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Research Article

Current Trends in Intensive Therapy of Peritonitis and Abdominal Sepsis

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Abstract

Introduction: Peritonitis is the most frequent complication of surgical emergencies of the abdominal organs and their injuries. This pathology is the cause of death in about 60% of cases of surgical emergencies. The course of this pathology depends on the nature and duration of the disease, the responsiveness of the macroorganism, and methods of treatment. Usually, several microorganisms act as an etiological factor. Urgent surgical treatment in order to eliminate the source of infection using the concept of damage control surgery, early adequate antibiotic therapy, the use of fluid resuscitation, inotropic and vasopressor support, efferent methods of therapy can minimize the development of complications and further progression of the disease with the implementation of the pattern of sepsis and septic shock, and save the lives of patients [32,33].

Materials and Methods: Literature sources of the PubMed database under the tags of 'peritonitis', 'sepsis', 'destructive pancreatitis' over the past 10 years were analysed.

Conclusion: Peritonitis and abdominal sepsis associated with its progression, despite the pluricausal structure of the pathology, require unified treatment approaches. Early sanitation of the pocket of infection, maintaining microcirculation at the proper level, the use of the principles of damage control surgery, and the early adequate prescription of antibiotic therapy with the creation of an appropriate concentration of drugs in the pocket is the key to success in the treatment of this category of patients.

Keywords: Peritonitis; Abdominal Sepsis; Septic Shock; Resuscitation

Introduction

Peritonitis, as an acute inflammation of the peritoneum, is the cause of abdominal sepsis, multiple organ failure, and mortality in a significant number of urgent surgical patients. Traditionally, there are primary, secondary, and tertiary peritonitis and four phases of its course: reactive, toxic, terminal phases, or, in case of a favourable course, recovery. The main method of treatment is surgical interference, the success of which depends on the phase of the disease and the degree of compensation of the patient's vital functions. The rapid progression of sepsis, septic shock, and multiple organ failure in peritonitis are associated with the peculiarities of the structure and functioning of the peritoneum, which will be highlighted below.

Materials and Methods

The peritoneum is a serous membrane with an area of up to 1.8 sq m, of which about 1 sq m is functionally active, with possible minor variations, containing about 50-100 ml of fluid, composed of 30 g/l of protein, 300 cells/ml of immune cells, about 44% of which are lymphocytes, about 50% are macrophages, and 2% are dendritic cells, eosinophils, complement, etc. This fluid is secreted by the serous membrane of the peritoneum and reabsorbed by the lymphatic system of the diaphragm through the lymphatic lacunae of the mesothelium and subsequently drained into the mediastinal lymphatic vessels containing valves that prevent the backflow of lymph. Normally, the peritoneal cavity does not contain bacteria. From 1 to 3 litres of lymph is drained daily from the abdominal cavity due to the movements of the diaphragm, negative intrathoracic pressure, and positive intra-abdominal pressure. This mechanism makes it possible to understand the rapid manifestation of systemic manifestations in peritonitis and the rapid spread of drugs, in particular antibiotics, administered intraperitoneally. Instead, intravenous administration of antibiotics promotes their rapid entry into the peritoneal cavity. Another mechanism of clearance is phagocytosis involving peritoneal macrophages. The functional area of absorption of the peritoneum is about 50% of the total one, electrolytes, proteins, and other substances pass through it freely, but the reabsorption ability is sharply reduced in the presence of adverse factors such as intra-abdominal hypertension, hypovolaemia, shock, dehydration, high pressure in the portal system, lymphatic block, and induration of the peritoneum itself. It should be noted that the 0.9% sodium chloride solution administered intraperitoneally is absorbed at a rate of 30-35 ml/h, and the hypertonic solution on the contrary has a dehydration effect on the intravascular space, mobilizing up to 300-500 ml of fluid into the peritoneal cavity. Similarly, fluid distribution occurs in peritonitis, when increased permeability of the membranes due to the action of bacterial toxins and cytokines causes redistribution of fluid into the abdominal cavity, which can cause hypovolaemia [8].

The main pathogenetic links of peritonitis are the development of an acute bacterial inflammatory process in a sterile environment with the clearance of biologically active substances and toxins into the lymphatic system and rapid generalization of the process, sympathetic activation with reduction of intestinal peristalsis, a blood shunt from splanchnic circulation with the development of hypovolaemia, uncontrolled bacterial growth in the intestine with subsequent translocation and bacteraemia, fluid sequestration into the peritoneal cavity and the development of abdominal compartment syndrome with a subsequent decrease in cardiac output and cytokine depression of myocardial function [10,48]. In the case of a full-scale picture of peritonitis as a manifestation of abdominal sepsis, in response to microbial aggression, the patient's body generates so-called pathogen-associated molecular patterns (PAMPs) that activate TLRs receptors of immune cells, which are ultimately responsible for the release of biologically active substances, the negative effects of which are realized at the organ level. Taking into account the above, in the presence of peritonitis in the inflammatory fluid, increased levels of interleukins 6, 8, 1-beta, tumour-necrotic factor, etc. can be determined. This biological cascade realizes itself at the organ level as formation of multi-organ failure syndrome, where the target organs for the first strike are the lungs with the development of acute respiratory distress syndrome and the kidneys with the development of acute renal dysfunction/failure. Along with the actual microbial aggression and the effects of cytokines at the tissue level, dysregulatory changes in immune reactions occur, microbial translocation and capillary leak syndrome develop with the formation of a false circle due to the deepening of ischemia-hypoxia at the level of the microcirculatory bloodstream [45,50]. Genetic defects in immunity and a distorted reaction of the macroorganism to an infectious agent complement the pattern of the development of multiple organ dysfunction syndrome [2].

The main goal of treatment of patients with peritonitis is the localization of the focus and its elimination [14,27]. The main directions of intensive care are the maintenance of an optimal level of volaemia, efforts aimed at combating microcirculatory disorders [8], creating an adequate therapeutic concentration of antibiotic in the peritoneum, combating septic shock, microbial translocation and multiple organ failure, abdominal compartment syndrome and intra-abdominal hypertension [44].

The concept of damage control surgery, used at the present stage, involves urgent surgical interventions with control of the source of infection and further expansion of operational tactics after stabilization of the patient [3]. The use of this tactic can

reduce mortality and reduce the number of cases of organ failure [4,7]. This concept, initially used in patients with polytrauma, in combination with the prevention and aggressive treatment of acidosis, hypothermia, and coagulopathy, allowed to achieve significant positive results and increase the survival of patients. The use of intensive abdominal lavage after the elimination of the foci of peritonitis, fluid accumulations, necrosequestrectomy, along with surgical strategies of 'relaparotomy as needed' and 'open abdomen', in particular in combination with the use of negative pressure, improves the consequences for patients with peritonitis [23]. The concept of second look operation in the first 36-48 hours in order to re-evaluate the inflammatory process of the peritoneum, sanitation and in the absence of contraindications, final closure of the abdominal cavity proved to be cost-effective and reduced the frequency of intestinal fistulas and postoperative abdominal wall hernia. 'Open abdomen' is effectively used in the presence of an insufficiently sanitized foci of peritoneal infection, for the prevention and treatment of abdominal compartment syndrome, and for controlling the content of the abdominal cavity. Negative effects of the strategy can be significant fluid losses, electrolyte disturbances, and intestinal fistulas. The COOL study proved the advantages of using devices that create negative pressure in the abdominal cavity in combination with the 'open abdomen' strategy, but the cluster of patients in whom this strategy will have advantages has not yet been definitively determined [23].

It should be noted that the inability to achieve control of the source of infection and inadequate antibiotic therapy are independent predictors of mortality; other factors affecting the prognosis are: acidosis with base deficit (BD), signs of coagulopathy, early development of abdominal compartment syndrome, high APACHE II score 24 hours after admission, respiratory distress syndrome. Thus, the risk of coagulopathy is ultra-high in patients who initially present acidosis with a pH less than 7.1, hypothermia less than 34 degrees C, a decrease in systolic blood pressure at admission to 70 mm Hg. According to PIPAS study, patients of over 80 years of age, with malignant neoplasms, acute cardiovascular diseases, and renal pathology have a worse prognosis. Obesity, high triglyceride levels, etiology, early surgical interventions are indicated as unfavourable predictors in acute destructive pancreatitis [24]. The use of the NEWS predictive scale correlates better with 10- and 30-day mortality than the previously proposed SIRS and qSOFA scales [5].

Empirical antibiotic therapy along with surgical sanitation of the focus, prescribed taking into account the source of peritonitis, is one of the main therapeutic options [26]. The use of antibiotic therapy parenterally in the first two hours after the induction of experimental peritonitis, combined with irrigation of the peritoneal cavity using an antibiotic solution, has proven to be effective with a significant effect on mortality in an experimental animal model. Taking into account local epidemiology, individual risk factors for multidrug-resistant flora and clinical severity of the process forms the basis for prescribing antibacterial therapy in cases of severe intra-abdominal infections, and it is especially necessary to note that delaying its onset for more than 3-6 hours significantly increases mortality. Short courses of antibiotic therapy against the background of adequate sanitation of the source of infection have proved their superiority and comparable results of treatment with the continued prescription of antibiotics [28]. Reassessment of the antibiotic therapy regimen after 48-72 hours, taking into account the results of microbiological examination of the abdominal cavity content and the use of de-escalation tactics, leads to effective sanitation of the abdominal cavity [39]. A special cohort of patients is those who have an individual risk of polyresistant flora, are immunocompromised, and require the prescription of a combination of antibiotics and the use of reserve drugs [36,40]. The basis of empiric antibacterial therapy of severe intra-abdominal infections is drugs with activity against aerobic gram-negative bacteria, aerobic streptococci, and strict anaerobes using antifungal drugs in case of risk of candida infection, where the most important factors are the dependence of patients on medical care facilities (dialysis, polychemotherapy), stay in the Anaesthesiology and Intensive Therapy Department, transplantation, decompensated pulmonary and hepatic pathology and frequent previous use of antibacterial drugs [40]. Particular attention is currently focused on ESCAPE microorganisms, carbapenemase producers and ESBL producers, where risk factors for infection are hospitalization for 48 hours in the previous 90 days, the use of broad-spectrum antibiotics for 5 days in the last 90 days, and colonization of ESBL within 90 days. The solution to the problem lies in the use of piperacillin-tazobactam, aztreonam, colistin, protected cephalosporins of the third generation (cefoperazone-sulbactam), tigecycline against the background of restrictions on the use of carbapenems and changes in antibiotic therapy regimens, taking into account the clearance and peak drug

concentration [1,11,35]. Taking into account the above, in 2017, the Global Alliance for Infections in Surgery developed 16 principles for the rational use of antibiotic therapy in case of surgical infections [15,41]. Alternative routes of antibiotic therapy have proven to be effective in the experiment, in particular, regional retroperitoneal lymphotropic administration of ceftriaxone created effective concentrations of the drug during the day [42].

One of the most important issues is still adequate fluid therapy, i.e. infusion therapy, which aims at adequate oxygen delivery to tissues and should be carried out in terms of monitoring haemodynamics, capillary leaks, and cumulative hydrobalance [6]. A combination of infusion fluids and vasopressors is used in the context of the problem, but the situation may be complicated by impaired utilization of oxygen by tissues, especially in the event of a delay in their use [12]. In the latest recommendations on intensive therapy of sepsis, the initial administration of 30 ml/kg of crystalloid solution in the first three hours has a weak strength of evidence and low quality of evidence, that is, the personalization of therapy with a re-evaluation of hydrobalance comes to the fore, combined with advanced monitoring and the use of dynamic parameters of blood circulation, which also allows dividing patients into 'responders' and 'nonresponders' [14]. These tests may include a leg raise test, a minivolemic load test, a positive end-expiratory pressure test, pulse pressure variability, etc. Despite the availability and relative uncomplicatedness of tests demonstrating an increase in cardiac output or its absence, this effect is not always necessary and can be short-lived. It should be noted that the use of volemic load in patients who are 'responders' is associated with clinical signs of improved organ perfusion, although there is currently no single marker that could unequivocally indicate the state of tissue perfusion, which requires multimodal evaluation.

Lactate as a marker of tissue hypoxia is quite unreliable, and its levels also depend on hypercatecholamineemia, liver dysfunction or insufficiency and, if inadequately assessed, can cause fluid overload [30]. However, such an isolated indicator as hyperlactataemia initiated by the development of hypoxia cannot serve as a marker of persistent hypoxia. One of the proposed new biomarkers that can stratify the prognosis in sepsis and septic shock with organ failure is considered to be pro-adrenomedullin [37] and a natriuretic peptide, which can also serve as a marker for adequate volemic resuscitation, although its isolated assessment is questioned and needs to be included in comprehensive examinations [31].

Instead, capillary refill time compared to lactate level examination shows a better correlation with mortality and organ dysfunction. In contrast, the capillary refill test in the ANDROMEDA SHOCK study [17] proved to be as effective as the lactate concentration [30]. Also, significant limitations of infusion therapy are necessary if the patient has intra-abdominal hypertension and abdominal compartment syndrome [16], as a result of the development of which there are changes in the functioning of the cardiovascular system already at pressure levels of 10-15 mm Hg in the form of a decrease in preload, cardiac output, and stroke volume, an increase in afterload, an increase in systemic vascular and pulmonary vascular resistance. With the development of ACS in the early period, impoverishment of the blood flow of the intestinal wall, a decrease in the level of diuresis, and the transition of metabolism to the anaerobic pathway develop, which is proved in experimental models.

It is also recommended to maintain the average blood pressure at 65 mm Hg, which is a strong recommendation with a moderate level of evidence, with which, however, some experts disagree indicating the need for dynamic assessments, namely, taking samples with an increase in blood pressure [44]. Infusion therapy in the early stages of peritonitis is liberal in nature and is characterized as massive [6]. A strong recommendation is also the use of crystalloids as first-line drugs in the resuscitation of liquids, but the recommendation for the use of albumin has medium strength of evidence. Hyperchloraemia and hypernatremia should be avoided, as hyperchloraemia causes decreased cortical blood flow in the kidneys and gastrointestinal mucosa, fluid retention, and hydrobalance changes towards hyperhydration and the development of hyperchloraemic acidosis, and sodium retention causes severe fluid retention and decreased water excretion. As a drug for the correction of oncotic pressure, the use of albumin in the form of a 20% solution is recommended. Other types of colloidal solutions, such as hydroxyethyl starch preparations, are associated with a high incidence of acute kidney damage and increased mortality.

Balanced crystalloids prove to reduce renal damage in critical patients, and albumin solution, although increasing mean blood pressure, showed no effect on mortality compared to crystalloids, although according to SSG recommendations, albumin can be used in patients with sepsis who received large volumes of crystalloids

during resuscitation [44]. Phase shock therapy using the concept of ROSE and timely restriction of infusion therapy in the deescalation phase, as well as the use of hyposmolar solutions to prevent overload with sodium and chlorides introduced into the intestinal lumen against the background of recovery and stimulation of peristalsis significantly reduces the number of organ dysfunction cases, in particular renal dysfunction [49].

They actively try to include sonographic features in the assessment of the patient's volemic status, including the diameter of the inferior vena cava, bedside assessment of the volume of the extravascular lung water, stroke volume, and cardiac output, in particular with the assessment of its fan-induced dynamic variability, which constitute an alternative to more costly and invasive methods, such as pulmonary artery catheterization and PiCCO (Pulse index Continuous Cardiac Output) monitoring. The wider use of sonographic techniques allows for a comprehensive diagnosis of sepsis-induced cardiopathy, which has a correlation with 90-day survival of patients [46].

Creating an adequate concentration of antibiotic in the peritoneum can be difficult with massive infusion therapy, since the pharmacokinetics and pharmacodynamics of antibacterial drugs (currently insufficiently studied) change [38]. The reasons are a change in the volume of distribution due to capillary leak syndrome, hyperdynamic circulatory reaction, and massive infusion therapy itself. The phenomenon of enhanced clearance and hypoalbuminemia are also important [47]. These negative effects can be prevented by changing the dose of the drug, the use of prolonged infusion, as well as the method of administration, in particular endolymphatic administration of drugs [25].

The positive effect of hemoperfusion using polymyxin B is noted in the experimental model of peritonitis [13,43], as well as the positive effect on the intestinal microcirculation and histological changes in the intestinal wall in the animal model of intestinal sepsis in pigs. There are also numerous reports of effective reductions in circulating interleukins and endotoxins in the case of Gram-negative sepsis due to the use of the said technology and increased survival in patients with septic shock [18,34]. Similar effects were found in the human population in the study of sublingual microcirculation, but without affecting the consequences [9]. Thus, for use in the human population, despite the beneficial immunological effects, such interventions are not currently recommended. Recently, interest has been renewed in the use of hemosorption technologies—hemoperfusion [29] with a positive clinical effect and the absence of complications and hemocoagulation disorders [19].

The study of biological markers in sepsis aims to prove the infectious nature of the disease, to establish the degree of compensation and the type of reaction of the macroorganism to the infectious agent, to promote the timely prescription and rotation of antibiotic therapy and to establish the degree of microcirculatory disorders. It is the microcirculation, the reactivity of which is the cause of hypoperfusion and organ dysfunction, that has been increasingly attracting attention with an emphasis on the markers of its damage, in particular the lipid peroxidation products, ischemia-inducible factor, tumour necrosis factor alpha, etc., interleukin-6, monocyte chemoattractant protein-1, genetic polymorphism. The successfully used term 'microcirculatory shock' is characterized by evident tissue hypoperfusion despite the normalization of systemic and regional blood flow [20]. Given the disorders in the microcirculation and their contribution to the development and regression of organ failure, finding markers indicating the state of the microcirculation looks promising. Thus, HIF-1 (hypoxia inducible factor), consisting of two subunits and belonging to the basic family of transcription factors, has proved its predictive capability in cardiovascular diseases, non-specific lung diseases, oncological pathology, and acute respiratory distress syndrome. This molecule consists of alpha and beta subunits and interacts with DNA during the development of hypoxia, which contributes to the expression of about 100 genes involved in adaptation to hypoxia, expression of vascular endothelial growth factor (VEGF), erythropoietin (EPO), and glycolytic enzymes. The role of the factor in cerebral ischaemia and cerebral ischaemic preconditioning is described, in particular, an increase in the resistance of CA1 pyramidal neurons to lethal ischaemia. This factor is also involved in the adaptive regulation of the response to hypoxia in kidney diseases, in particular acute renal failure, diabetic nephropathy, and kidney cancer [21].

Anaesthetic tactics acquire certain features, due to the common presence of hypovolemia in the patient, reduced respiratory and

cardiovascular reserves, compromised renal blood flow, abdominal compartment syndrome, and liver failure with possible changes in the metabolism of drugs [32].

Conclusion

Peritonitis and abdominal sepsis associated with its progression, despite the pluricausal structure of the pathology, require unified treatment approaches. Early sanitation of the pocket of infection, maintaining microcirculation at the proper level, the use of the principles of damage control surgery, and the early adequate prescription of antibiotic therapy with the creation of an appropriate concentration of drugs in the pocket is the key to success in the treatment of this category of patients.

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