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**PATHOGENESIS AND TREATMENT OF PERITONITIS**

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**Abstract.** Peritonitis remains an unsolved problem in modern surgery up till now. A great number of techniques that may improve the results of treatment of this pathology have been elaborated up till now. A clear-cut notion about the

principal aspects of peritonitis pathogenesis will help to choose a maximal effective combination of these techniques and improve the results of treatment of this terrible complication.

**Key words:** peritonitis, pathogenesis, treatment.

In spite of decades of painstaking work, the problem of treating peritonitis remains topical up till now.

The complexity of pathogenesis and a large-scale character of changes in the organism do not still make it possible to raise the efficacy of treatment in case of this particular pathology [23, 33]. Lethality in case of wide-spread forms of acute peritonitis makes up 40-85% [14, 15].

The object of this bibliographical review was to remind of the principle components of the pathogenesis of peritonitis once again, to acquaint a reader with new treatment modes of this pathology which have been elaborated over the last 10 years.

**Pathogenesis of acute peritonitis**

Peritonitis, irrespective of the causes that have given rise to it, is a bacterial inflammation.

A conventional definition is pertinent, while setting forth the pathogenesis of peritonitis of four aspects which are closely correlated:

- 1) Mechanisms of isolating the pathological process in the peritoneal cavity;
- 2) Immunogenesis in peritonitis;
- 3) Pathogenesis of visceral dysfunctions;
- 4) Endotoxicosis in peritonitis;

Each of these aspects is a manifestation of a single trigger mechanism – the mechanism of a universal inflammatory reaction of every living thing to a damaging action (mechanical, chemical, thermal), including the action of pathogenic microbes.

The following phases should be singled out in an inflammatory response:

1. Alteration: a) primary, b) secondary;
2. Exudation: a) vascular responses, b) fluid extravasation, c) margination of leukocytes, d) emigration of leukocytes, e) extravascular responses (chemotaxis, phagocytosis);
3. Proliferation (regeneration, reparation) [24].

Primary alteration arises in response to a direct action of a damaging factor and reactions of primary alteration, with the participation of inflammatory mediators [26] – histamine, serotonin, plasmatic, and tissular kinins, prostaglandins, leukotriens, lysosomal enzymes, anaphylatoxins [18].

The following picture will be able to illustrate the second phase of inflammation – the phase of exudation: during the first three 24 – hour periods peritoneal inflammation is of a serofibrinous nature. On a microscopic

examination the peritoneum is stratified and thickened at the expense of an edema. The minute arteries and arterioles of the tela subserosa are olegimic, their walls are thickened due to plasmatic transudation. The venous vessels are dilated and plethoric. A moderate infiltration with lymphocytes and neutrophilic granulocytes, as well as slight depositions of fibrin are observed. In case of electron microscopy a swelling and partial desquamation of mesotheliocytes, enlarged intercellular spaces are seen. Typical solitary thickened microvilli, depositions of leukocytes and fibrin filaments are typical for preserved mesotheliocytes. In 5 -10 days peritonitis definitively assumes a fibrinopurulent or purulent character (leukocyte migration). In case of a histologic study the abdomen is considerably thickened, fibrinous or fibrinopurulent exudate with a predominant majority of neutrophilic granulocytes and lymphocytes, tiny abscesses and foci of necrosis stasis, fibrin and mixed thrombi are observed in the vessels. In case of electron microscopy mesotheliocytes are detected only on isolated sites in the form of swollen vacuolated cells with broad intercellular spaces and missing microvilli [33]. The phase of proliferation will look like this: the tela subserosa peritonei with signs of marked fibrosis. Subsequently there occurs an organization of exudate with the formation of adhesions among the intestinal loops and the development of encysted abscesses.

**Immune factors**

As is generally known, the intensity of a local inflammatory reaction in the zone of infection depends primarily on the concentration of the tumor necrosis factor (TNF) – the product of the phagocytic activity of macrophages. TNF stimulates the release of interleukins (IL – 1, IL – 6, IL – 8 and others). IL-1 is conducive to the formation of T-helpers which provide the proliferation of T-lymphocytes, IL-2 secretion and also enhance the formation of TNF- $\lambda$  which induces an accessory activation of macrophages.

**Enteral insufficiency in peritonitis**

In a complex of visceral abnormalities stipulated by the prevalence of peritonitis enteral insufficiency stands out separately because it serves as one of the releasers of endotoxicosis. All other disturbances are mediated by endotoxicosis and may be regarded as its manifestations.

Enteral insufficiency embraces: disturbances of the peristaltic function of the intestine, disturbances of the microbial ecosystem disorders of the processes of absorption and reabsorption, barrier dysfunctions.

The sequence of events in progressive peritonitis may be presented in the following way. At the beginning under the influence of an inflammation of the parietal and, particularly, of the visceral peritoneum the ability of the intestine to "alimentary" peristalsis is inhibited reflexively and that is regulated by the central and neuroendocrine mechanisms. The functions of the pacemaker of autonomic metasympathetic nervous system of the intestine is preserved at that but the MMC induction (the migrating myoelectric complex) is inhibited. However, in case of a natural development of the pathological process, a parietic dilatation of the intestinal loops and their repletion with the contents results in ischemia of the intestinal wall and hypoxic damage of its intramural metamural metasympathetic nervous apparatus.

Under the conditions of intestinal paresis that has developed another mechanism of the development of endotoxiosis joins in. The intrainestinal microbiological ecosystem is disturbed. In the process solitary microorganisms, migrating to the upper portions of the small intestine perish in the hypoxic setting there under the action of the digestive enzymes, releasing endo-, and exotoxins [35, 40].

Products of incomplete protein hydrolysis are accumulated in the intestinal lumen, leading to a decay process. In case of intestinal dysfunction there arises an increased pool of ammonia from which endogenous nitrates and nitrites are synthesized under the action of nitrate reductases. Nitrate reductases are produced by the colon bacillus, Klebsiella, Proteus, blue pus bacillus etc.

Enteral insufficiency spreads to the secretory-resorptive function, disturbing a correlation of these processes. Under parietic conditions hypoxia of the intestinal wall results in a disturbance of active reabsorption. Hence, a repletion of the intestinal loops with liquid contents. Apart from this, another digestive function of the intestinal wall is disturbed due to the same cause – the barrier one, ensuring a selective possibility of the penetration of products of the parietal digestion through the intestinal wall [35].

#### Endogenous intoxication in peritonitis

In case of generalized (diffuse) peritonitis the following phenomena serve as a source of endotoxiosis: a) a focus of traumatic or infectious – inflammatory destruction in the organs of the peritoneal cavity; b) the contents of the peritoneal cavity that interact with a highly resorptive and highly reactive peritoneal field; c) the contents of the intestine with biochemical and bacterial factors.

At the incipient stage destructive processes in the organs are of a local nature and stipulate only reactive changes in the peritoneum and the organism as a whole. In the process of involving the peritoneum in an infectious process the situation drastically changes: first of all, there occurs an enhanced resorption of derivatives of the destruction of purulent exudation – mesothelial dysfunction. An increase of the size of the stomata of the mesothelial cells of the peritoneum 2-6 times is typical, as a result bilateral passive permeability of the mesothelial barrier is enhanced. Due to enhanced permeability a very rapid permeation of the abdominal contents into the blood and lymph is observed [33].

A reactive disorder of the intestinal motility at the incipient stage gradually transforms into profound paresis that is accompanied with ischemia of the intestinal wall. As a result, both sources – the peritoneal cavity with purulent contents and the contents of the parietically dilated intestine, supplementing and intensifying each other, lead to a culmination of endotoxiosis, reaching the level of the systemic tissular metabolism. Now there is every reason to speak of real multiple organ failure whose basis is made up of deep systemic metabolic disorders at the cellular and tissular levels [35].

The process of toxicosis is closely connected with lipid peroxidation (LPO) [13, 34]. A particular role in the onset of endotoxiosis is played by the products of lipid peroxidation which exert a damaging effect on the cell membrane and cellular organelles whose breakdown derivatives possess cytotoxic properties. Normal functioning of the systems and organs under the conditions of deranged oxygen metabolism is possible due to the activity of the antioxidant system which is made up of substances that inhibit free radical processes.

#### Treatment of peritonitis

The whole complex of treatment measures in peritonitis may be divided into those which are undertaken prior to an operation (preoperative preparation), during an operation and during the postoperative period.

Preoperative preparation embraces: an elimination of cellular dehydration, a normalization of the volume of circulating plasma (VCP), a restoration of ion-electrolyte, acid - base, colloid-osmotic balances, an elimination of tissular hypoxia, the use of the detoxication therapy, antibiotic therapy [6]. The whole complex of preoperative therapy must last no longer than 1.5 – 2 hours [35].

The following actions are performed in the process of a surgical intervention: the source of peritonitis is eliminated, intraoperative sanitation and rational drainage of the abdominal cavity are performed, the intestine, being in the state of paresis, is intubated and drained, conditions for a prolonged sanitation of the peritoneal cavity during the postoperative period are created [8, 35, 44], a maximally rapid recovery of intestinal peristalsis is provided.

During the postoperative period enteral-probing therapy, wholesome alimentation of the organism and rational antibioticotherapy are provided.

#### Elimination of the causes of peritonitis

In order to eliminate the sources of infection the most rapid and simple method of surgical interference is used.

#### Sanitation of the peritoneal cavity

Apart from already known techniques of this particular procedure, new, no less interesting and promising ones are been elaborated.

The application of ozonized solutions. The application of ozonized solutions applied locally possess pronounced bactericidal, immunomodulatory, anti-inflammatory, virological, fungicidal, cytostatic, analgesic properties [27, 35].

The application of local and systemic regional intraabdominal endolymphatic ozonotherapy exerts a stimulating effect on the intestinal peristalsis and

accelerates a normalization of the processes of endogenous intoxication [27, 35, 36]

Photomodified lavage [32] is based on biologically determined staining of microorganisms with one of the stains directly from a nidus of infection with further radiation of the nidus of infection by monochromatic radiation that coincides in frequency with the absorption spectrum of the stain. As a result of an activation of the stain absorbed by a microorganism, there occurs an activation of active forms of oxygen that possess a membranotoxic effect, as a result of this, there occurs an elimination of a microorganism.

The application of laparoscopic sanations of the peritoneal cavity in peritonitis decreases the rate of pyoinflammatory complications of postoperative wounds, it is more effective in comparison with ordinary procedures of peritoneal cavity sanitation (upon achieving an appropriate level by an operating surgeon). Taking into account promising prospects of laparoscopic technologies, and the cavity of their enlistment under the conditions of domestic medicine, this particular technique becomes still more interesting [14, 39, 43].

#### **Intubation of the intestine**

Intubation of the intestine is an important component of treating peritonitis and dynamic ileus [24]. Marked dystrophic disturbances, necrobiotic, infiltrative processes, hemodynamic disorders and disturbances of the processes of absorption [25], marked intoxication and a great likelihood of the development of a complicated adhesive process necessitates the use of an intestinal tube.

Intestinal intubation performs the following functions [5]: a) decompression – detoxication function; b) prophylactic; c) supporting.

The duration of using a tube depends on the function it performs. Thus, the duration of using a tube for the decompressing – detoxicating function makes up  $4.8 \pm 1.0$  days, and the supporting function -  $6.0 \pm 1.4$  [3].

Intestinal decompression may be effectively performed with Miller-Abbot's tube. But the latest models of nasointestinal tubes [5, 21, 7] are developed permanently and are enlisted to practical activities.

Enteral – probing therapy performs the detoxicating function, in the first place. The standard procedure includes [7] intestinal lavage (a physiological solution) and enterosorption (2-4% NaCl solution and 10% enterogel solution [5, 7].

A mixture for a combined action contains a 2-4% solution of sodium chloride and 10g of enterogel in a 100 ml solution. The mixture obtained in a volume of 600 – 800 ml is introduced through a tube into the small intestinal lumen and is retained there for a certain period of time. Then, in some time, the content of the intestine is removed and fractional lavage is performed with an isotonic sodium chloride solution [2].

Intestinal lavage may be performed: a) by means of “mild” solutions of antiseptics. Thus, the use of the “Dioxysol - Darnytsa” antiseptic in a dilution 1:50 made

it possible to reduce essentially the number of pathological microorganisms in all the segments of the intestine [25]; b) by means of various ozonized solutions [21, 17] – the method of parieto – cavital sanitation of the intestine [21] enables to use ozonized solutions, employing highly dispersive flows, insuring an essential level of contact of the ozonized solution with the intestinal wall; c) a combination of drugs – a saline of sodium chloride, nitrofurazone solution, 4% solution of sodium hydrogen carbonate, ozonized (an ozon concentration – 4 mg/ml water (an overall volume – 0.5 - 1.5l)). Afterwards a 15 % mixture of enterodez or polyhepan in 400 ml of 5% glucose was used with 1 hour exposure. Aspiration of the intestinal contents was carried out afterwards [17].

One of the methods, enabling to raise the efficacy and expand indications for nasointestinal drainage is the use of programmed intestinal decompression [21].

#### **Recovery of intestinal peristalsis**

On recovering small intestinal peristalsis a decrease of the intensity of intoxication syndrome is observed. A proposed multidrug regimen of a combined use of  $\lambda$ -tocopherol acetate, essential phospholipids, ATP, calcium preparations and pneumomassage of the organs of the digestive tract has made it possible to improve the results of treating patients with peritonitis [1].

The use of constant electric current of low density in stimulating the intestinal activity is pathophysiologically substantiated. A static electric field creates conditions for contracting of the smooth musculature, due to which the intestinal function is stimulated [11, 4].

#### **Early enteral tube feeding**

The use of early enteral tube feeding is feasible in the majority (86.1%) of the patients with diffuse purulent peritonitis, 12-24 hours following an operative interference. It starts with glucose – saline solutions with further switch-over to the simplest nutritional mixtures. Probiotics are used for the purpose of correcting dysbiotic disorders, while using non-enzymatic formulae, enzymes are added [8].

The use of benzonal as an inductor of the monooxygenase system of the liver in the postoperative period in a dose of 0,1g per os. 3 times a day during 6 circadian periods, normalizes the  $\lambda$ -PO [34, 38] processes and the functioning of the antioxidant system (AOS) [31, 19].

Positive results have been obtained, when using glutamine [43] (this amino acid occupies a leading position in the metabolism of the small intestine) and pectin (a prebiotic, contributing to an elevation of the content of DNA and RNA of enterocytes). The medications are used since the first 24-hours period of the postoperative period [25, 28].

#### **Antibiotic therapy**

Up to the present moment the most substantiated procedure is the technique of empirical mono- or combined antibiotic therapy in a diescalation regimen. The diescalation regimen of therapy envisages a broad starting spectrum of antibiotics (to exert an effect on the entire

foreseen spectrum of microorganisms), and a subsequent (in 24-32 hours) switch-over to a course of therapy of a narrowed spectrum on the basis of a microbiological examination for the purpose of a maximum effective influence upon one or several causative agents) [19, 37].

The preparation of choice in case of initial therapy of severe forms of peritonitis is "Ertapenem". The medication is effective in relation to the microorganisms of the Enteriobacteriaceae species, including those which produce  $\beta$ -lactamases of an enlarged spectrum, methicillin-sensitive staphylococcus aureus, coagulase-negative staphylococci, streptococci, polyresistant pneumococci. In case of the absence of an opportunity of using preparations of this particular group not bad results are achieved as a result of using cefoperazone sulbactam and a combination of cefataxim and metronidazole [41].

On obtaining the results of a microbiological examination and antibioticograms in 24-32 hours after starting antibiotic therapy purposeful antibiotic therapy is used. Its strategy depends on the results of a microbiological examination [3, 19].

Antibiotic therapy must take into account not only the characteristics of microorganisms, but also ways of their translocation. And this means that it is necessary to create high concentrations of antibiotics in the systems of the portal veins and the vena cava, as well as in the parietal and visceral components of the lymphatic system [14, 15].

Thus, the knowledge and understanding the processes of the pathogenesis of acute peritonitis and paralytic intestinal obstruction, resulting from it, are necessary for a right choice of a policy and strategy of treatment of this complication.

Up-to-date modalities of treating peritonitis are constantly being elaborated and they may essentially raise the chances of a patient and a doctor to gain a victory in the struggle with this disease.

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## ПАТОГЕНЕЗ ТА ЛІКУВАННЯ ПЕРИТОНІТУ

*В.П. Польовий, В.Д. Фундіур, Ю.В. Фундіур*

**Резюме.** Перитоніт залишається й досі не вирішеною проблемою сучасної хірургії. На даний момент розроблена велика кількість методик, що можуть покращити лікування цієї патології. Чітке уявлення про основні аспекти патогенезу перитоніту допоможуть вибрати максимально ефективну комбінацію цих методик, покращити результати лікування даного грізного ускладнення.

**Ключові слова:** перитоніт, патогенез, лікування.

## ПАТОГЕНЕЗ И ЛЕЧЕНИЕ ПЕРИТОНИТА

*В.П. Полевой, В.Д. Фундиур, Ю.В. Фундиур*

**Резюме.** Перитонит все еще остаётся не решенной проблемой современной хирургии. На данный момент разработано огромное количество методик, которые могут улучшить результаты лечения этой патологии. Четкое понимание основных аспектов перитонита поможет выбрать максимально эффективную комбинацию этих методик, улучшить результаты лечения этого грозного осложнения.

**Ключевые слова:** перитонит, патогенез, лечение.

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