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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

OPTIMIZATION OF TREATMENT OF GENERALIZED PURULENT PERITONITIS

Speciality: 3213.01 - Surgery

Field of science: Medicine

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GENERAL CHARACTERISTICS OF WORK

The actuality of the subject. Notwithstanding numerous scientific studies in various fields, a perfect idea on the tactics of diagnosis and treatment of acute purulent inflammatory diseases of the abdominal organs has not been formed yet[1,2] .

Though that generalized purulent peritonitis has always been on the focus of clinicians, the failure to treat it radically has been repeatedly and consistently reflected in the recent researches[3]. The frequent occurrence of various variants of complications indicates the need for more in-depth study of the pathogenesis of peritonitis and dictates new research.

Notwithstanding that the range of modern treatments of peritonitis is very rich, they need to be systematized on a scheme[4]. It is also known that bacterial pathogens in peritonitis are triggers of the activation of immunocompetent cells. The complex cytokine being the basis of protection against infection activates a cascade of interactions, it can completely shake the body's defense ability and lead to the development of toxic shock [5].

Despite the generalized prevalence of peritonitis, severe and complex clinical course, improvement of early diagnosis and operative treatment, application of modern antibacterial drugs, new methods of intra and postoperative rehabilitation of the abdominal cavity, as well as methods of efferent detoxification of the body, lethality of

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peritonitis varies between 20-60% [6]. Intra-abdominal complications requiring relaparotomy occur at 20.8-46% of patients undergone surgery [7].

Mortality in peritonitis varies depending on the etiological structure of the disease, the initial somatic and immunological status of the patient, the characteristics of the course of the pathological process, the prevalence and severity of peritoneal damage, as well as various treatments.

Disruption of the body's immune mechanisms at patients with peritonitis leads to cytokine immunodeficiency and increase in antimicrobial peptides associated with the synthesis and reception of cytokines [8]. Basing on numerous researched scientific sources, it can be stated that the role of cytokines, antimicrobial peptides, indicators of the antioxidant system in the pathogenesis of generalized peritonitis, their relationship with endogenous intoxication, the prognostic significance of these indicators has not been fully studied yet [9].

As well, the use of both classical and combined efferent (membrane plasmapheresis, cryopheresis, intravascular ultraviolet and laser radiation) and enzyme therapy, their effect on the course of peritonitis has been evaluated so far only by proving on the basis of clinical monitoring [10].

Comparative monitoring of changes in the dynamics of lipid peroxidation products, cytokines and antimicrobial peptides in the

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blood as a result of combined treatment methods (during classical and single efferent therapy) can help to optimize the treatment of generalized purulent peritonitis. The above-mentioned facts substantially reflect the urgency of peritonitis and indicates the need for new research.

Object of research: Patients with generalized purulent peritonitis.

The purpose of the research is to optimize the treatment of the pathogenesis of generalized purulent peritonitis by studying the variability of cytokines and antimicrobial peptides.

Research objectives:

1. Identification of indicators of lipid peroxidation (DC, MDA and catalase) and the role of endogenous intoxication (MMP, PA) that allows earlier and objective detection in the generalized peritonitis; Determination of the role of individual indicators of cytokine profile (IL-2, IL-6, IL-8 and TNF-α) depending on the severity of generalized purulent peritonitis;
2. Studying the development of the severity of generalized purulent peritonitis depending on antimicrobial peptides (lactoferrin, endotoxin and BPI) and assessing the correlation between the indicators of endogenous intoxication syndrome, antimicrobial peptides and cytokine profile in the treatment of generalized purulent peritonitis;
3. Comparative evaluation of the effectiveness of drug treatment of generalized purulent peritonitis in the dynamics.
4. Investigating the role of Efferent and Enzymotherapy in the treatment of generalized purulent peritonitis;
5. Development of an algorithmic table of effective treatment and prognostic significance based on the assessment of the short and long-term results of the treatment of generalized purulent peritonitis.

Research methods:

- Clinical researches;
- Biochemical enzyme-immunoassay;
- Mathematical and statistical analysis

Basic scientific provisions of defense:

– Increased concentration of inflammatory cytokines in the blood serum in the generalized peritonitis indicates the development of immunodepression;

– The determination of the concentration of antimicrobial peptides: lactoferrin, endotoxin and BPI is of particular importance for the early diagnosis of generalized purulent peritonitis;

– Notwithstanding that the classic treatment of patients with generalized purulent peritonitis for 10 days leads to partial normalization of the immune and oxidative system and decrease in the intoxication degree, no effective result is observed in this treatment;

– It has been confirmed that drug therapy with immunomodulators and broad-spectrum antibacterial drugs in the classical regimen for the treatment of peritonitis cannot completely prevent the development of the disease;

– It has been proven that the use of efferent and enzyme therapy is adequate for generalized purulent peritonitis along with other methods of treatment and significantly increases the vital mobility of patients;

– The newly developed algorithm program can serve as a prognostic and basic document for the treatment of peritonitis;

Scientific novelty of the research:

– The conducted researches revealed the pathogenetic mechanisms of generalized purulent peritonitis, made it possible to develop criteria for the early and differential diagnosis of this process;

– The nature of violations of the cytokine status, AMP and lipid peroxidation in generalized purulent peritonitis, the severity of manifestation was determined in a complex form depending on the severity of the disease, their clinical and prognostic value was justified, the degree of endogenous intoxication was determined, these indicators were comparatively evaluated in the dynamics of the effectiveness of various treatment methods;

– The study of the role of antimicrobial peptides and cytokines in the pathogenesis of generalized peritonitis led to the introduction of immunomodulators, efferent and enzyme therapy

having a normalizing effect on the observed metabolic disorders and more satisfactory treatment results;

– A computer program-algorithm was developed with the forecast of the development and complications of peritonitis, the selection and systematization of pathogenetically substantiated methods of treatment, monitoring of antimicrobial and cytokine changes;

Theoretical and practical significance of the research:

- Pathogenetic treatment of generalized purulent peritonitis carried out taking into account immune parameters and markers of endogenous intoxication accelerates the rehabilitation of patients and improves their life quality;

- Investigation of the correlation between the results of biochemical and immunoenzyme analyzes and clinical signs can allow to predict the effectiveness and dynamics of treatment and to choose the right treatment tactics;

- Early and sustained recovery of patients with generalized purulent peritonitis, improvement of overall results and the effectiveness of combined treatment have been proven;

- The role of antimicrobial peptides in the row of "diagnostic and treatment criteria" has been confirmed in practice and can be used by practical surgeons as an auxiliary criterion in the treatment of peritonitis;

Relation of research to the problematic plan of the medical sciences. The topic of the thesis is included in the research plan of the III Department of Surgical Diseases of the AMU.

Approbation of the dissertasion. Separate fragments of the thesis were discussed at the scientific and practical conference dedicated to the 120th anniversary of A. Aliyev (2017, Baku), "International Black sea coastline countries scientific research symposium" (2021, Turkey), "4th Health science and innovation congress "(2021, Baku), "1st International health sciences, biomedical and innovative approach congress" (2021, Turkey), at the conference "Actual problems of medicine" (2021, Baku), dedicated to the 100th anniversary of T.A. Aliyev.

The initial discussion of the thesis took place at a meeting of the Azerbaijan Medical University with the participation of employees of the I, II, III departments of surgical diseases, departments of general surgery, pediatric surgery, traumatology and orthopedics, oral cavity and plastic surgery on December 22, 2021 (Minutes No. 4) and the official approbation took place on February 28, 2022 (Minutes No. 1) at the meeting of the Approbation Commission of ED.2.06 Thesis Council of the Azerbaijan Medical University, conducting scientific seminars.

Application of the work. The results of the research work are used in the daily practice of the bases of the III Department of Surgical Diseases of the Azerbaijan Medical University, as well as the scientific information obtained as a result of clinical, laboratory and instrumental studies are used in the educational process of the Department of Biochemistry.

The organization where the dissertation was performed. The thesis work was carried out at the III Department of Surgical Diseases of the Azerbaijan Medical University, the surgical department of Azersu Construction Joint Hospital and the educational and clinical biochemistry laboratory.

Published scientific papers on the dissertation. The main provisions and results of the thesis work are reflected in 10 articles published in scientific journals recommended by the Higher Attestation Commission of Azerbaijan (including 2 works certified by the Intellectual Property Agency, 3 published abroad), as well as 5 theses (including 3 abroad).

Volume and structure of dissertation. The dissertation is written in the Azerbaijani language in A4 format, in "Times New Roman" 14 fonts and with 1.5 line spacing. It is comprised of 177 pages (total volume of characters 219 356) consisting of table of contents, list of abbreviations and symbols, 3 chapters (15446+87048+24715) including introduction (9548 characters), literature review (49779 characters), research materials and methods, obtained results and their discussion, conclusion (16122 characters), the results, practical recommendations (695 characters), a list of references used. The list of references includes 245 sources 8 out of

which are published in the Azerbaijani, 117 in the Russian and 120 in the foreign languages. The thesis is illustrated with 10 tables, 4 figures and 25 graphics.

MATERIALS AND METHODS OF RESEARCH

The contingent of the research is comprised of 97 patients aged 17-69 with the diagnosis of generalized purulent peritonitis of various genesis and degree of coverage in the bases of the III Department of Surgical Diseases of the Azerbaijan Medical University in 2014-2020. 41 (42,3%) out of the patients operated on due to purulent peritonitis were men and 56 (57,7%) were women. 37 (38,1%) out of patients were over 45 years of age and 20 (54,1%) out of them were women and 17 (45,9%) men. 40 patients out of 46-59 aged patients were 25 (62,2%) women and 15 (37,5%) were men. 11 patients (55,0%) out of 20 (20,6%) 60-69 aged patients participated in our research were women and 9 patients (45,0%) were men. The control group consisted of 16 practically healthy people of appropriate age (men - 7, women - 9).

34 patients had destructive appendicitis, 23 patients had peripheral ulcers of the stomach (9 patients) and duodenum (14 patients), 11 patients had destructive perforative cholecystitis, 15 patients had pyoinflammatory gynecological pathology and 4 patients had acute intestinal obstruction, perforation of intestinal diverticula (10 patients) and these pathologies were the etiological cause of generalized purulent peritonitis.

According to the stage of development of peritonitis, patients were divided into 3 subgroups: subgroup I - 16 patients in the pre-sepsis (reactive) stage; subgroup II - 72 patients with septic stage; subgroup III - 9 patients with septic shock at risk;

According to the results of the preoperative clinical examination of patients included in the research, in patients with generalized peritonitis of group I in the preoperative (reactive) stage, 3 people (60%) had high fever before surgery, 3 people (60%) had abdominal pain, 3 people (60%) had nausea, vomiting was observed in 3 people (60%), intestinal paresis in 2 people (40%); In group II, 2

people (40%) had fever, 2 people (40%) had abdominal pain, 2 people (40%) had nausea, 2 people (40%) had vomiting, 1 person (20 %) had intestinal paresis; In group III, high temperature was observed in 4 people (66.7%), abdominal pain in 3 people (50%), nausea in 4 people (66.7%), vomiting in 3 people (50%), intestinal paresis in 2 people.

In the septic (toxic) stage, fever was observed in 8 people (33.3%), abdominal pain in 8 people (33.3%), nausea in 7 people (29.2%), vomiting in 2 people (8.3%) %), intestinal paresis in 4 (16.7%) people; In group II, 6 people (25%) had fever, 7 people (29.2%) had abdominal pain, 8 people (33.3%) had nausea, 6 people (25%) had vomiting and 5 people (20.9%) had intestinal paresis; In group III, 9 people (37.5%) had high fever, 9 people (37.5%) had abdominal pain, 8 people (33.3%) had nausea, 3 people (12.5%) had vomiting and 4 people (16.7%) had intestinal paresis in the preoperative period.

Clinical observations show that the clinical course of the disease is aggravated in the shock-prone septic (terminal) stage, since in this stage, in the preoperative period, 1 person (33.3%) had high temperature, 2 people (66.7%) had abdominal pain, nausea was observed in 1 person (33.3%), vomiting in 2 people (66.7%), intestinal paresis in 1 person (33.3%); In group II, 1 person (33.3%) had a fever, 1 person (33.3%) had abdominal pain, 1 person (33.3%) had nausea, 1 person (33.3%) had vomiting, 2 people (66.7%) had intestinal paresis; In group III, 2 people (66.7%) were diagnosed with fever, abdominal pain, vomiting, nausea, intestinal paresis in 1 person (33.3%) and abdominal pain in 1 person (33.3%).

In order to predict the severity of generalized purulent peritonitis and to evaluate the results of treatment, we used the Mannheim Peritonitis Index (MPI) scale proposed by M. Linder. According to this scale, 3 degrees of severity of patients were determined. Clinical evaluation was conducted among 97 patients with a diagnosis of generalized purulent peritonitis. Upon Mannheim scale, I degree included 35 patients (36.1%), II degree included 55 patients (56.7%) and the third degree included 7 patients (7.2%). The

clinical course of peritonitis depends on the degree, duration and phases of the process.

Basing on the treatment scheme, patients were divided into 3 groups. Group I included 32 patients receiving classical treatment, group II included 32 patients treated with plasmapheresis in addition to classical treatment and immunocorrection, and group III included 33 patients receiving cryopheresis, extracorporeal and intravenous ultraviolet radiation, extracorporeal infrared radiation, intravenous laser radiation and enzyme therapy in addition to those used in group II. In this group of patients, along with laparotomy and elimination of the pathological source, rehabilitation of the abdominal cavity, 2 transnasal tubes were inserted including 1 thin (stomach) and 1 large diameter tubes, the tracheal ligament was fully opened (Strong's operation), the thin probe passed from the stomach to the duodenum. It was placed palpatorically at a distance of 40-50 cm from the opening of the small intestinal loop (intubation). The placement of this probe was aimed at decompression, enteral nutrition, injection of vobenzim with colloidal starch (50 ml of liquid solution) (3 times) after the onset of peristalsis. The operation was completed by draining the abdominal cavity.

Between 2017 and 2020, the condition of operated patients involved in the research, as well as healthy individuals who formed the control group was monitored in the long run with questionnaires and various examinations and adequate measures were taken in accordance with the pathological changes occurred at them.

During the research, biochemical and immunoenzyme examinations were carried out in the Laboratory of Scientific Research and Biochemistry of Azerbaijan Medical University. The concentration of TNF-α and IL-2, IL-6, IL-8 cytokines in the blood serum was carried out by the "sandwich" method using a reagent kit of the company "Vector-Best" (Russian Federation).

The concentration of lactoferrin, endotoxin and BPI in the blood serum was determined using a reagent kit of “Immun Diagnostic” firm (Germany). Enzyme-linked immunosorbent assays were calculated on the basis of standard curves in the Stat Fax 303

Plus (USA) immunoenzyme analyzer (λ = 450 nm, differential filter 650 nm).

Parametric and non-parametric methods were used to clarify the obtained results. In this case, the non-parametric U-Wilcoxon (Mann-Whitney) criterion was applied and absolute risk calculated. All calculations were performed in Microsoft Excel XP computer software in EXCEL-MSOFFICE-2013 spreadsheet and SPSS-20 package program and the results were shown in tables and diagrams.

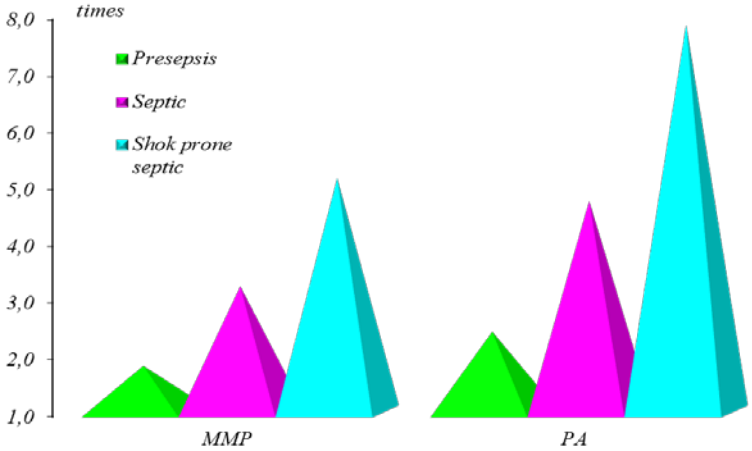
ANALYSIS RESEARCH RESULTS

Indicators of endogenous intoxication, indicators of endogenous intoxication, cytokine profile and condition of antimicrobial peptides in the blood serum of patients in the preoperative period

Indications of endogenous intoxication. The concentration of MMP in the control group ranged from 0.32 to 0.69 g/l and the average indicator was 0.539 ± 0.029 g/l (graphic 1) in the carried out research.

The concentration of MMP in the blood of patients in the pre-sepsis (reactive) stage was 86.4% (pU <0.001) respectively, compared to the control group, this indicator was increased 3.3 times

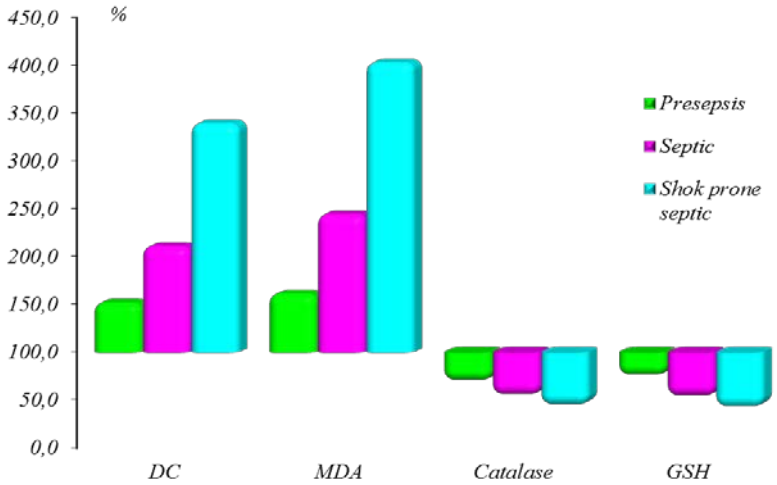
(pU <0.001) in septic (toxic) patients and 5.3 times (pU = 0.001) in septic patients at shock-prone patients.



Graphic 1. Indicators of lipid peroxidation

In the control group the proteolytic activity (PA) varied from 0.98 to 2.13 and averaged 1.58 ± 0.10 in this research. Compared to the control group, PA in the blood of patients in the pre-sepsis (reactive) stage increased 2.5 times (pU <0.001), in the septic (toxic) stage 4.6 times (pU <0.001), 8.0 times (pU = 0.001) in septic (terminal) shock-prone patients.

In the research, the concentration of DC in the control group ranged from 0.11-0.54 D_{233}/ml and the mean indicator is 0.434 ± 0.025 D_{233}/ml (graphic 2).



Graphic 2. Antioxidant system and indicators of endogenous intoxication

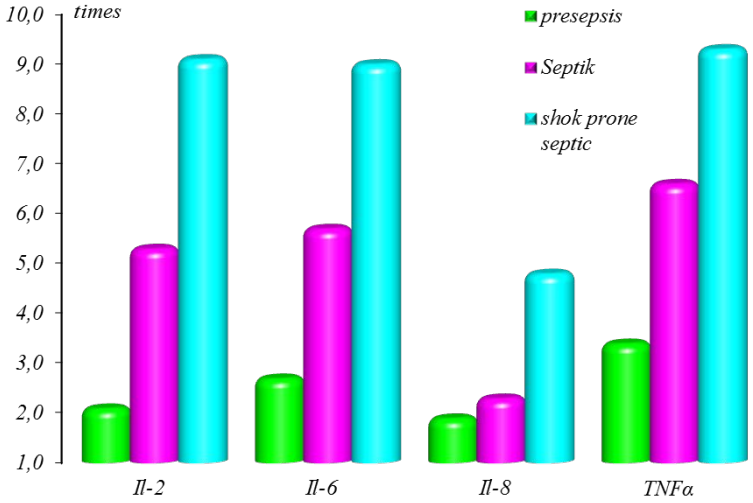
Compared to the control group, the concentration of DC in the blood of patients in the pre-sepsis (reactive) stage was 53.7% (pU = 0.001), in the septic (toxic) stage - 2.2 times (pU <0.001), in septic (terminal) shock-prone patients 3.8 times (pU = 0.001) higher.

In the research, the concentration of MDA in the control group ranged from 1.45 to 6.05 nmol/ml and the mean indicator is 3.82 ± 0.33 nmol/ml. The concentration of MDA in the blood of patients with pre-sepsis (reactive) stage was 67% (pU = 0.005), in the septic (toxic) stage - 2.5 times (pU <0.001), in septic (terminal) shock-prone patients - 4, 2 times (pU = 0.001) higher than of the control group.

According to the results of the research, the activity of catalase in the control group varies from 6.4 to 19.8 mcg / l and the average indicator was 15.8 ± 0.9 mcg/l. Compared to the control group, the catalase activity was decreased 30.1% (pU = 0.002) in the blood of patients with pre-sepsis (reactive) stage, 45.4% (pU <0.001) in septic (toxic) stage, 2.2-times (pU = 0.006) in shock prone septic (terminal) patients/

In the research, the concentration of GSH in the control group ranged from 1.11 to 2.93 μmol / gr.HB and the mean indicator is 1.58 ± 0.11 μmol / gr.HB. Compared to the control group, the concentration of GSH in the blood decreased 26.4% (pU = 0.001) in patients in pre-sepsis (reactive) stage, 46.7% (pU <0.001) in septic (toxic) stage, 2,4 times (pU = 0.001) in shock prone septic (terminal) patients.

Cytokine status and antimicrobial peptides. In the control group, the concentration of IL-2 varied in the range of 1.8-6.1 pg/ml and the mean indicator is 3.4 ± 0.4 pg/ml (graphic 3).



Graphic 3. Cytokine profile in patients with generalized purulent peritonitis

In the pre-septic (reactive) stage of generalized purulent peritonitis, the concentration of IL-2 in both groups was 2.1 times

(pU = 0.003), and in septic (toxic) patients 5.5 times (pU <0.001) higher than in the control group. A statistically significant 9.4 times (pU = 0.002) increase was observed in shock prone patients in septic stage. The concentration of IL-6 in the control group varies in the range of 0.8-3.6 pg/ml and the average indicator is 2.1 ± 0.2 pg/ml. Compared to the controlled group, IL-6 was 2.7 times (pU = 0.002) more in patients with pre-sepsis (reactive) stage of generalized purulent peritonitis, IL-5.8 times (pU <0.001) in the septic (toxic) stage, 9.3 times (pU = 0.002) more in shock-prone septic (terminal) patients.

The concentration of IL-8 in the control group varies from 17.6 to 45.1 pg/ml and the average indicator was 35.2 ± 2.9 pg/ml. Compared to the control group, the proliferative purulent peritonitis in pre-sepsis (reactive) patients was 2.0 times (pU = 0.004), in septic (toxic) patients 2.4 times (pU <0.001) and in septic (terminal) patients at risk of shock 4.8 times (pU = 0.002) higher.

The concentration of TNF-α in the control group varies from 2.8 to 7.6 pg / ml and the mean indicator is 4.4 ± 0.5 pg/ml. According to the results of the research, compared to the control group, the concentration of TNF-α was 3.5 times (pU = 0.001) higher in patients with pre-sepsis (reactive) stage of generalized purulent peritonitis, 6.6 times higher in septic (toxic) (pU <0.001) patients and 9.8 times (pU = 0.002) higher in shock-prone septic (terminal) patients.

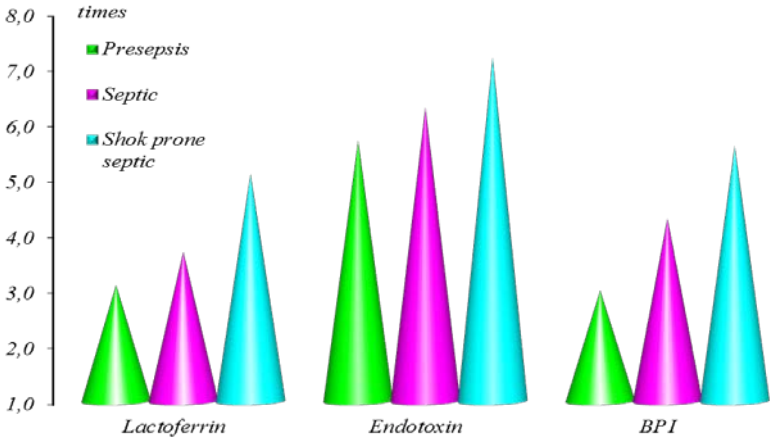
The concentration of lactoferrin in the control group varies in the range of 0.17-2.18 mcg / g, the mean indicator is 0.98 ± 0.20 mcg/g.

The mean concentration of lactoferrin was 3.2 times (pU = 0.003) more in patients with pre-sepsis (reactive) stage of generalized purulent peritonitis, 3.8 times (pU <0.001) more in septic (toxic) patients and 5.3 times (pU = 0.003) more in septic shock-prone patients.

The concentration of endotoxin in the control group ranged from 0.49 to 0.488 ng / ml and the mean indicator was 0.23 ± 0.05 ng/ml. Compared to the control group, the endotoxin concentration was 5.8 times (pU = 0.002) higher in septic (toxic) patients, 6.3 times

(pU <0.001) higher in patients in pre-sepsis (reactive) stage of generalized purulent peritonitis, 7.4 times (pU=0,003) in septic (terminal) shock prone patients (graphic 4).

The concentration of BPI in the control group ranged from 0.05 to 0.81 ng/ml and the mean indicator was 0.450 ± 0.105 ng/ml. Compared to the control group, the average concentration of BPI in patients with pre-sepsis (reactive) stage of generalized purulent peritonitis was 3.0 times (pU = 0.002) higher, in septic (toxic) patients 4,4 times (pU<0.001) higher, in shock-prone septic (terminal) patients 6.1 times (p_U=0,007) higher.



Graphic 4. AMP concentration in patients with generalized purulent peritonitis

Results of treatment performed in different periods after surgery

In all 3 groups of patients with generalized purulent peritonitis, the effect of spontaneous treatment on the course of the disease was monitored according to the changes that occurred on days I, V and X of the stages of peritonitis. The results obtained during the monitoring were compared with both clinical and laboratory examinations.

According to the results of postoperative clinical observations, in the pre-sepsis (reactive) stage in patients with generalized peritonitis, against the background of classic postoperative treatment in group I, notwithstanding that 3 people (60%) had fever in the first day, 3 people (60%) had abdominal pain, 2 people (40%) had nausea, 2 people (40%) had vomiting and 2 people (40%) had intestinal paresis. On the 5th day of treatment, though that 1 person (20%) had abdominal pain, 1 person had nausea, 1 person (20%) had intestinal paresis, high fever was normalized and no vomiting was observed. Intestinal peristalsis didn't recover in 1 person (20%). No clinical signs were observed on the 10^{th} day.

Along with the classic treatment of group II in the pre-sepsis (reactive) stage, on the first day after surgery, high temperature was completely normalized in patients with the use of immunomodulators and plasmapheresis, no vomiting was observed, abdominal pain was noted in 1 person (20%) sensation, nausea in 1 person (20%) and persistent intestinal paresis was noted in 2 people (40%). No fever, abdominal pain or vomiting were reported on 5th and 10th days, but nausea was observed in 1 person (20%) till the end of treatment.

In addition to the classical treatment in group III in the pre-sepsis (reactive) stage, in the background of immunomodulators on the first day after surgery the temperature was completely normalized in patients, no vomiting was observed, 1 person (16.7%) had abdominal pain, 1 person (16, 7%) had nausea and persistence of intestinal paresis was observed in 2 people (33.3%). No fever, abdominal pain or vomiting were reported on the 5^{th} and 10^{th} days, but nausea (16.7%) was observed in 1 person and intestinal paresis in 1 person (16.7%) till the end of treatment.

As a result of classical treatment after surgery in the sepsis (toxic) stage, in Group 1, on the first day 8 people (33.3%) had fever, 7 people (29.2%) had abdominal pain and 5 people (20.8%) had nausea, vomiting was observed in 2 people (8.3%) and intestinal paresis in 4 people (16.7%). On the 5^{th} day of treatment, 3 people (12.5%) had fever, 3 people (12.5%) had abdominal pain, 3

people (12.5%) had nausea, 2 people (8.3%) had vomiting and 2 people (8.3%) had the symptoms of intestinal paresis. Notwithstanding that the clinical course was slightly relieved on the 10th day, 1 person (4.2%) had fever and 1 person (4.2%) had intestinal paresis. Abdominal pain, nausea, and vomiting were not observed in these patients.

After complex treatment, including immunotherapy in the sepsis (toxic) stage, in group II on the 1st day 5 people (20.8%) had fever, 5 people (20.8%) had abdominal pain, 6 people (25%) had nausea, 6 (25%) people had vomiting and 4 people (16.7%) had intestinal paresis. On the 5th day of treatment, a relative relief was observed in the clinical course of patients, as on the 1st day 2 people (8.3%) had fever, 2 people (8.3%) had abdominal pain and 3 people (12.5%) had nausea, 4 people (16.7%) had vomiting and 3 people (12.5%) had intestinal paresis. On the 10th day, high fever, abdominal pain and vomiting were eliminated, 1 person (4.2%) had nausea and 2 people (8.3%) had intestinal paresis.

In group III, where efferent and enzyme therapy was used in addition to classical treatment in the sepsis (toxic) stage, on the first day 4 people (16.7%) had fever, 3 (12.5%) had abdominal pain, 4 (16.7%) had vomiting, 2 (8.3%) people had intestinal paresis, on the 5th day of treatment 2 people (8.3%) had nausea, and 1 person (4.2%) had on the 5th day of treatment. On the 10th day, nausea was observed in only one person.

In in shock prone patients included in group I receiving classic treatment in the septic stage, on the 1st day after surgery 1 person (33.3%) had high temperature, 1 person (33.3%) had abdominal pain, and 1 person (33.3%) had nausea, on the 5th day 1 person (33.3%) had high temperature, 1 person (33.3%) had abdominal pain, nausea and paresis was observed in 1 person (33.3%; $p = 0.025$). On the 10th day no fever, abdominal pain and intestinal paresis were observed, but nausea remained in 1 person (33.3%).

In shock-prone patients receiving immunotherapy and plasmapheresis in addition to the classic treatment, on the first day after complex treatment in group II, 1 person (33.3%) had fever, 1

person (33.3%) had abdominal pain, 1 person (33,3%) had nausea and intestinal paresis. On the 5th day, 1 person (33.3%) had high temperature, 1 person (25.0%) had abdominal pain and 1 person (33.3%) had nausea and intestinal paresis. On the 10th day, no fever, abdominal pain, nausea, or vomiting were reported, but 1 person (33.3%) continued to have intestinal paresis.

In 3 shock prone patients included in group III, on the first day after the surgery 1 (33.3%) people had nausea, sometimes vomiting, the second had high fever, abdominal pain, and the third had general weakness and adynamia. The symptoms disappeared on the 5th day in all 3 patients.

Absolute risk (AR) and Absolute risk difference (ARD) were examined in groups during the postoperative analysis of the clinical symptoms of the patients included in the research. Thus, in patients included in group III, AR for high temperature was 0.70 before the surgery, 0.06 5 days after the surgery and was not recorded after 10 days (AR = 0). Compared to group I, ARD1 was 0.31 and 0.09, respectively, 5 and 10 days after the surgery. Compared to group II, ARD2 was -0.13 and -0.03 on the mentioned days.

For pain, AR was 0.58 before the surgery, 0.06 5 days after the surgery and was not observed after 10 days (AR = 0). Compared to group I, ARD1 was -0.38 and -0.06, respectively, 5 and 10 days after the surgery. Compared to group II, ARD2 for pain was -0, 10 and -0.06 on the mentioned days.

AR for nausea was 0.39 before the surgery, the risk was reduced from the first day after the surgery and was not recorded on the 5th day (AR = 0). Compared to group I, ARD1- was -0.22 and -0.06. Compared to group II, ARD2 was -0.13 on the 5th day and was not recorded on the 10th days (AR = 0).

AR for vomiting was 0.58 before the surgery, 0.21 on the first day after the surgery and was not observed after 5 and 10 days (AR = 0). Compared to group I, this indicator was -0.25 and -0.06 and compared to group II, AR was -0.13 5 days after the surgery and wasn’t recorded 10 days after the surgery (ARD2 = 0).

AR for intestinal paresis was 0.58 before the surgery and 0.03 5 days after the surgery. After 10 days, it was not recorded (AR =

0). Compared to group I, 5 and 10 days after the surgery, this indicator was -0.19 and -0.06 respectively and compared to group II, this indicator was -0.06 5 days after the surgery and 10 days after the surgery it was not recorded (AR D2 = 0).

Thus, our research showed that the absolute risk of developing clinical symptoms in group III patients receiving concomitant treatment is lower than in other groups. Timely and correct selection of appropriate treatment measures reduces the risk of developing symptoms in the clinical course of the disease. This indicates early recovery in patients included in group III.

Early recovery in patients with pathogenetic treatment using laboratory tests for endogenous intoxication (OMP, PA), LPO products (DC, MDA), antioxidant system indicators (catalase, GSH), bacterial permeability-enhancing protein (BPI), endotoxin, antimicrobial peptides, lacteferrin and cytokines on IL-2, IL-6, IL-8, TNF-α groups has been researched and proved.

In group III, a statistically significant decrease in MMP concentration decreased 46.3% (pW <0.001) 5 days after surgery and 2.4 times (pW <0.001) after 10 days. The MMP concentration was 22.3% (pW <0.001) and 27.7% (pU <0.001) lower, respectively, at 5 and 10 days compared to group I. Compared to group II, on the 10th day it was 11.7% (pW = 0.006) lower.

Compared to the preoperative results, the DC concentration 5 days after the operation was 35.8% (pW = 0.001) and 10 days after 43.0% (pW <0.001) less. Compared to group I, after 5 days, the concentration of DC decreases 22.9% (pU = 0.001) and 10 days after 30.4% (pU <0.001). Compared to group II, the concentration of DC did not differ significantly from 5 days after surgery - 8.4% (pU = 0.245), after 10 days - 3.5% (pU = 0.572).

In group III, the MDA concentration decreased 2.0 times (pW <0.001) 10 days after surgery compared to preoperative results. Compared to group I, 34.8% (pU <0.001) statistical decrease in MDA concentration was observed 10 days after the surgery. Compared to group II, the concentration of MDA decreased significantly by 19.9% (pU = 0.010) 10 days after the surgery.

In group III, compared to preoperative results, PA levels decreased 2.5 times (pW <0.001) 5 days after surgery and 4.4 times (pW <0.001) 10 days after surgery. In this group, PA was 25.2% (pU = 0.001) and 42.4% (pU <0.001) lower, respectively, on the 5th and 10th days compared to group I. Compared to group II, the level of PA on the 10th day decreased by 14.8% (pW = 0.002).

In group III, catalase activity increased by 38.6% (pW <0.001) 5 days and by 66.3% (pW <0.001) 10 days after surgery. In this group, on the 10th day, the catalase activity increased by 20.3% (pU <0.001) compared to group I and by 6.9% (pU = 0.135) compared to group II.

In group III, compared with preoperative results, on the 10th day 78.8% (pW <0.001) increase was observed in GSH concentration. On the 10th day, the concentration of GSH in this group increased 26.1% (pU <0.001) compared to I group and 8.0% (pU = 0.055) compared to II group.

In the main group of patients IL-2, IL-6, IL-8 TNF-α increased 3.4 times, 2.5 times; 2.2 times and 4.2 times (Pw <0, 001; P_U<0.001) respectively compared to the preoperative period, and the corresponding day of group I.

In group III, on the 5th and 10th days, the concentration of IL-2 in the background of treatment is significantly lower than in group I and they are 2.5 times (pU <0.001) and 5.1 times (pU <0.001) less respectively. Compared to group II, the concentration of IL-2 decreased 27.2% (pU = 0.001) on the 5th day and 26.9% (pU = 0.012) on the 10th day.

In this group, on the 5th and 10th days, the concentration of IL-6 decreased 2.0 times (pU <0.001) and 4.9 times (pU <0.001) respectively, compared to group I. Compared with group II, it decreased by 11.4% (pU = 0.172) on the 5th day and by 29.8% (pU <0.001) on the 10th day.

In the main group, the concentration of TNF-α decreased significantly - 2.4 times (pW <0.001) 2 days after surgery and 4.2 times (pW <0.001) (Table 1) 10 days after surgery.

Table 1

Changes of TNF in groups at different stages of generalized purulent peritonitis M ± m (M_{min}-M_{max})

Indicator	Group / Stage	I	II	III	Control
TNF-α	Preseptic (reactive)	14,4±1,2 11,4-20,3*	15,4±1,1 (10,3-18,0)*	15,9±1,5 (9,6-21,1)*	4,4±0,5 (2,8-7,6)
	Septic (toxic)	28,7±2,1 5,1-47,0*	29,2±1,1 (19,7-39,8)*	30,5±1,4 (16,6-40,2)*	
	Shock prone Septic (terminal)	38,0±7,8 22,5-56,4**	43,1±6,9 (23,1-60,8)**	45,7±11,6 (22,6-59.6)*	

Note: *-Statistical difference relative to the Control Group * - p <0.001*
*-Statistical accuracy of the difference relative to the Control Group ** p <0.05*

In Group III, IL-8 concentration decreased 36.4% (p_W = 0.001) on the 5th day and 2.2 times (p_W <0.001) on the 10th day after the surgery. In this group, on the 5th and 10th days IL-8 concentration decreased by 35.9% (pU=0.001) and 41.0% (pU <0.001) respectively compared to group I. Compared to Group II, the concentration of IL-8 decreased by 17.9 (pU = 0.093) and 19.3% (pU = 0.006) after 5 days (Table 2).

Table 2

Changes of IL-8 in different stages of generalized purulent peritonitis M±m (M_{min}-M_{max})

Indicator	Group / Mərh	I	II	III	Control
IL-8	Preseptic (reactive)	62,6±5,1 39,6-79,6*	70,1±6,9 40,8-86,0**	71,6±6,4 35,5-89,7*	35,2±2,9 (17,6-45,1)
	Septic (toxic)	79,0±6,7 29,5-145,7*	83,5±5,1 44,0-140,2*	88,7±7,2 45,5-135,4*	
	Shock prone Septic (terminal)	164,9±47,0 84,5-290,5**	169,7±72,3 91,2-296,4**	175,4±62,7 101-300*	

Note: *-Statistical difference relative to the Control Group * - p <0.001*
*-Statistical accuracy of the difference relative to the Control Group ** p <0.05*

In group III, in 10 days lactoferrin from antimicrobial peptides decreased 2.3 times, endotoxin 2.7 times, and BPI 2.9 times (p_U

<0.001, Pw <0, 001) both relative to the preoperative indicators and the corresponding days of group I. It indicates the adequacy of treatment .

The results of our research give reason to say that modern tactics and strategies for the development of purulent peritonitis require a comprehensive etiological, pathogenetic, detoxificating, immunocorrecting, efferent and enzyme therapy.

Correlation between endogenous intoxication indicators, cytokine profile, antimicrobial peptides and clinical signs in generalized purulent peritonitis

Correlation between endogenous intoxication indicators, antimicrobial peptides and cytokine profile at different stages in patients with generalized peritonitis have been evaluated (Table 3).

Table 3

Correlation between clinical signs and indicators

Göstəricilər	p	Temperatur	Ağrı	Ürəkbulanma	Qusma	B.Parez
DK	ρ	-0,053	0,033	0,075	-0,007	-0,073
	p	0,634	0,766	0,505	0,951	0,517
MDA	ρ	-0,102	0,063	0,077	0,100	-0,194
	p	0,362	0,576	0,494	0,372	0,081
Katalaza	ρ	-0,005	-0,038	-0,135	0,110	-0,046
	p	0,961	0,735	0,227	0,327	0,680
GSH	ρ	0,008	0,086	-0,037	0,148	0,057
	p	0,942	0,442	0,739	0,185	0,612
OMP	ρ	0,136	0,026	0,038	0,089	0,125
	p	0,222	0,817	0,735	0,429	0,262
PA	ρ	0,112	-0,025	-0,163	0,027	-0,045
	p	0,315	0,821	0,143	0,810	0,686
Il-2	ρ	0,128	0,016	-0,110	-0,302*	0,010
	p	0,401	0,915	0,474	0,044	0,948
Il-6	ρ	0,156	-0,142	0,018	-0,094	-0,239
	p	0,306	0,352	0,907	0,539	0,114
Il-8	ρ	0,024	0,144	-0,135	-0,132	0,159
	p	0,878	0,345	0,375	0,387	0,298
TNF-a	ρ	0,285	0,150	-0,227	-0,199	-0,028
	p	0,058	0,325	0,134	0,190	0,857
Laktoferrin		0,046	0,059	0,058	-0,091	0,330
	ρ					
	p	0,825	0,776	0,778	0,657	0,100
Endotoksin		-0,169	0,137	0,035	0,111	0,249
	ρ					
	p	0,409	0,505	0,866	0,590	0,220
BPI	ρ	-0,501**	0,169	-0,081	0,013	0,104
	p	0,009	0,409	0,694	0,950	0,612

The study of the correlations between both clinical signs and biochemical indicators of all patients involved in the research showed that the reduction in BPI in these patients was accompanied by high temperature (ρ = -0.437; p = 0.002). Vomiting (ρ = 0.327; p

= 0.001) may also increase in patients with nausea. A positive correlation was shown between MDA with DC ($\rho = 0.343$; $p<0.001$), MMP ($\rho = 0.415$; $p <0.001$), proteolytic activity ($\rho = 0.313$; $p = 0.001$), IL-2 ($\rho = 0.484$; $p <0.001$), IL-6 ($\rho = 0.359$; $p = 0.003$), IL-8 ($\rho = 0.308$; $p = 0.011$), TNF-α ($\rho = 0.506$; $p <0.001$), lactoferrin ($\rho = 0.514$; $p<0.001$) and BPI ($\rho = 0,486$; $p = 0,001$). The inverse relationship between the activity of DC and catalase ($\rho = -0.272$; $p = 0.005$) and the concentration of GSH ($\rho = -0.276$; $p <0.004$) indicates an acceleration of the generation of active oxygen radicals as a result of weakening of the antioxidant system. The same trend is observed between MDA and these indicators, as there is an inverse relationship between MDA and catalase ($\rho = -0.368$; $p <0.001$) and GSH ($\rho = 0.304$; $p = 0.001$).

Thus, in addition to traditional treatment in patients, the complex application of immunotherapy prevents immunodeficiency and cytokine imbalance, reduces endogenous intoxication, stabilizes LPO processes, prevents enteral deficiency and restores the basic functions of the small intestine, allows correction of clinical-laboratory indicators of systemic inflammatory process, reduces the risk of postoperative sepsis and endotoxicosis and reduces lethality indicators. Early prediction of the course and development of peritonitis, early postoperative complications can help to the timely implementation of a well-optimized intensive care program and the development of a specific treatment program, taking into account changes in immune status, cytokine profile, lipid peroxidation processes, organ failure and endotoxicosis. This treatment program can be considered as timely and correct application of efferent and enzyme therapy.

Based on the above-mentioned facts, we have developed an algorithm-computer software schedule accurately and correctly reflecting the provisions of the diagnostic and treatment program. (Figure 1.)

Long-term researches have shown that 46 out of 97 patients had various types of chronic, sometimes exacerbated pathologies in the abdomen or other areas. The most common of these (20 patients) was conjunctival obstruction and 12 out of those patients underwent

repeated surgery. Studies show that complications are most common (58.6%) in patients haven't undergone to plasmapheresis or cryopheresis. The results of long-term laboratory tests showed that the indicators continued to exceed the norm in these patients.

The results of long-term laboratory tests of the members of the Control Group also revealed some interesting points. Thus, noting the tendency of the results of laboratory tests to be high in the initial examinations, in the long run, 4 out of 16 people developed peritonitis, 3 - destructive appendicitis and 3 - destructive cholecystitis and they underwent surgery.

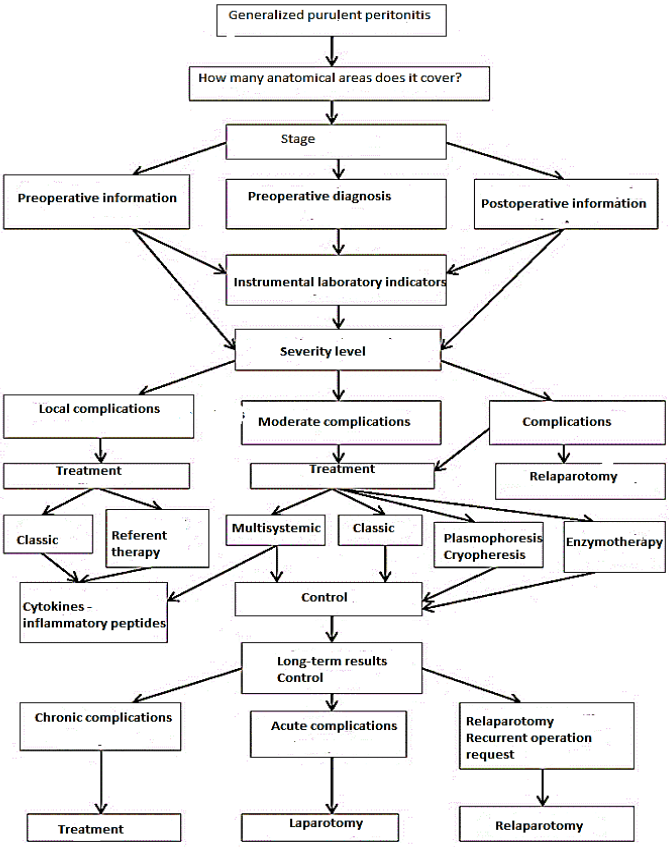


Figure 1. Table of prognostic and therapeutic algorithms of generalized purulent peritonitis.

Thus, the comprehensive treatment of patients with generalized purulent peritonitis allows to obtain good and desirable results and it is the evidence of solution of the problem on a pathogenetic basis proved by the mentioned laboratory examinations.

CONCLUSIONS

1. Endogenous antimicrobial peptides and some cytokines play an important role in the pathogenesis of generalized purulent peritonitis and are considered adequate indicators for optimal evaluation of treatment outcomes. Representatives of antimicrobial peptides in the blood serum of patients comprising III group treatment - lactoferrin, endotoxin, BPI decreased by 2.3 times, 2.7 times and 2.9 times (p_w <0,001) respectively, while IL-2, IL-6 and IL-8 TNF-α decreased 3.4 times, 2.5 times, 2.2 times, and 4.2 times, (p_w <0,001) respectively compared to Group I. It proved the adequacy of the treatment [1,2,3,4,7,9,10,11,12].

2. In the case of generalized purulent peritonitis, the maintenance of a naso-enteral probe for the purpose of decompression, enteral nutrition and enzymotherapy is added to the surgical protocol. Patient included n Group III was confirmed to have a good postoperative period based on results of analyzes [5,6].

3. Basic treatment of generalized purulent peritonitis is guaranteed when combined with efferent therapy and enzymotherapy. Clinical improvement and early recovery occurs in patients of Group III included in the research [4,5,7,13].

4. Adequate diagnosis, prognosis and optimization of treatment of generalized purulent peritonitis can be achieved only if carried out according to the algorithm program [6,14,15].

5. It was proved that development of various complications even requiring relaparathomy was observed in the early postoperative period in 18.8% patients and in the long-term period in 43.4% patients during postoperative follow-up and 58.6% were found to be in patients receiving classical treatment. This provides a basis for the regular medical check-up of these patients in the postoperative period [8].

PRACTICAL RECOMMENDATIONS

1. In order to predict the development and complications of generalized purulent peritonitis, it is recommended to determine the indicators of LPO reactions reflecting the level of endogenous intoxication, medium molecular weight peptides, proteolytic activity, AMP and inflammatory cytokines in acute pathologies of the abdominal organs.

2. With generalized purulent peritonitis, drainage of the gastrointestinal tract is one of the important conditions for the timely restoration of immunodeficiency, multiple organ failure and homeostasis in general.

3. It is recommended to study and select the effective treatment of generalized purulent peritonitis in accordance to the developed algorithmic scheme.

4. Persistent treatment of generalized purulent peritonitis can be achieved through a combination of efferent and enzyme therapy.

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List of abbreviations

AMP	– antimicrobial peptides
BPİ	– bacterial permeability increasing peptide
DC	– dien conjugated
IL	– Interleukin
LPO	– lipid peroxidation
MDA	– malondialdehyde
MMP	– median molecular weight peptide
PA	– proteolitic activity
TNF-α	– Tumor necrosis factor

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