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# Prediction and Prevention of Endothelial Dysfunction in the Lungs in Abdominal Sepsis

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**Abstract** The use of the methods developed by us for predicting and preventing endothelial dysfunction in the lungs in the complex treatment of abdominal sepsis has reduced 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 the prevention of the development of multiple organ failure was proved by a decrease in the average SOFA level in general gradation by 1.5 times, in hepatic dysfunction by 1.7 times and in renal dysfunction by 1.5 times.

**Keywords** Abdominal sepsis, Peritonitis, Syndrome of systemic

## 1. Introduction

Currently, there is an increase in the incidence of sepsis, and the mortality rate remains extremely high [1,3,5]. It is recognized that the syndrome of systemic inflammatory response of the body 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 by Stewart et al. 896,000 deaths, 20 million years of life lost, and 25 million disability-adjusted life years lost per year were reported, associated with a total of 11 urgent general surgical conditions. 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 important type of sepsis worldwide [8,10,12].

The cause of abdominal sepsis in the form of diffuse peritonitis is considered a poor prognostic indicator, since its mortality rate can reach 20% [13,15,17,31,32,33].

This problem also causes relevance due to the need for long–term the stay of patients in the intensive care unit. This, in turn, raises economic issues of budget resource losses. 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 range from 7.6% to 36.0% [14,16,18,26,27,28,29,30].

Intra-abdominal contamination and secondary peritonitis are a constant source of pathogen-associated molecular patterns (through spillage of intestinal contents) and through direct damage to internal organs and abdominal organs. This "motor of multisystem organ failure" provides continuous cytokine fuel for a raging systemic response. For example, TNF-α and IL-1 are important pro-inflammatory cytokines. Each of them has been shown to induce vascular permeability, which leads to pulmonary edema and bleeding [1,2,5,34.35,36]. IL-6 is a key molecule in initiating a febrile reaction, activating lymphocytes, 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 in the study of the mechanisms of sepsis development. During bacterial, fungal or viral infection, exogenous molecular patterns associated with pathogens and molecular patterns associated with endogenous damage cause activation of the endothelium 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 appropriate to limit the spread of bacteria, as well as to control leukocyte recruitment and bacterial elimination. 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 [7,9,37,38,39].

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Thus, it is very difficult to distinguish between appropriate activation and endothelial dysfunction, especially considering that the response of endothelial cells may differ in different organs [4,7,40,41].

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 multiple organ failure caused by sepsis [9,11,18].

Despite their inherent limitations, experimental animal models of sepsis and in vitro studies provide a better understanding of the multiple pathways that are induced in endothelial cells in response to infection and how they are regulated. The study of activation pathways that lead to endothelial dysfunction caused by sepsis is a promising direction towards limiting organ failure caused by sepsis [2,8,19].

There is no data in the literature on the role and place 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 dangerous complications of generalization of infection, and thereby improve the results of treatment of patients with abdominal sepsis.

**The aim 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.

## 2. 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 study did not include: patients, provided the patient is under the age of 18 years; in the presence of pregnancy in patients; 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 in therapeutic measures based on methods of preventing endothelial dysfunction in the lungs.

Male patients prevailed (63.6%), in adulthood (35.0%) and at a young age (32.1%). The average age of the patients was 46.3±9.4 years.

The diagnosis of abdominal sepsis was formed according to a stepwise scheme, including: nosological disease, which is the main cause of abdominal sepsis; the type of prevalence of complications of the disease in the form of peritonitis or purulent necrotic process; the type of abdominal sepsis (sepsis syndrome, severe sepsis or septic shock, which was identified according to criteria adopted at the ASSR/SSSM Conference; a nosological disease of a concomitant nature with the determination of the phase or degree of their development.

The scope of surgical intervention corresponded to 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; decompression of the intestine by intubation of the intestine or stoma; drainage of the abdominal cavity.

In the main group of patients, the tactics of surgical measures differed from the control depending on the degree of endothelial dysfunction in the lungs and were complemented by conditions of peritoneal dialysis and intestinal lavage, as well as the installation and infusion of drugs of an intraportal catheter through a circular ligament of the liver.

The experiments were carried out on 106 white Wistar laboratory rats weighing 200-250 grams, of both sexes, who were on a regular laboratory diet. The planned experimental studies, which included sampling, biopsies and autopsy, were based on the principle of the conditions specified in the 1986 Council of Europe Convention on the Protection of Animals.

The animals were divided into the following series of experiments: Control – 10 intact animals, not subjected to any influences and manipulations, which were on a standard grain diet. The main group consisted of 50 animals in which an experimental model of abdominal sepsis was reproduced using our improved technique.

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.

Blood sampling in experimental studies was carried out 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 whole body 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, the value reflecting the "delay" or "production" of the substrate in the endothelial system of the lungs.

The whole complex of studies of patients with abdominal sepsis was reduced to 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-Kalifa Leukocyte Intoxication Index were also actively used.

The level of C-reactive protein (mg/l), thrombomodulin (ng/ml), Willebrand factor (IU/dL), intercellular and cellular adhesion molecules (ng/ml) were studied using an enzyme

immunoassay; nitrites and nitrates (%), peroxynitrite (mmol/l), the activity of nitric oxide synthase (mmol/min/l) according to the Griss method modified by A.P. Solodko et al. on the SF-46 spectrophotometer at a wavelength of 520 nm.

The whole range of studies met the criteria of translational medicine, which used the entire range of studies, which allowed extrapolating 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 course of the pathological process, be characterized by high reproducibility and low mortality.

We borrowed the principle of damage to the dome of the cecum, proposed by H. Mutlak in 2013, as the basis for reproducing the model. 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. The variant of changing the reactivity of the macroorganism was worked out by us in series-B, which was carried out by pre-injection into the abdominal cavity of antilympholine-Kr at a dose of 0.03 mg per 100 grams of animal for 48 hours. The effectiveness of this reproduction option has been proven by our domestic scientists in modeling surgical sepsis against the background of purulent-necrotic soft tissue diseases (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 the comparative analysis, it was proved that the reproducibility of the primary focus of destruction in series-A was absent, in series-B was 57.1%, and in series-C – in all the studied cases. 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 maximal in series-C (71.4%), whereas in series-A and series-B this indicator did not exceed 42.9%. All Series-A animals died within 9 hours of simulation, whereas in series-B the mortality rate started from 18.9±5.9 hours of simulation and reached 28.6%. At the same time, 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 developed by us made it possible to achieve the formation of a number of pathogenetic mechanisms that have a reasonable 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 fecal matter enters the abdominal cavity and toxic shock develops; to achieve a change in the reactivity of the body, 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 lung system in the dynamics of the development of an experimental model of abdominal sepsis.

## 3. Results and Their Discussion

It was revealed that morphological changes in the endothelial system of the lungs in the dynamics of the development of an experimental model of abdominal sepsis can be characterized as stage-by-stage transformations that lead to destructive consequences during the progression of the pathological process. At the same time, if the early periods (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 date (72-96 hours) – structural changes, with obvious 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 (first of all) and throughout the body, which characterizes the starting position of the formation of multiple organ dysfunction.

The obtained data on morphostructural changes in lung tissue created conditions for assessing the features of molecular and biochemical changes in the endothelial system of the lungs in the dynamics of the development of an experimental model of abdominal sepsis.

The dynamics of changes in the content of proinflammatory cytokine IL-1β in various blood samples in the dynamics of the development of an experimental model of abdominal sepsis showed an increase in this indicator as in a mixed venous blood sample at the entrance to the lungs from 11.92±1.02 pg/ml after 6 hours of disease modeling to 42.91±11.91 pg/ml after 72 or more hours from the onset of the disease ($p<0.05$). These values were reliable 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). A similar shift in indicators was also noted 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 ($p<0.05$). These changes were also significant in relation to the control (0.02±0.005 pg/ml) and to the 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 left 49.51±18.51 pg/ml and 50.09±21.64 pg/ml, respectively. The minimum values in the corresponding blood samples were IL-6 (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 studied proinflammatory cytokines was also noticeable and varied during the development of an experimental model of abdominal sepsis. With respect to the proinflammatory cytokine TNF-α, there is a significant difference in both 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 comparative groups.

In general, the level of changes in the concentration of the studied proinflammatory cytokines in various blood samples in the dynamics of the development of an experimental model of abdominal sepsis was corrected by the endothelial lung system. 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, apparently, was not enough to develop a "violent" response of the body. This period was characterized by a small (local) release of proinflammatory cytokines from a purulent inflammatory focus. As the purulent-inflammatory process progresses, in subsequent follow-up periods, the lungs not only cease to make a corrective effect, but also begin to produce proinflammatory cytokines themselves, which can primarily be noted in relation to IL-6 and IL-8. Apparently, this reaction was associated with certain response changes in the endothelial system of the lungs, which we described below.

The dynamics of changes in the NOx content in various blood samples in the dynamics of the development of the experimental model of abdominal sepsis was characterized by an excess of values in the arterial blood sample throughout the study. The abdominal sepsis model resulted in an increase in NOx from 20.21±5.63 mmol/l to 39.12±6.26 mmol/L in a mixed venous blood sample, and from 25.75±3.13 mmol/L to 46.17±8.14 in an arterial blood sample ($p<0.05$). Against the background of these changes, we identified changes in the concentration of the metabolic product of the conversion of NOx components, in particular NO3- to OONO-.

The average peroxynitrite content in the mixed venous blood sample at the entrance to the lungs increased from 1.53±0.42 mmol/l to 4.91±1.18 mmol/l, and in the arterial blood sample from 0.69±0.13 mmol/l to 6.11±2.82 mmol/l ($p<0.05$).

We noted an increase in peroxynitrite in various 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 compensatory capabilities of the endothelial lung system itself.

As evidence to the above conclusion, we consider the dynamics of changes in the activity of the iNOS enzyme in the studied blood samples at the entrance and exit from the lungs, the activity of which increases in the arterial blood sample at the exit from the lungs (1.29±0.93 mmol/min/l) than at the entrance to the mixed venous blood sample (1.17±0.51 mmol/min/l) as abdominal sepsis progresses.

In the dynamics of the development of the experimental model of abdominal sepsis, identical changes occurred in the concentration of intercellular and cellular adhesion molecules.

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 arterial blood sample, respectively).

In the dynamics of modeling abdominal sepsis, the differentiated position of the venous-arterial difference of C-reactive protein is significantly reduced. At the same time, if in the early stages of reproduction of 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 (up to 0.7 times). The identical nature of the changes was noted by us with respect to thrombomodulin. The leveling of the values of the venous-arterial difference in this period of experiments was also noted by us in relation to vWF.

Analysis of the venous-arterial difference showed that the endothelial system of the lungs reacted sensitively to the changes in the focus 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 the development of an 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 our 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 phase course of the pathological process.

The first phase of endothelial dysfunction in the lungs develops within 24 hours of modeling abdominal sepsis. It begins with the involvement of endothelial cell receptors in the recognition of pathogen-induced proinflammatory cytokines IL-1β and TNF-α. Their intake occurs locally, in small portions into the venous bloodstream from the inflammatory focus of the abdominal cavity. In addition, activation of endothelial cells provokes an increase in the regulated activity of induced nitric oxide synthase (iNOS), which leads to overproduction of NO. An overabundance of NO, primarily due to NO3-, reacts with reactive oxygen species, as a result of which peroxynitrite ($ONOO^-$) begins to form intensively. This toxic product is the main starting key to endothelial cell apoptosis.

The second phase of endothelial dysfunction in the lungs (24-48 hour period of development of abdominal sepsis) is characterized by the onset of endothelial cell apoptosis against the background of increased expression of ICAM-1 and VCAM-1. Violation of the integrity of endothelial cells and expression of cellular and intercellular adhesion molecules creates conditions for increased exudation with the development of capillary leakage syndrome. The recruitment of leukocytes and polymorphonuclear neutrophils increases, which contribute to the active production and release of proinflammatory cytokines IL-6 and IL-8 into the systemic circulation (arterial blood). It triggers a "cytokine storm" and tissue factor expression occurs.

The third phase of endothelial dysfunction in the lungs

(72-96 hour period of development of abdominal sepsis) is characterized by induction of the functional properties of endothelial cells towards the procoagulant and antifibrinolytic phenotype, which is the starting position for the development of disseminated intravascular coagulation syndrome. Endothelial cells subjected to apoptosis and recruited leukocytes express tissue factor, as well as the production of C-reactive protein. As a result, stimulation of thrombomodulin production begins. This "vicious circle" is closed by the release of activated endothelial cells of vWF. Such a transformation in the procoagulant and antifibrinolytic system contributes to the development of thrombosis of the prealveolar, and subsequently postalveolar capillary network.

As our studies have shown, in animals of the control series of experiments, there is a constant release of NO, which corresponds to the physiological functions of the endothelial system.

It is known that this factor reflects a violation of the vasomotor function of the endothelium. This allows you to maintain a balance of vascular tone, and by relaxing their muscle layer. This action is known as anti-aggregative and obliterating.

Next, we attempted to develop and comparatively evaluate the effectiveness of methods for predicting and preventing endothelial dysfunction in the lungs in abdominal sepsis.

The nature of changes in endothelial dysfunction indicators in survivors and deceased patients with abdominal sepsis showed their high dependence on surgery. Thus, among the surviving patients, C-reactive protein in venous blood before surgery averaged 3.65±1.02 mg/l, and after surgery it decreased to 1.28±0.24 mg/l ($p<0.05$). At the same time, in deceased patients, the level of this indicator before surgery was 4.03±0.61 mg/l, and after surgery it increased to 6.59±1.17 mg/l ($p<0.05$). That is, in this case, we found an inverse relationship of changes in the content of this endothelial dysfunction market, depending on the outcome of the patient's treatment. We also noted a similar nature of changes in relation to changes in thrombomodulin (before surgery 0.18±0.02 ng/ml, after surgery 0.15±0.03 ng/ml in surviving patients and 0.51±0.04 ng/ml in deceased patients with abdominal sepsis; $p<0.05$), Willebrand factor (before surgery 152.9±21.7 IU/dL, after surgery 38.9±7.12 IU/dL in surviving patients and 273.3±34.9 IU/dL in deceased patients with abdominal sepsis; $p<0.05$), intercellular molecules (before surgery 4.02±0.91 ng/ml, after surgery 3.11±0.74 ng/ml in surviving patients and 6.92±1.03 ng/ml in deceased patients with abdominal sepsis; $p<0.05$) and cellular adhesion (before surgery 5.16±1.13 ng/ml, after surgery 4.13±0.94 ng/ml in surviving patients and 8.98±1.41 ng/ml in deceased patients with abdominal sepsis; $p<0.05$), nitrates (before surgery 55.3±9.3%, after surgery 25.9±3.7% in surviving patients and 89.4±17.9% in deceased patients with abdominal sepsis; $p<0.05$), peroxynitrite (before surgery 2.18±0.22 mmol/l, after surgery 0.53±0.02 mmol/l in surviving patients and 5.12±1.04 mmol/l in deceased patients with abdominal sepsis; $p<0.05$) and induced nitric oxide synthase (before surgery 0.43±0.02 mmol/min/l, after surgery 0.25±0.04 mmol/min/l in surviving patients and 1.17±0.7 mmol/min/l in deceased patients with abdominal sepsis; $p<0.05$).

The comparison was also carried out by the number of clinical and laboratory signs of systemic inflammatory response syndrome and indices of sepsis severity. Based on the correlation analysis and differentiation of digital values, we constructed a graphical dependence in the change of biochemical parameters of the endothelial system in the lungs of survivors and deceased patients with abdominal sepsis, the calculation formula of which allowed us to create a software product called "EDLAS" (Endothelial dysfunction in the lungs in abdominal sepsis). This program included 5 laboratory and 5 clinical parameters (the duration of the disease, the number of signs of systemic inflammatory response syndrome, the age of the patient, the level of C-reactive protein, Willebrand factor, cell adhesion molecules and peroxynitrite in venous blood).

When diagnosing the degree of endothelial dysfunction of the lungs, taking into account the phase approach in assessing the detected disorders, we identified compensated (0-3 points), sub- (4-7 points) and decompensated (8-10 points) levels.

A comparative assessment of the specificity of the method we developed for predicting endothelial dysfunction in the lungs in abdominal sepsis showed that "EDLAS", unlike "MODS", "SOFA" and "SAPS", according to 70 patients in the survivors/deceased section, had more reliable parameters according to the C-criterion ($x2=13.65$; $p<0.05$).

The smallest comparative difference in the sensitivity of the method we developed was revealed in relation to MODS (Se=-0.063), which is known to be responsible for assessing multiple organ dysfunction, the key link in which is endothelial dysfunction in the lungs. Apparently, therefore, the specificity was also distinguished by a minimal difference (Sp=-0.139).

The maximum discrepancy in sensitivity and specificity of methods for assessing the severity of a patient's condition and predicting a fatal outcome was revealed between the method we developed and SAPS (Se=-0.263 and Sp=-0.239), which is known to have a wider range of applications in clinical practice.

This eventually made it possible to develop a prognostic and tactical algorithm that allows you to optimize the actions of the surgeon. Based on the testing of this program in patients of the control group, we were able to establish that the prognostic probability of developing severe sepsis, septic shock and death may be low, high and critical, which was confirmed by us using a comparative assessment of the sensitivity and specificity of the method.

Having been able to predict the likelihood of developing endothelial dysfunction in the lungs in patients with abdominal sepsis, we were able, by making adjustments to the complex of therapeutic measures, to develop an appropriate algorithm that improved the results of treatment of patients with abdominal sepsis.

In general, therapeutic tactics for abdominal sepsis retained their unchanged postulates, these are: infection

control, detoxification therapy, therapy aimed at stimulating the activity of body systems and others.

A decrease in the intake of proinflammatory cytokines into the systemic bloodstream from the focus of the purulent-inflammatory process was achieved by using peritoneal and enteral lavage in a flow-fractional mode using oxygenated dialysis solutions, as well as oxygenated lavage. The effectiveness of these treatment methods has been confirmed by specific clinical examples, where in abdominal sepsis, as a result of advanced peritonitis, due to the combined use of oxygenated solutions both into the abdominal cavity (peritoneal dialysis) and to improve the apical oxygen supply of enterocytes, positive treatment outcomes were achieved.

In order to prevent the aggravation of the severe form of generalization of the purulent-inflammatory process, we used intraportal administration of Sulodexide at a dose of 600 units and Dimephosphone at a dosage of 50 mg / kg / day, which were administered daily from the first day of the postoperative period.

All this served as the foundation for the development of a therapeutic and preventive algorithm in the postoperative period in the form of oxygenated peritoneal dialysis, complex oxygenated enteral sanitation and therapy, and long-term intraportal catheter therapy using pathogenetically justified medications that block the flow of proinflammatory cytokines into the systemic bloodstream and thereby prevent the development of endothelial dysfunction in the lungs.

In a comparative assessment of the effectiveness of the algorithms we developed for the application of methods for predicting and preventing endothelial dysfunction in the lungs in patients with abdominal sepsis, we compared gender, age of patients, etiological cause of the disease, chronology of the development of the underlying disease, severity of septic manifestations (sepsis syndrome, severe sepsis and septic shock), Mannheim index, nature and volume of performedthe stage of surgery and the degree of development of endothelial dysfunction in the lungs using the software product "EDLAS" developed by us.

In the postoperative period, the dynamics of changes in endothelial dysfunction in the lungs was not unambiguous. Thus, only in 12.9% of patients it showed a low probability of defeat. At the same time, in 28 (40.0%), the degree of endothelial dysfunction in the lungs predicted the likelihood of developing severe sepsis, and in 33 (47.1%) patients – critically high, which could lead to the development of septic shock.

We compared all local therapeutic measures and their effect on the clinical and laboratory manifestation of the systemic inflammatory response syndrome of the body. In almost half of the cases (47.1%), 4 clinical and laboratory signs of systemic inflammatory response syndrome were noted in patients. According to 3 clinical and laboratory signs of systemic inflammatory response syndrome, we noted in 35.7% of patients. Only 12 patients (17.1%) had two clinical and laboratory signs of systemic inflammatory response syndrome.

A comparative assessment of the dynamics of changes in organ failure on the SOFA scale in patients with abdominal sepsis revealed significant differences between the control and main groups starting from the 3rd day of treatment, when the difference in values was a decrease from 9.48±0.53 units to 6.83±0.61 units ($p<0.05$).

A comparative assessment of the effectiveness of the developed algorithms for the application of methods for predicting and preventing endothelial dysfunction in patients with abdominal sepsis was carried out according to the criteria of the average number of clinical and laboratory signs of systemic inflammatory response syndrome per 1 patient, the average duration of severe sepsis and septic shock, the average level of SOFA, mortality and number of bed days.

In patients of the control group, the average number of clinical and laboratory signs of systemic inflammatory response syndrome was 3.6± 0.4 units per 1 patient. At the same time, the average duration of severe sepsis was 9.8±4.6 days, and septic shock was 5.9±3.8 days.

The assessment of the general level of manifestation of multiple organ dysfunction/insufficiency on the SOFA scale among patients of the control group reached the level of 6.3± 2.75 units. At the same time, for liver failure, the average SOFA level was 1.7 ± 0.3 units, and for renal failure - 1.2± 0.15 units.

Among the patients of the control group, 25 (35.7%) patients died, and the average bed of days of inpatient treatment was equal to an average of 18.2± 5.7 days.

As a result of the application of the prognostic and preventive measures developed by us for endothelial dysfunction in the lungs in patients with abdominal sepsis, in the main group of patients, compared with the control group, we achieved a decrease in the average number of clinical and laboratory signs of systemic inflammatory response syndrome by 2.2± 0.32 units per 1 patient.

The average duration of severe sepsis in the main group of patients, compared with the control group, decreased by 2.6 ± 0.47 days, and septic shock – by 2.8± 0.35 days.

A comparative assessment of the overall level of manifestation of multiple organ dysfunction/insufficiency on the SOFA scale, as a result of the active use of measures for predicting and preventing endothelial dysfunction in the lungs, allowed in the main group of patients, compared with the control group, to reduce this indicator by 2.0± 0.21 units, for liver failure – by 0.7 ± 0.1 units, and for renal failure - 0.4±0.11 units.

Among the patients of the main group, 12 (17.1%) patients died, and the average bed of days of inpatient treatment equated to an average of 13.4 ± 4.1 days.

Thus, the application of the methods developed by us for predicting and preventing endothelial dysfunction in the lungs in the complex treatment of abdominal sepsis has reduced 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 the prevention of the development of multiple

organ failure was proved by a decrease in the average SOFA level in general gradation by 1.5 times, in hepatic dysfunction by 1.7 times and in 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 developed by us, prevention of endothelial dysfunction in the lungs in patients with abdominal sepsis, allowed, compared with the control group of patients, to reduce the incidence of deaths from 35.7% to 17.1% (2.1 times) and the duration of beds / days from 18.2±5.7 beds/day to 13.4±4.1 beds/day.

## 4. Conclusions

1. The optimal model of abdominal sepsis is to reproduce it against the background of suppression of the general reactivity of the body of experimental animals with the creation of a focus of colliquation necrosis of the colon wall. Due 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.
2. Local endothelial dysfunction in the lungs is characterized by a low release of proinflammatory cytokines IL-1β and TNF-α into the venous bloodstream, which activate endothelial cells and the nitroxyergic regulation system at the prealveolar level. This leads to the onset of endothelial cell apoptosis and increased expression of ICAM-1 and VCAM-1, which turns into a systemic lesion. The progression of the pathological process in the form of induction of the functional properties of endothelial cells towards the procoagulant and antifibrinolytic phenotype, which is the starting point for the development of disseminated intravascular coagulation syndrome.
3. For the prognostic assessment of endothelial dysfunction in the lungs in abdominal sepsis, the optimal indicator is an integrated software product called "EDLAS" (Endothelial dysfunction in the lungs in abdominal sepsis), which includes parameters such as the duration of the disease (hours), the number of signs of systemic inflammatory response syndrome of the body (number), the patient's age (years), the level of C-reactive protein (mg/l), Willebrand factor (IU/dL), VCAM-1 (ng/ml) and peroxynitrite (mmol/l) in the central venous blood system.
4. The application of the methods developed by us for predicting endothelial dysfunction in the lungs in the complex treatment of abdominal sepsis has reduced 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.
5. The main therapeutic measures in the postoperative period should include methods for the prevention of endothelial dysfunction in the lungs, which include oxygenated peritoneal dialysis, complex oxygenated enteral sanitation and therapy, and long-term intraportal catheter therapy using pathogenetically justified medications that block the flow of proinflammatory cytokines into the systemic bloodstream and thereby prevent the development of endothelial dysfunction in the lungs.
6. The effectiveness of the use of targeted methods for the prevention of the development of multiple organ failure has been proven by a decrease in the average SOFA score in general gradation by 1.5 times, in hepatic dysfunction by 1.7 times and in renal dysfunction by 1.5 times.
7. An integrated approach to the development of therapeutic measures in the postoperative period, according to the conditions of the methods developed by us for predicting and preventing endothelial dysfunction in the lungs in patients with abdominal sepsis, allowed, compared with the control group of patients, to reduce the incidence of deaths from 35.7% to 17.1% (2.1 times) and the duration of the bed / days with 18.2±5.7 beds/day to 13.4±4.1 beds/day.

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