefore, CAP is accompanied by a systemic body response to inflammation in the lung tissue, and its components determine the pathogenetic mechanisms of disease development and play an important role in the course of pneumonia [5, 23]. Thus, in particular, under the influence of an infectious agent, free radical oxidation of lipids is activated through a cascade of reactions, which contributes to the development of oxidative stress, accompanied, among other things, by endothelial dysfunction with damage to biological macromolecules and cell membrane structures [1, 16].

A number of authors note that the endothelium is involved not only in the formation of a barrier between the blood and vascular smooth muscle cells, but also provides a dynamic equilibrium of vasoconstrictor and vasodilator factors regulating the processes of hemostasis, affecting vascular permeability and participating in the immune response of the body [30, 33].

To date, there is evidence that the endothelium is a neuroendocrine system that performs secretory, hemostatic, and vasotonic functions, and also participates in the processes of inflammation and remodelling of the vascular wall [23].

Consequently, the endothelium becomes a direct target for damage in inflammatory processes in the body, and endothelial dysfunction can affect damage to the membranes of the cells of internal organs under conditions of oxidative stress [28]. In view of this, in recent years, more attention has been paid to the role of the vascular endothelium in the pathogenesis of community-acquired pneumonia [1].

It has been shown that in patients with CAP, endothelial dysfunction is expressed in an imbalance of opposite vasodilating, vasoconstrictive, anticoagulant and procoagulatory factors [1, 17]. It should be noted that the activation of systemic inflammation and the reaction of the hemostatic system in the pulmonary vessels and tissues are considered important for maintaining activity at the site of an infectious damage, making this relationship necessary in regards to the formation of a pathological barrier between healthy and damaged tissue [27].

At the same time, chronic inflammation leads to structural changes in the vascular endothelium, specifically to enrichment of the basement membrane with sulfated glycosaminoglycans, which makes them similar to the endothelium of lymph node venules, which contribute to a faster release of lymphocytes, and further development of angiogenesis [30]. An increase in inflammatory infiltrate in the lung tissue enhances mechanical compression of arterioles, which ultimately increases the pressure in the pulmonary artery.

Thus, a vicious circle, based on endothelial dysfunction, arises in CAP, the end result of which is oxidative stress, which further leads to the development of respiratory failure, impaired ventilation-perfusion relationships, aggravation of hypoxia and worsening of the disease course [20].

The liver occupies a special place in the development of inflammatory response, as it is the organ that maintains homeostasis of the whole organism, while affecting the development of any given disease [30]. The liver is directly involved in the processes of detoxification and elimination of waste products of infectious agents, is central to

the regulation of the acute phase inflammatory reaction, the metabolism of biologically active and antibacterial substances [7, 35].

Liver tissue damage is based on both tissue hypoxia resulting from impaired oxygen utilization in hepatocytes and the action of toxic substances (drug products), as well as circulatory hypoxia, resulting from local or central hemodynamic disorders (shock, traumatic injuries, liver cirrhosis) [15].

A similar scenario of the development of the pathological process with different initiating agents forms liver diseases that can occur, at a more or less extent, with an acute inflammatory reaction [7].

In addition, the liver takes part in the synthesis of immunity factors that are directly involved in the inactivation of foreign cells and antigens [1]. Thus, Kupffer cells along with hepatocytes produce group E prostaglandins and acute-phase proteins (neutralizing proteases), which are intensively produced during inflammation. The hypothalamic-pituitary-adrenal axis is activated by interacting with a complex cascade of reactions through the secretion of corticotropin-releasing factor, and thereby an inflammatory response is further activated [29].

Intrahepatic hemodynamics disorder in the presence of vascular system remodelling is important in the pathogenesis of liver damage in inflammatory processes in the lungs, which may be associated with damage to the endothelial lining of the hepatic sinusoids and the early development of endothelial dysfunction [32].

According to a number of authors, the interaction of the immune system components with protein and lipid metabolism in the liver plays a certain role in the development of liver dysfunction [7, 23, 29, 31]. Thus, the hepatocytes themselves are damaged with the excessive production of both cytokines and acute-phase proteins, which ultimately leads to changes similar to different forms of hepatitis [20]. The pathogenetic mechanisms of liver damage in CAP (especially chlamydial, legionella and viral etiology) are diverse. They are characterized by hepatomegaly with the development of cytolysis and an inflammatory reaction, with subsequent progression of fibrosis [19].

Liver damage as organ dysfunction in the systemic inflammatory reaction syndrome is observed in 21%, and the incidence of its development in the general population of patients with CAP is 2.7% [4].

As noted above, tissue hypoxia also plays a significant role in the pathogenesis of hepatocyte damage, leading to dysfunction of mitochondria, depletion of adenosine triphosphate (ATP) reserves with activation of free radical processes [15]. Among cell metabolites with oxidative properties, the central role belongs to the reactive oxygen species (ROS). It should be emphasized that ROS perform the most important regulatory and metabolic functions in the body under physiological conditions [25]. However, the uncontrolled generation of ROS with the failure of the protective antioxidant system causes oxidative modification of proteins, nucleic acids, initiates free radical oxidation of lipids in membranes, which leads to membrane-destroying processes [4, 12].

The tissue of both the lungs and the liver has a high metabolic activity and, accordingly, significant energy needs, which determines its high sensitivity to hypoxia [20, 35].

At the same time, the need for correction of the resulting disorders of its functional state is obvious and requires the development of new pathogenetic approaches in complex therapy of CAP. Today the priority role in the implementation of therapeutic approaches to the normalization of the body cell metabolism is given to oxidation substrates, the use of which in a number of diseases marked the beginning of the so-called "metabolic correction" [27].

This circumstance determines the urgency of finding new ways to optimize pathogenetic therapy, including, in particular, the support of not only adequate tissue perfusion and oxygenation, but also cellular metabolism [13]. Thus, it is possible to use drugs that include succinate-containing compounds to correct hypoxia and to normalize the metabolic processes in cells and tissues in critical conditions [9]. The most rapid way of correcting tissue hypoxia is succinate oxidase oxidation, which is achieved by increasing the activity of succinate dehydrogenase and improving the penetration of exogenous succinate into the cell's mitochondria.

The presented drugs have the ability to enhance the therapeutic effect of some medications

(including antibiotics), have antiplatelet effect due to membrane stabilizing effect on blood cells, including platelets, improve blood rheology and hemodynamics, weaken the effect of osmotic shock on the cell, which is associated with the formation of stable complexes with blood albumin and membrane proteins due to strong hydrogen bonds [18, 24].

Experimental models of liver damage have shown that succinate-containing drugs implement antioxidant, membrane stabilizing, antihypoxic and detoxifying pharmacological effects, providing a generally cytoprotective effect, which enables to consider them as promising compositions with hepatoprotective activity, which are obviously necessary in complex therapy of CAP [9].

Thus, early hepatic functional impairment as well as the resulting endothelial dysfunction is currently an important but poorly understood area in the pathogenesis of CAP. We would like to note in the review, that such changes can have a significant impact on the course of CAP. We also tried to substantiate the relevance of new approaches to the correction of systemic disorders arising in CAP.

Conflict of Interests

The authors declare no conflict of interests.

References:

1. Akzamov A.A., Urazmetov M.D., Madaminov A.A. The immune status of laboratory rats with an experimental liver failure. Immunology. 2005; 1: 34-39 [In Russian].
2. Belkov S.A., Novozhenov V.G., Gordeev M.N. Pneumonia at patients with chronic alcoholism. M.: Publishing house of Institute of Psychotherapy. 2001: 64 p. [in Russian].
3. Bereznyakov I.G. Community-acquired pneumonia. Diseases and antibiotics. 2009; 2: 38-42 [in Russian].
4. Rudnov V.A., Belsky D.V., Dekhnich A.V.Infections in ORIT of Russia: results of a national multicenter research. Clinical microbiology and antimicrobic therapy. 2011; 3(4): 294-304 [in Russian].
5. Vladimirov Yu.A., Archakov A.N. Peroxide oxidation of lipids in biological membranes. M.: Science. 1972; 252 p. [in Russian].
6. Geltser B.I., Koryavchenkov I.V., Kosciusko A.V. A condition of system of cytokine at nozokomialny pneumonia. Cytokines and inflammation. 2005; 1: 265-267 [in Russian].
7. Gordeev M.N. Features of a course of pneumonia at patients with chronic alcoholism. Clinical medicine. 2002; 2: 17-19 [in Russian].
8. Goretskaya M.V., Sheybakh V.M., Doroshenko E.M.A range of free proteinogenny amino acids in Lymphocytes. Journal of the Gorodninsky state university. 2008; 3(23): 89-90 [in Russian].
9. Dvoretsky L. I. Complication and mistakes in therapy of community-acquired pneumonia. The Messenger of the practical doctor. 2015; Special issue 1: 29-33 [in Russian].
10. Kochegarova E.Yu., Kolosov V.P. Value of pro-calcitonin and cytokine in forecasting of the complicated course of community-acquired pneumonia. Bulletin of physiology and pathology of breath. 2011; 40: 48-49 [in Russian].
11. Lazarev V.V., Helimskaya I.A., Klebanov G.I. Influence of Reamberin of 1.5% for Infusion solution on antioxidant activity of plasma of blood in the post-narcotic period at Children. Bulletin of intensive therapy. 2004; 4: 28-31 [in Russian].
12. Li L.A. Application of metabolic energotropny therapy for correction of deficiency of power supply of immunocompetent cages at children with community-acquired pneumonia. The bulletin of physiology and pathology of breath. 2015; 57: 35-39 [in Russian].
13. Lysikova M., Wald M., Masinovski Z. Mechanisms of inflammatory reaction and impact on them by means of proteolytic enzymes. Tsitokina and inflammation. 2004; 3: 48-53 [in Russian].
14. Mirkhaydarov A.M., Farkhutdinov U.R., Farkhutdinov R.R. The immune status of patients with community-acquired pneumonia and efficiency of an immunovenin in complex therapy. The Medical bulletin of Bashkortostan. 2016; 11: 12-15 [in Russian].
15. Nonikov V.E. Some aspects of antibiotic treatment of bronchopulmonary infections. RMZh. 2013; 7: 416-418 [in Russian].
16. Obolensky S.V. Reamberin — new means for infusional therapy in practice of medicine of critical conditions: method. Recommendation. SPb. 2002; 23 p. [in Russian].
17. Okovity S.V., Bezborodkina N.N., Uleychik S.G. et al. Structurally functional changes of a liver at chronic hepatitises and Cirrhosis. Gepatoprotektors. M. 2010: 17-22 [in Russian].

18. Okhrimenko S.M., Guryev N.Yu., Kalimang P.A. Adaptation of enzymes of lipidic and nitrogenous exchange at rats at the oxidative stress caused by salts of cobalt and Mercury. Bulletin of Karazin Kharkiv National University. Series: biology. 2005; 1-2: 56-60 [in Russian].
19. Pokrovsky M.V., Pokrovsky T.G., Kochkanov V.I. Endotelioprotektivnye effects of L-arginina at experimental modelling of deficiency Nitrogen oxide. Experimental and clinical pharmacology. 2008; 71(2): 29-31 [in Russian].
20. Romanova E.N., Serebryakova O.M., Govorin A.V., Filev A.P. Polyorgan dysfunction at patients with the flu H1N1/09 complicated Pneumonia. The Transbaikal medical bulletin. 2017; 1: 107-116 [in Russian].
21. Ryazanov of N.V., Zhukova O.B. Molecular bases of a dizregulyation of the programmed death of lymphocytes at a chronic viral infection. The Bulletin of the Siberian medicine. 2006; 2: 23-27 [in Russian].
22. Senatorov A. S., Kondratova I.Yu., Sukhoruko V.S. Power scarce states as risk factor of the complicated course of pneumonia at children of the first year of Life. Health of the child. 2009; 5(20): 123 [in Russian].
23. Stelmakh V.V., Kozlov V.K., Ivanova V.F., Samusenko I.A. Efficacy of the infusion hepatotropic drug remaxol in the pathogenetic therapy of chronic viral hepatitis at the cirrhotic stage. Terr. Archive. 2015; 8: 67–72 [in Russian].
24. Sidorenko S.V. Modern problems of an anitibiotikorezistentnost of causative agents of extra hospital respiratory and uric infections. Messenger of the practical doctor. 2015; Special issue 1: 8-11 [in Russian].
25. Silvestrov V. P., Chuchalin A.G. Long pneumonia. Pulmonology. 2009; 3: 5-6 [in Russian].
26. Sinopalnikov A.I., Kozlov R.S. Extra hospital infections of airways: the management for Doctors. SPb. 2007; 352 p. [in Russian].
27. Skulachev V. P. The phenomena programmed Death. Mitochondrions, cages and bodies: role of active forms of oxygen. Sorosovsky educational journal. 2001; 7(6): 4-10 [in Russian].
28. Chuchalin A.G., Sinopalnikov A.I. Extra hospital pneumonia at adults: practical recommendations about diagnostics, treatment and Prevention. Clinical microbiology, antimicrobic therapy, chemotherapy. 2010; 3: 12-15 [in Russian].
29. Shoykhet Ya.N., Momot A.P. About a role and interrelation of haemo static and inflammatory reactions in formation of the centers of purulent destruction of bodies and Fabrics. Problems of clinical medicine. 2008; 4 (16): 102-117 [in Russian].
30. Shchekotova A.P., Bulatova I.A., Krivtsov A.V. Interrelation of weight of damage of a liver with polymorphism of a gene IL 28B at patients with chronic hepatitis C. Basic researches. 2013; 12: 186-190 [in Russian].
31. Yarilin, A.A. Tsitokina in a timus. Tsitokina and inflammation. 2003; 2: 3-11 [in Russian].
32. Bakhshadeh S. et al. Technological innovation for collective awareness system. Technological innovation for collective awareness system. 2007; 62: 456-479.
33. Carmeliet P., Jain R.P. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2000; 19: 298-301.
34. Chetta A., Zanini A., Olivieri D. Therapeutic approach to vascular remodeling in astma. Pulm. Pharmacol. Ther. 2007; 20: 1-8.
35. Gibson F.S., Hayashi C., Gudino C.V. Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specifici innate immune inflammatory pathway. Mol. Oral. Microbiology. 2004; 25(5): 305-316.
36. Liu F., Helmy A. Endothelin ETA receptor/lipid peroxides / COX-2/TGF-β1 signalling underlies aggravated nephrotoxicity caused by cyclosporine plus indomethacin in rats. British Journal of Pharmacology. 2003; 172: 426-429.
37. Zanini A., Chetta A., Imperatori A.S. The role of the bronchial microvasculature in airway remodelling in asthma and COPD. Respir. Res. 2010; 11: 132.
38. Schumacker P.T. et al. Mitochondria in lung biology and pathology: morethan just a powerhouse. Am. J Physiol. Lung Cell Mol. Physiol. 2014; 11: 962–974.
39. Smith M.K., Mooney D.J. Hypoxia leads to necrotic hepatocyte death. Biomed. Mater Res. 2007; 80(3): 520-529.
40. Sun J., Yuan Y., Qin H. Serum from hepatectomized rats induces the differentiation of adipose tissue mesenchymalstem cells into hepatocyte-like cells and upregulates the expression of hepatocyte growth factor and interleukin-6 in vitro. Int. J. Mol. Med. 2013; 31(3): 667–75.

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