MODERN VIEWS ON THE PATHOGENETIC RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATION AND THE IMMUNE SYSTEM WITH A BILE PERITONITIS, COMPLICATED ABDOMINAL SEPSIS

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Abstract: *this review presents the modern views on the pathogenetic link between systemic inflammation and the immune system with a bile peritonitis, complicated abdominal sepsis, which opens up new opportunities for the development of pathogenetic substantiation of methods of correction of cellular and humoral immunity in a variety of pyo-inflammatory and septic complications. In the last decade, works have been published on the universality of the triggering mechanism in the development of peritonitis, based on which the leading role belongs to the syndrome of systemic inflammatory reaction and endogenous intoxication.*
Keywords: *biliary peritonitis, systemic inflammation, abdominal sepsis, immune system.*

СОВРЕМЕННЫЕ ВЗГЛЯДЫ НА ПАТОГЕНЕТИЧЕСКУЮ ВЗАИМОСВЯЗЬ МЕЖДУ СИСТЕМНЫМ ВОСПАЛЕНИЕМ И ИММУННОЙ СИСТЕМОЙ ПРИ ЖЕЛЧНОМ ПЕРИТОНИТЕ, ОСЛОЖНЕННОМ АБДОМИНАЛЬНЫМ СЕПСИСОМ

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Аннотация: *в обзоре представлены современные взгляды на патогенетическую связь между системным воспалением и иммунной системой при желчном перитоните, осложненном абдоминальным сепсисом, что открывает новые возможности для разработки патогенетического обоснования методов коррекции клеточного и гуморального иммунитета при различных гнойно-воспалительных и септических осложнениях. В последнее десятилетие опубликованы работы об универсальности пускового механизма при развитии перитонита, в основе которого ведущая роль принадлежит синдрому системной воспалительной реакции и эндогенной интоксикации.*
Ключевые слова: *желчный перитонит, системное воспаление, абдоминальный сепсис, иммунная система.*

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The modern development of medical technologies in surgery, despite the positive aspects, also has drawbacks, which in the past were not encountered by practical healthcare [1]. According to data published in the periodical literature, more than 2.5 million endoscopic operations on the gallbladder and biliary tract are performed annually in the world, which has a significant effect on the increase in the incidence of iatrogenic complications, one of which is biliary peritonitis [2–4]. Complications during laparoscopic operations were noted 1.5 times more often than during open operations, and biliary peritonitis occurs in up to 0.5% of cases, of which 12.2% is fatal [5, 6].

The problem of biliary peritonitis is becoming especially relevant against the background of the global trend of increasing the number of patients suffering from gallstone disease. Statistical data indicate that all over the

world, gallstone disease affects from 10 to 15% of the population [7]. The results of large-scale epidemic studies of the last two decades have led to the understanding that the real prevalence of gallstone disease in people of the white race in the older age group reaches 30% and is in close correlation with the epidemic growth of other "diseases of civilization" occurring with profound metabolic disorders: atherosclerosis, metabolic syndrome and type 2 diabetes mellitus. At the same time, the widespread introduction of the technique of endoscopic cholecystectomy at the turn of the millennium did not come close to solving this problem as a whole: the frequency of gallstone disease among residents of megacities continues to increase rapidly [8]. Despite the urgency of the presented problem, biliary peritonitis, complicated by abdominal sepsis, continues to remain practically out of the field of vision of researchers, and the few works that take place are narrowly focused, which was the reason for a systematic approach to studying the relationship between systemic inflammation and humoral immunity.

Abdominal sepsis of any etiology is based on a complex of pathophysiological reactions, which is a set of symptoms characterized by metabolic disorders, which leads to endogenous intoxication, disruption of the structural organization of cell membranes and vascular endothelium, coagulation and fibrinolysis, disruption of protective systems, formation of vicious autocatalytic circles with the threat of the development of irreversible morphological changes [12, 16]. The complex of the described changes is a consequence of neuroendocrine and humoral dysregulation in the body in combination with signs of infectious inflammation, immune distress syndrome and multiple organ failure [17, 21]. Against the background of these disorders, the intestine is inevitably involved in the pathological process with the development of intestinal insufficiency, which includes impaired motor, secretory, absorption and barrier functions, which causes changes in the quantity and quality of the intraluminal and parietal microflora, translocation of toxins and microorganisms into the lumen of the abdominal cavity and the portal bed, disruption of the phagocytic activity of Kupffer cells with their subsequent entry into the systemic circulation [22, 26]. As a result of numerous studies, it has been established that among the microorganisms isolated from the gallbladder of patients with cholecystitis and gallstone disease, opportunistic enterobacteriaceae occupy the leading place as a result of functional and structural changes in the intestine [27]. It is well known that five interrelated systems are involved in the defense of the body: endothelial cells, platelets, leukocytes, the coagulation system and the complement system. The most important condition for the functioning of these systems is their purposeful interaction with each other. The systems presented above have a powerful auto-aggressive potential, therefore, it is possible for the development of such situations when the inflammatory process goes beyond the defensive reaction. The cascade of the inflammatory response in peritonitis can be triggered by the release of various mediators: cytokines (tumor necrosis factor α (TNFα, interleukin (IL) -1, IL-6, IL-8, IL-10, etc.), complement (C3a, C5a) , coagulation factors (Hageman factor), kinins (bradykinin), lipid metabolites (prostaglandins, leukotrienes), proteases (elastase, collagenase), toxic oxygen products (superoxides, HO, OH-), nitric oxide (NO), protein or proteolysis [12]. Under the influence of factors such as TNFα and IL-1, endothelial cells lose thrombomodulin and heparin-like molecules [13]. The results of numerous studies indicate that it is cytokines, thrombin, as well as hypoxia that induce the synthesis of TF endothelial cells, which stimulates the synthesis of the plasminogen activator inhibitor (PAI-1) and leads, respectively, to an increase in the procoagulant and decrease in the profibrinolytic properties of the endothelium. [14, 16]. The activated endothelium can localize or promote inflammation. It is believed that the development of the systemic inflammatory response syndrome occurs when the process captures the integrative function of the vascular endothelium [17, 18]. as well as hypoxia are inducers of TF endothelial cell synthesis, which stimulates the synthesis of plasminogen activator inhibitor (PAI-1) and leads, respectively, to an increase in procoagulant and a decrease in profibrinolytic properties of endothelium [14, 16]. The activated endothelium can localize or promote inflammation. It is believed that the development of the systemic inflammatory response syndrome occurs when the process captures the integrative function of the vascular endothelium [17, 18]. as well as hypoxia are inducers of TF endothelial cell synthesis, which stimulates the synthesis of plasminogen activator inhibitor (PAI-1) and leads, respectively, to an increase in procoagulant and a decrease in profibrinolytic properties of endothelium [14, 16]. The activated endothelium can localize or promote inflammation. It is believed that the development of the systemic inflammatory response syndrome occurs when the process captures the integrative function of the vascular endothelium [17, 18].

Stimulation of endothelial cells of proinflammatory endothelial cells, in turn, triggers a whole cascade of reactions, which is preceded by an increase in the transcription of NF-kB molecules and activating protein-1 (AP-1) [29], which is proved by the ability of many natural and synthetic antioxidants block the activation of NF-kB and, accordingly, suppress the stimulating effects of cytokines on endothelial cells [20, 21]. It is believed that the activation of NF-kB depends on the formation of oxygen radicals, while antioxidants maintain NF-kB in an inactive form, and this is the reason for the inhibition of the expression of genes encoding adhesive molecules [22].

Speaking about the role of cytokines in the pathogenesis of peritonitis, it is necessary It is worth dwelling on the significance of growth factors - transforming growth factor β (TGFβ) and platelet growth factor (PDGF), which are released in the early phase of inflammation. These factors are responsible for the formation of matrix

proteins and the migration of fibroblasts, thereby determining the repair processes. The severity of fibrotic changes depends on the size of the formed complexes of matrix proteins and the degree of migration of fibroblasts to the site of injury. The balance between growth factors determines the relationship between the formation and resorption of scar tissue, ie. violation of this balance is the main one in the formation of pronounced adhesions (adhesive process) in the outcome of peritonitis. The complex of the described changes in patients with peritonitis is the basis of the systemic inflammatory response syndrome. Therefore, in relation to patients with peritonitis, it is well known that the physiological mechanism of regulation of the expression of adhesive molecules on the endothelium of blood vessels is the production of nitroxide radical NO by these cells, which blocks cytokinin-induced expression of adhesive molecules through the NF-kB mechanism. In particular, it was shown that NO significantly increases the expression of I-kBa, a cytosolic inhibitor of NF-kB [53]. This effect of NO leads to a decrease in the number of adhesive molecules ICAM-1, E-selectin and P-selectin, as well as the secretion of some cytokines, including IL-6 [24].

Thus, the protective response of endothelial cells to infection by binding agonists such as histamine or thrombin is aimed at maintaining the integrity of the vessel. In this case, one of the most powerful inducers of cytokine synthesis are the components of the bacterial cell wall: lipopolysaccharide, peptidoglycans, muramyldipeptides. The central molecule for triggering the inflammatory response in the development of the systemic inflammatory response syndrome is CD14 - protein mol. 55 kDa, associated with glycosylphosphatidylinositol. For CD14, a universal type receptor is present in monocytes, macrophages, and neutrophils, which captures the primary signals of any damage to a macroorganism, regardless of its etiology [23]. Further intracellular signal transmission occurs due to the activation of associated intracellular signaling cascades, leading to phosphorylation and regulation of the functions of many cellular proteins. The most important median is the main regulator of the inflammatory process, the transcription factor NF-kB, which is a critical point of intersection of a number of signaling pathways, including those leading to the synthesis of pro-inflammatory cytokines [4, 8]. In this case, biogenic amines, activation products of the hemostasis and complement systems, some free radicals, acute phase proteins, proteinase inhibitors, etc. can serve as regulatory mediators of mutual activation [19, 20]. An attribute condition of systemic inflammation as a typical pathological process and its clinical expression - systemic inflammatory response syndrome, are the structural and functional rearrangement of endothelial cells, primarily at the level of postcapillary venules, and the disorder of microcirculatory hemodynamics mediated by this, in which the interests of all organs are affected to one degree or another. It has now been proven that the nature of the development of the systemic inflammatory response syndrome is largely determined by the state of the vascular endothelium [11], which ensures blood fluidity, preventing contact between its elements and subendothelium procoagulants through the expression of various membrane-bound components located on the cell surface (heparin-like molecules, tissue factor (TF) inhibitors, thrombomodulin). Having close contact with blood, endothelial cells are involved in immune processes and processes of activation of the coagulation system. Endothelial cell activation can be induced by cytokines, peroxidation processes, or proteolysis [12]. Under the influence of factors such as TNFα and IL-1, endothelial cells lose thrombomodulin and heparin-like molecules [15]. The results of numerous studies indicate that it is cytokines, thrombin, as well as hypoxia that induce the synthesis of TF endothelial cells, which stimulates the synthesis of the plasminogen activator inhibitor (PAI-1) and leads, accordingly, to an increase in procoagulant and a decrease in profibrinolytic properties of the endothelium [14, 15]. The activated endothelium can localize or promote inflammation. It is believed that the development of systemic inflammatory response syndrome occurs in the event that if the process captures the integrative function of the vascular endothelium. Stimulation of endothelial cells with proinflammatory cytokines entails microvascular thrombosis and microbleeds in various tissues with damage to organ functions (lungs, kidneys, adrenal glands). Cytokines disrupt the fibrinolytic balance of the endothelial surface, shifting it towards coagulation by increasing the expression of PAI-1. In general, the net effect of pro-inflammatory cytokines on endothelial cells inevitably leads to increased coagulation and inhibition of fibrinolysis. Activated endothelial cells, in turn, produce cytokines themselves, which, to one degree or another, are involved in the pathogenesis of the inflammatory response. Activation of cytokine receptors located on the surface of endothelial cells, in turn, triggers a whole cascade of reactions, which is preceded by an increase in the transcription of NF-kB molecules and activating protein-1 (AP-1) [29], which is proved by the ability of many natural and synthetic antioxidants to block the activation of NF-kB and, accordingly, suppress the stimulating effects of cytokines on endothelial cells [20, 21]. It is believed that the activation of NF-kB depends on the formation of oxygen radicals, while antioxidants maintain NF-kB in an inactive form, and this is the reason for the inhibition of the expression of genes encoding adhesive molecules [22]. Speaking about the role of cytokines in the pathogenesis of peritonitis, it is necessary to dwell on the importance of growth factors - transforming growth factor β (TGFβ) and platelet growth factor (PDGF), which are released in the early phase of inflammation. These factors are responsible for the formation of matrix proteins and the migration of fibroblasts, thereby determining the reparation processes. The severity of fibrotic changes depends on the size of the formed complexes of matrix proteins and the degree of migration of fibroblasts to the site of injury. The balance between growth factors determines the relationship between the

formation and resorption of scar tissue, i.e. violation of this balance is the main one in the formation of pronounced adhesions (adhesive process) in the outcome of peritonitis. The complex of the described changes in patients with peritonitis is the basis of the systemic inflammatory response syndrome. Consequently, in relation to patients with peritonitis who have clinical and laboratory changes characteristic of this syndrome, the concept of peritoneal (abdominal) sepsis is quite appropriate. It is common knowledge that the physiological mechanism of regulation of the expression of adhesive molecules on the endothelium of blood vessels is the production of nitroxide radical NO by these cells, which blocks the cytokinin-induced expression of adhesive molecules through the NF-kB mechanism. In particular, it was shown that NO significantly increases the expression of I-kBa, a cytosolic inhibitor of NF-kB [23]. This effect of NO leads to a decrease in the number of adhesive molecules ICAM-1, E-selectin and P-selectin, as well as the secretion of some cytokines, including IL-6 [24]. Thus, the protective response of endothelial cells to infection by binding agonists such as histamine or thrombin is aimed at maintaining the integrity of the vessel. In this case, the function of cells is rapidly rebuilt to implement procoagulant, vasoconstrictor and proinflammatory actions, and these changes, as a rule, reversible. According to modern data, the effect of NO in the systemic inflammatory response syndrome is far from unambiguous. For example, inflammatory mediators, especially TNFα, IL-1 and platelet activating factor (PAF), promote the formation of inducible (iNOS), which has antimicrobial and antioxidant effects, reduces platelet aggregation and leukocyte adhesion. Simultaneously, in endothelial cells, TNFα induces the expression of the synthesis of molecules that trigger the process of blood coagulation in the microvasculature, which leads to vascular occlusion and local cessation of blood flow directly at the site of infection, inhibits the thrombomodulin / protein-C anticoagulant pathway, and also blocks the dissolution of fibrin by stimulating PAI -1 type I. At the same time, NO through iNOS can interact with oxygen radicals, forming compounds (peroxynitrites) that are more active and cytotoxic than their precursors, causing cell damage and organ dysfunction [30]. From this point of view, damage to the cells that form the endothelial lining of vessels is directly related to organ dysfunction.

Thus, at present there is every reason to assert that the formation of a reaction of generalized inflammation initiated by an infectious agent lies at the heart of abdominal sepsis. It is the uncontrolled release of endogenous inflammatory mediators and the lack of mechanisms that limit their damaging effect that are the causes of organ-systemic disorders. Therefore, consideration of abdominal sepsis in the form of a systemic response to an infectious focus accurately reflects the essence of the changes taking place.

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