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METHOD FOR PREDICTION AND PREVENTION OF ENDOTHELIAL DYSFUNCTION IN THE LUNG IN ABDOMINAL SEPSIS

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Summary. The use of the methods we developed for predicting and preventing endothelial dysfunction in the lungs in the complex treatment of abdominal sepsis made it possible to reduce the frequency of the average number of laboratory signs of systemic inflammatory response syndrome and the average duration of severe sepsis by 2.6 times, and septic shock by 2.8 times. The effectiveness of the use of targeted methods for preventing the development of multiple organ failure was proven by reducing the average SOFA score for general grading by 1.5 times, for hepatic dysfunction - by 1.7 times, and for renal dysfunction - by 1.5 times.

Key words: lungs, endothelial dysfunction, abdominal sepsis.

Relevance. Currently, there is an increase in the incidence of sepsis, and mortality remains extremely high (1,3,5). It is recognized that the body's systemic inflammatory response syndrome plays a major role in the formation of pathogenetic mechanisms leading to the development of multiple organ failure and death in sepsis (2,4,6).

Sepsis, affecting both developing and developed countries, is a huge source of lost lives, livelihoods and resources. Using data from the Global Disease Prevalence Study, Stewart et al reported 896 000 deaths, 20 million years of life lost, and 25 million disability-adjusted life years lost per year associated with just 11 general surgical emergencies. The scale of DALYs lost due to this disease is also staggering (7,9,11). Abdominal sepsis accounts for 1% of all hospital admissions and is the second most common type of sepsis worldwide (8,10,12,25,26,27,28). The cause of abdominal sepsis in the form of diffuse peritonitis is considered a poor prognostic indicator, since its mortality can reach 20% (13,15,17,29,30,31,32,33,34). This problem also makes it relevant due to the need for long-term stay of patients in the intensive care unit. This, in turn, raises economic issues of loss of budget resources. Throughout the last century, abdominal sepsis has been and remains a dangerous disease in which dysfunction of vital organs develops as a result of the aggression of introduced microorganisms. The high incidence of abdominal sepsis is

accompanied by high mortality, which can vary from 7.6% to 36.0% (14,16,18,35,36,37,38). Intra-abdominal contamination and secondary peritonitis are a constant source of pathogen-associated molecular patterns (via spillage of intestinal contents) and through direct damage to internal and abdominal organs. This "engine of multisystem organ failure" provides continuous cytokine fuel for the raging systemic response. For example, TNF-α and IL-1 are important proinflammatory cytokines. Each has been shown to induce vascular permeability, leading to pulmonary edema and hemorrhage (1,2,5). IL-6 is a key molecule in initiating the febrile response, lymphocyte activation, and also plays a role in hematopoiesis. It has also been shown to cause myocardial depression (19,21,23). Over the past 20 years, the recognition of the endothelium as a full-fledged system has led to a large number of experimental and clinical studies, including the study of the mechanisms of development of sepsis. During bacterial, fungal, or viral infection, exogenous molecular patterns associated with pathogens and molecular patterns associated with endogenous damage cause endothelial activation and can disrupt its structure and function, that is, provoke the development of endothelial dysfunction (20,22,24). Endothelial changes associated with sepsis should be considered useful to limit the spread of bacteria, as well as to control leukocyte recruitment and bacterial clearance. However, severe and persistent phenotypic changes in the endothelium can contribute to impaired microcirculatory blood flow, tissue hypoperfusion, and the development of life-threatening multiple organ failure (1,7,9,39,40). Thus, it is very difficult to distinguish between corresponding activation and endothelial dysfunction, especially given that the endothelial cell response may vary between organs (2,4,7,41). Although some experimental studies have been encouraging, recent clinical trials highlight the need for a better understanding of the pathophysiological mechanisms of septic shock and multiorgan failure caused by sepsis (9,11,18). Despite their inherent limitations, animal models of sepsis and in vitro studies provide insight into the multiple pathways that are induced in endothelial cells in response to infection and how they are regulated. Studying the activation pathways that lead to sepsis-induced endothelial dysfunction is a promising avenue toward limiting sepsis-induced organ failure (2,8,19). There is no data in the literature on the role and location of endothelial dysfunction in the lungs in the progression of abdominal sepsis. This, in turn, would create conditions for the development of methods for predicting and preventing serious complications

of generalized infection, and thereby improve the results of treatment of patients with abdominal sepsis.

The purpose of the study is to improve the results of treatment of patients with abdominal sepsis by developing methods for predicting and preventing endothelial dysfunction in the lungs.

Material and methods. The results of a comprehensive examination and treatment of 140 patients with abdominal sepsis who were treated and examined at the Navoi regional branch of the Republican Center for Emergency Medical Care for the period from 2018 to 2023 were analyzed. The following were not included in the study: patients, provided the patient was under 18 years of age; if patients are pregnant; in the presence of concomitant pathologies in the form of acute myocardial infarction, acute cerebrovascular accident, acute malignant hematological diseases. The control group of patients consisted of 70 patients with abdominal sepsis, in whom the results of experimental studies were introduced and tested, which were based on methods for predicting the development of endothelial dysfunction in the lungs. The main group of patients consisted of 70 patients with abdominal sepsis, who used new approaches to treatment, which were based on methods of preventing endothelial dysfunction in the lungs. The majority of patients were male (63.6%), mature (35.0%) and young (32.1%). The average age of the patients was 46.3±9.4 years. The scope of surgical intervention complied with approved standards and included: revision of the abdominal cavity; identification and, if possible, elimination of the source of abdominal sepsis; sanitation of the abdominal cavity with antiseptics; intestinal decompression by intestinal intubation or stoma; drainage of the abdominal cavity. In the main group of patients, the surgical tactics differed from the control depending on the degree of endothelial dysfunction in the lungs and were supplemented by the conditions of peritoneal dialysis and intestinal lavage, as well as the installation and infusion of drugs of an intraportal catheter through the round ligament of the liver. The experiments were carried out on 106 white Wistar laboratory rats weighing 200-250 grams, of both sexes, fed a regular laboratory diet. The planned experimental studies, which included sampling, biopsies and necropsies, were based on the conditions specified in the 1986 Council of Europe Animal Welfare Convention. The animals were divided into the following series of experiments: Control – 10 intact animals, not subjected to any influences or manipulations, fed a standard grain diet. The main one was 50 animals in which the experimental model of abdominal sepsis was reproduced using our improved

method. The reproduction of the experimental model of abdominal sepsis was carried out in stages, by changing the reactivity of animals and creating a purulent-necrotic focus in the abdominal cavity. In experimental studies, blood was collected separately at the entrance and exit from the lungs. In this case, the blood at the entrance to the lungs is mixed venous blood, which came from the inferior and superior vena cava. At the exit from the lungs we received arterial blood, which was universal for the entire organism as a whole. This technique was developed and tested by a group of researchers at the Tashkent Medical Academy. Each value obtained in different blood samples was also subjected to calculation of the venous-arterial difference, that is, a value reflecting the “delay” or “production” of the substrate in the endothelial system of the lungs. The entire complex of studies of patients with abdominal sepsis consisted of continuous monitoring of the state of homeostasis and functional activity of vital organs. For this purpose, functional, instrumental and laboratory research methods were carried out. Integral rating diagnostic methods, such as APACHE II, SAPS, SOFA, and the Kalf-Kalif Leukocyte Intoxication Index, were also actively used. Among the indicators of the endothelial system, the level of C-reactive protein (mg/l), thrombomodulin (ng/ml), von Willebrand factor (IU/dL), intercellular and cellular adhesion molecules (ng/ml) was studied using an enzyme-linked immunosorbent analyzer; nitrites and nitrates (%), peroxynitrite (μmol/l), nitric oxide synthase activity (μmol/min/l) according to the Griess method modified by A.P. Solodko et al. on an SF-46 spectrophotometer at a wavelength of 520 nm.

The entire set of studies met the criteria of translational medicine, which used the entire body of research, which made it possible to extrapolate the results of experimental studies into clinical practice. Next, we were faced with the task of developing an experimental model of abdominal sepsis, which could be as close as possible to the clinical conditions of the pathological process, characterized by high reproducibility and low mortality. As a basis for reproducing the model, we borrowed the principle of damage to the dome of the cecum, proposed by H. Mutlak in 2013 (). This method was defined by us as series-A. However, this modeling method is aimed at reproducing fecal peritonitis and is not directly related to the model of abdominal sepsis. We tested a variant of changing the reactivity of the macroorganism in series-B, which was carried out by preliminary injection into the abdominal cavity of anti-lympholin-Kr at a dose of 0.03 mg per 100 grams of animal for 48 hours. The effectiveness of this reproduction option was proven by our

domestic scientists when modeling surgical sepsis against the background of purulent-necrotic diseases of soft tissues (Okhunov A.O., 2012). Taking into account the shortcomings of modeling in this series, we developed our own method for reproducing abdominal sepsis, which we designated as series-C. As a result of a comparative analysis, it was proven that the reproducibility of the primary focus of destruction in series A was absent, in series B it was 57.1%, and in series C it was 57.1% in all studied cases. The reproducibility of peritonitis in series-B was only in 42.9% of animals, in series-C - in 85.7% of rats in this series. The reproducibility of abdominal sepsis was maximum in series-C (71.4%), while in series-A and series-B this figure did not exceed 42.9%. All animals in series A died within 9 hours of simulation, while in series B, mortality began at 18.9 ± 5.9 hours of simulation and reached 28.6%. Moreover, in 57.1% of cases in this series of experiments, regression of the pathological process was noted. Mortality in series-C was noted in 14.3% of cases, and it began at 24.6 ± 2.1 hours and reached only 14.3%. Thus, the model of abdominal sepsis we developed made it possible to achieve the formation of a number of pathogenetic mechanisms that have a justified place in clinical practice: achieving the development of the primary focus of the purulent-inflammatory process without opening or puncturing the intestinal cavity, in which only feces enter the abdominal cavity and toxic shock; achieve a change in the body's reactivity, which made it possible to achieve the development of all phases of sepsis (from systemic inflammatory response syndrome to severe sepsis), without regression of the inflammatory process, as a result of its limitation. Next, we determined the features of changes in the morphological picture of the endothelial system of the lungs in the dynamics of development of an experimental model of abdominal sepsis. Results and its discussion. It was revealed that morphological changes in the endothelial system of the lungs in the dynamics of development of an experimental model of abdominal sepsis can be characterized in the form of stage-by-stage transformations leading to destructive consequences during the progression of the pathological process. Moreover, if the early stages (6-48 hours) of the development of abdominal sepsis were characterized by stagnant morphofunctional changes in the prealveolar capillary network of the lungs, then at a later stage (72-96 hours) - structural changes, with clear signs of destruction of the endothelial system of the lungs. All together leads to the beginning of the development of irreversible processes both in the lungs (primarily) and in the entire body, which characterizes the starting position of the formation of multiple organ dysfunction. The obtained

data on morphostructural changes in lung tissue created the conditions for assessing the characteristics of molecular-biochemical changes in the endothelial system of the lungs in the dynamics of development of an experimental model of abdominal sepsis. The dynamics of changes in the content of the pro-inflammatory cytokine IL-1β in various blood samples during the development of an experimental model of abdominal sepsis showed an increase in this indicator both in a mixed venous blood sample at the entrance to the lungs from 11.92±1.02 pg/ml after 6 hours of modeling the disease to 42.91±11.91 pg/ml after 72 hours or more from the onset of the disease ($p<0.05$). These values were significant both in relation to the indicators in the control series of experiments (0.04±0.006 pg/ml) and in relation to the indicators in the comparative series of experiments (0.06±0.002 pg/ml).

We noted a similar shift in the indicators in the arterial blood sample at the exit from the lungs - an increase from 10.93±0.79 pg/ml in a 6-hour period to 44.16±6.29 pg/ml in a 72-hour period or more period ($p<0.05$). These changes were also significant in relation to the control (0.02±0.005 pg/ml) and comparative (0.03±0.002 pg/ml) group of experiments. The maximum average value in both the mixed venous blood sample and the arterial blood sample was IL-8, the level of which was 49.51 ± 18.51 pg/ml and 50.09 ± 21.64 pg/ml, respectively. IL-6 was released with minimal values in the corresponding blood samples (4.81±1.13 pg/ml and 5.7±1.65 pg/ml, respectively). At the same time, the dynamics of changes in the remaining pro-inflammatory cytokines studied were also noticeable and varied during the development of the experimental model of abdominal sepsis. Regarding the pro-inflammatory cytokine TNF-α, a significant difference can be identified both in the mixed venous blood sample at the entrance to the lungs (52 times; $p<0.0001$) and in the arterial blood sample at the exit from the lungs (48 times; $p<0.001$) between the control and comparison groups. In general, the level of change in the concentration of the studied pro-inflammatory cytokines in various blood samples in the dynamics of the development of the experimental model of abdominal sepsis was subject to correction by the endothelial system of the lungs. The peritoneal inflammatory process was characterized by the release of proinflammatory cytokines, in particular IL-1β and TNF-α, into the mixed venous bed already in the early stages of modeling abdominal sepsis. However, such a flow of cytokines was apparently not enough for the development of a “violent” response of the body. This period was characterized by a small (local) release of proinflammatory cytokines from the purulent-inflammatory focus. As the purulent-inflammatory process

progresses, in subsequent periods of observation, the lungs not only cease to have a corrective effect, but also begin to produce pro-inflammatory cytokines, which can primarily be noted in relation to IL-6 and IL-8. Apparently, such a reaction was associated with certain response changes in the endothelial system of the lungs, which we described below. The dynamics of changes in NOx content in various blood samples during the development of the experimental model of abdominal sepsis was characterized by exceeding the values in the arterial blood sample throughout the study. The model of abdominal sepsis led to an increase in NOx from 20.21±5.63 μmol/L to 39.12±6.26 μmol/L in a mixed venous blood sample, and from 25.75±3.13 μmol/L to 46. 17±8.14 in arterial blood sample ($p<0.05$). Against the background of these changes, we identified changes in the concentration of the metabolic product of the transformation of NOx components, in particular NO3- into OONO-.

The average peroxynitrite content in the mixed venous blood sample at the entrance to the lungs increased from 1.53±0.42 μmol/l to 4.91±1.18 μmol/l, and in the arterial blood sample from 0.69±0.13 μmol /l to 6.11±2.82 μmol/l ($p<0.05$). We noted an increase in peroxynitrite in various blood samples depending on the timing of the development of an experimental model of abdominal sepsis, which was characterized by a transition from a state of transient phenomena to steadily progressive ones, indicating the depletion of the compensatory capabilities of the pulmonary endothelial system itself. The dynamics of changes in the content of ICAM-1 and VCAM-1 was characterized by a progressive increase in various blood samples in the dynamics of the development of an experimental model of abdominal sepsis (from 4.02±0.92 ng/ml to 5.52±0.98 ng/ml and from 5 ,16±0.92 ng/ml to 8.91±0.98 ng/ml in mixed venous and from 1.18±0.11 ng/ml to 6.31±0.95 ng/ml and from 2, 19±0.11 ng/ml to 9.03±0.95 ng/ml in an arterial blood sample, respectively). In the dynamics of modeling abdominal sepsis, the differentiated position of the venous-arterial difference in C-reactive protein decreases significantly. Moreover, if in the early stages of reproducing the experimental model of abdominal sepsis (6-12 hour period) the venous-arterial difference decreased by 1.2 and 1.5 times, then starting from the 24-48 hour period it decreases even more (to 0.7 times). We also noted an identical nature of changes in relation to thrombomodulin. We also noted a leveling of the values of the venous-arterial difference in this period of experiments in relation to vWF. Analysis of the venous-arterial difference showed that the endothelial system of the lungs reacted sensitively to changes occurring in the site

of destruction. At the same time, the main character of the endothelial system of the lungs at the first stage was reduced to blocking the flow of pathological substrates into the systemic arterial bloodstream, and at the second stage of development of the experimental model of abdominal sepsis, the lungs cease to create a barrier to the generalization of the inflammatory process, opening the way for the development of multiple organ dysfunction. Based on the analysis, we experimentally substantiated the mechanism of endothelial dysfunction in the lungs in the dynamics of the development of abdominal sepsis, which was characterized by a phased course of the pathological process. Thus, the use of the methods we developed for predicting and preventing endothelial dysfunction in the lungs in the complex treatment of abdominal sepsis made it possible to reduce the frequency of the average number of laboratory signs of systemic inflammatory response syndrome and the average duration of severe sepsis by 2.6, and septic shock by 2. 8 times. The effectiveness of the use of targeted methods for preventing the development of multiple organ failure was proven by reducing the average SOFA for general grading by 1.5 times, for hepatic dysfunction - by 1.7 times, and for renal dysfunction - by 1.5 times. An integrated approach to the development of therapeutic measures in the postoperative period, according to the conditions of the method we developed for the prevention of endothelial dysfunction in the lungs in patients with abdominal sepsis, allowed, in comparison with the control group of patients, to reduce the frequency of deaths from 35.7% to 17.1% (2.1 times) and the duration of bed/days from 18.2±5.7 beds/day to 13.4±4.1 beds/day.

Выводы: The optimal model of abdominal sepsis is its reproduction against the background of suppression of the general reactivity of the body of experimental animals with the creation of a focus of liquefaction necrosis of the wall of the large intestine. Thanks to this, the full development of the primary focus of the purulent-inflammatory process and all phases of sepsis (from systemic inflammatory response syndrome to severe sepsis) is achieved.

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