THE ROLE OF CYTOKINES IN THE IMMUNOPATOGENESIS OF ACUTE PANCREATITIS (review article)

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Abstract

The article deals with the main issues of etiology, pathogenesis, classification, clinic, diagnosis and treatment of acute pancreatitis, taking into account the current positions of the participation of the immune system, namely the cytokine system in the development of acute pancreatitis.

Keywords: *acute pancreatitis, immunity, cytokines.*

INTRODUCTION

Acute pancreatitis (AP) remains one of the most common pathologies of the digestive system with an ambiguous prognosis (19, 18), and ranks third in the structure of surgical diseases after acute appendicitis and acute cholecystitis (6, 8).

OP is an aseptic inflammation of the demarcation type, which is based on necrosis of the acinar cells of the pancreas, and enzymatic aggression, followed by expanding necrosis and dystrophy of the gland, in which it is possible to damage the surrounding tissues and distant organs, as well as systems and the addition of a secondary purulent infection (15). To date, acute pancreatitis remains one of the most pressing problems in abdominal emergency surgery (1).

According to the WHO, there is a trend towards an increase in the number of young and middle-aged patients with OP, which is often associated with unfavorable ecology, living conditions, the incidence of cholelithiasis, obesity, and alcohol abuse (5, 18). Despite the successful achievements in improving the methods of treatment of acute pancreatitis, the overall mortality in its mild forms is 3.9 to 21%, and in severe forms it reaches up to 70%. Lethal outcome in patients with acute infected pancreatitis occurs during the first day due to progressive toxic shock and the development of multiple organ failure, or later, as a result of the formation of purulent-septic complications (3.54).

According to the Atlanta classification revised in 2012, OP develops in two phases (20). In the early phase, which usually ends by the end of the first week, systemic disturbances are secondary to local inflammation of the pancreas. As the disease progresses, a generalized inflammation occurs, defined as

systemic inflammatory response syndrome (SIRS). If SIRS persists, there is an increased risk of organ failure and local complications. Determining the duration of organ failure is important. If it resolves within 48 hours, it is called "transient organ failure"; if it persists for more than 48 hours, it is called "persistent organ failure". When an organ failure affects more than one organ, it is called multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS) (20,55). The late phase is characterized by persistence of systemic signs of inflammation or local complications. During this stage, the immune system is suppressed, making the pancreatic tissue more susceptible to infection as a result of translocation of intestinal bacteria. The resulting sepsis and multiple organ failure are subsequently major causes of late complications and mortality (28,57). According to this classification, there are: acute edematous (interstitial) pancreatitis, sterile and infected pancreatic necrosis, which are links in a single pathogenesis (12).

The transition of acute pancreatitis from one type to another is due to the initial severity of the patient and the volume of destruction, leading to the development of severe risk factors (4, 9, 10-11, 45, 48). By severity, a mild, moderate, and severe form is distinguished, which are determined by the development of SIRS, complications, and the severity of multiple organ disorders according to the SOFA scale (14). In severe AP, the local inflammatory process intensifies and spreads through the bloodstream throughout the body, leading to a systemic inflammatory response (35,56). A detailed assessment of the severity and prediction of the outcome of AP are fundamental principles for an adequate choice of conservative therapy and timely surgical tactics (2).

Numerous studies of the pathogenesis of OP have been published; however, the exact mechanism of this pathology remains unclear (44). Even when several mechanisms for the pathophysiological process of OP have been proposed, none of them is completely informative (53).

Premature trypsin activation is the most widely accepted theory as the underlying mechanism for initiating pancreatic tissue autodigestion and subsequently local and systemic inflammatory processes. The initial events of OP occur in acinar cells, which can act as inflammatory cells in the pancreas (23). An excessive inflammatory response is a common aspect of these mechanisms. This process is characterized by the release of pro- and anti-inflammatory cytokines and other inflammatory mediators that attract and activate neutrophils, monocytes, and lymphocytes, as well as adhesion molecules and oxygen free radicals, leading to mitochondrial dysfunction and microcirculatory damage in the pancreas (44, 50, 55, 54).

In OP, a wide range of changes in the homeostatic parameters of the organism is determined (13). It is well known that as a result of tissue damage and/or infection, a complex sequence of reactions unfolds in the human body aimed at preventing further destruction, isolating and destroying the pathogen, activating reparative processes, and restoring the initial homeostasis (16). Given that the pathogenesis of the disease is directly related to the cytokine response of the body, it is proposed to determine the concentrations of pro-inflammatory and anti-inflammatory mediators. Elevations of both types of cytokines occur early and persist for several days in the systemic circulation. High concentrations of IL -1β, IL -6, IL - 8, IL -10,

IL -12, TNF-α indicate a severe course of AP, although they cannot be predictors of a lethal outcome in a particular patient (30, 41; 49; 32).

Cytokines are a family of low molecular weight proteins (mass 16-25 kDa) that are secreted by many cells, including macrophages and monocytes. These are regulatory mediators of the immune response, acting both on their producing cells and on adjacent cells. There are: interleukins (IL / IL), which, in turn, are divided into pro-inflammatory (IL -1, IL -8, etc.) and anti-inflammatory (IL -4, IL -10, IL -14, IL -18, etc.).); interferons (IFN / IFN) (-α, -β, -γ) - with a pronounced antiviral effect; tumor necrosis factors (TNF) (-α and -β) – cytokines with cytotoxic and regulatory action; chemokines - chemoattractants for leukocytes; growth factors and some others (17). All cytokines realize their effects through specific cell surface receptors. Most cytokines have pleiotropic activity and show multiple functional effects on a variety of target cells. Although cytokines elicit a "beneficial" inflammatory response to limit tissue damage, overproduction of these pro-inflammatory agents can be even more dangerous than the initial stimulus [52]. The term cytokine storm is not well defined, but refers to a particular type of uncontrolled immune response.

Cytokine storm in OP is a potentially fatal immune response consisting of positive feedback between cytokines and immune cells. When the immune system fights infectious agents, cytokines signal immune cells such as T-lymphocytes and macrophages to head to the site of infection. Additionally, cytokines activate cells, stimulating them to produce even more cytokines. A cytokine storm has the potential to cause significant tissue and organ damage. These facts explain the mechanism by which the release of large amounts of cytokines contributes to the progression of severe SIRS in AP (7).

To date, it is known that inflammatory mediators play a leading role in the pathogenesis of AP: pro- inflammatory cytokines such as IL -1, IL -6, IL -8 and tumor necrosis factor (TNF -α), as well as cyclooxygenase and other mediators (43). The results of their influence are an increase in vascular permeability, migration of leukocytes, local tissue damage, generalization of the inflammatory response, damage to the organs of natural detoxification with the development of multiple organ failure (21).

Tumor necrosis factor (TNF/TNF)-α is an important inflammatory cytokine that is involved in the pathogenesis of AP by directly damaging acinar cells and leading to necrosis, inflammation, and edema (22). The main producers of TNF-α, monocytes and macrophages, also secrete neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B- and T-lymphocytes when they are involved in the inflammatory process. It activates endothelial cells, stimulates angiogenesis, enhances migration and activates leukocytes. This cytokine, which is the first to be released, is the main mediator of immune responses (21). The expression of TNF-α in the pancreas increases with the onset of AP. El - Ashmawy et al. (26) conducted a study in a mouse model of L-arginine-induced pancreatitis to investigate the underlying molecular mechanisms of OP. They confirmed that the concentration of TNF-α in the pancreas was markedly increased after administration of L-arginine. This may be due to the overproduction of reactive oxygen species (ROS), which activate nuclear factor kappa-B (NF- κB), followed by the activation of various inflammatory cytokines, especially IL-1β and TNF-α. TNF-α receptor levels have been found

to, indicators of TNF-α activity, are elevated in patients with severe AP, and TNF-α blockade reduces mortality and alleviates the course of experimental AP (39).

Interleukin (IL/ IL)-1 is well known as an integral early component of the acute inflammatory process (41). IL -1β is a secretory cytokine that acts both locally and systemically. IL -1 is produced by many cells in the body. Its main sources in the body are monocytes and macrophages, as well as Langerhans cells, Kupffer cells in the liver, endothelial cells, fibroblasts, keratinocytes, microglial cells, natural killers, neutrophils, T-lymphocytes, except for T-helpers, dendritic cells, etc. Hartman H. et al. (29) in their AP severity study found that IL-1 levels predicted severe AP on admission with the same accuracy as IL-6 (82% versus 88%, respectively) and that the IL-1 receptor antagonist had the best accuracy among various markers, including IL-6 and CRP, within the first 48 hours. After 48–72 h, IL-1 levels were found to predict pancreatic necrosis with an accuracy of 88%, and the ratio of IL-1:IL-1 receptor antagonists could identify septic complications with an accuracy of 72%. (22)

Interleukin (IL / IL)-6 is the main stimulator of protein synthesis in the acute phase in the liver and is the main mediator in the synthesis of fibrinogen, CRP and hepcidin. IL-6 is synthesized by macrophages, endothelial cells, and fibroblasts shortly after being stimulated by microbial products. The role of IL-6 in early and accurate prediction of the severity of AP has been confirmed by numerous studies (34, 40). Soyalp, M. et al. (48) found that elevated IL-6 increased in line with the severity of pancreatitis, suggesting that IL-6 may act as a predictive tool for OP. IL-6 has the best sensitivity and specificity for early assessment of severe AP among various pro-inflammatory and anti-inflammatory cytokines. However, the analysis of IL-6 has a significant drawback, which consists in the fact that its concentration in serum decreases very quickly with certain activities (34). In Garipati research Sathyanarayan et al (2007) found that an elevated level of IL -6 is a prognostic factor for organ failure and severe pancreatitis, and also indicates its pathophysiological significance in OP (27).

Among all cytokines, Interleukin (IL/IL)-8 stands out in the pathophysiology of AP, as its level has been shown to be significantly elevated in the development of AP, and its level has been reported to be associated with the severity of AP (36). Interleukin (IL)-8 is a member of the chemokine family CXC, which mediates recruitment polymorphonuclear neutrophils, basophils, eosinophils and lymphocytes in the foci of inflammation. IL -8 acts as a neutrophil activator and as a chemoattractant. Several studies have shown promising results in the early prediction of severe AP. Rau B et al. (42) confirmed the role of IL-8 in monitoring major complications in patients with necrotizing pancreatitis with multiple organ failure. Various studies have confirmed that IL-8 levels rise in the first 24 hours after symptom onset, and a rapid decrease after 3–5 days is a good marker of multiple organ failure and death from sepsis in patients with OP (25).

In studies of the role of TNF-α, IFN-γ, IL-1, IL-2, IL-4, IL-6, IL-8 in the prediction of acute destructive pancreatitis, Salienko S.V. established that from the first day of the development of acute destructive pancreatitis, several parallel and interdependent processes are observed: the formation of pancreatic necrosis (superantigen) with the development of a blockade of a full-fledged immune response against the background of

hyperproduction of cytokines (especially IL-8 and TNF-α) causing a number of symptoms of endotoxicosis, and also involved in the genesis of multiple organ failure and early deaths. The author came to the conclusion that if we evaluate the ratio of cytokines, then during this period there is a deficiency of IL-2 and a relative deficiency of IFN-γ, which predetermines violations of the cell-mediated immune defense system. It was also found that, along with a continuing increase in the values of the pool of pro-inflammatory cytokines, there is a rapid increase in the concentration of anti-inflammatory IL-4 in the blood serum, leading, on the one hand, to the suppression of macrophage activity and the secretion of IL-1, TNF-α, IL-6, on the other hand. – to an increase in the cytotoxic activity of macrophages, induction of massive cell apoptosis (16).

chemoattractant protein 1 (MCP-1 or CCL2) is a prototypical inflammatory chemokine that targets monocytes, T-lymphocytes, and other cells expressing the CC chemokine receptor (CCR2) (24). Notably, MCP-1 not only provides chemotactic signals for the recruitment of monocytes from the bloodstream to tissues, but is also responsible for monocyte activation and induction of a respiratory burst. In fact, increased expression of MCP-1 has been found during acute and chronic pancreatitis in both animal models and human tissues, suggesting a contribution of this chemokine to the pathogenesis of mononuclear infiltration (46,31). However, MCP-1 is only one of several chemokines that are upregulated in pancreatitis, and evidence for its pathogenic role was lacking.

Ohmoto K et al, when comparing clinical and laboratory data, it was found that the level of IL-6 in serum showed a significant correlation with markers of the severity of acute pancreatitis, which indicates that IL -6 is a useful indicator of the severity of this disease. The ratio of IL -10/ IL -6 was significantly lower in patients with severe acute pancreatitis, indicating the predominance of the pro-inflammatory response in these patients. However, in patients receiving continuous regional arterial infusion of a protease inhibitor and antibiotics, the IL -10/ IL -6 ratio in patients with severe acute pancreatitis was significantly elevated (38).

Since the discovery of Th17 cells, the cytokine IL-17 has become the object of increasing attention and discovery. According to the literature, IL-17 causes many acute inflammatory diseases. IL-17 acts on a range of cellular targets in tissues and immune cells and plays a vital role in innate and adaptive immunity (17). Dysregulation cytokine systems are usually included in the OP, and targeted therapy for IL-17 is of great importance. Inhibition of IL-17A and its receptor or simultaneous inhibition of IL-17A and IL-17F contributes to the interruption of signaling pathways important for the development and maintenance of OP. Accordingly, biologics that act on IL-17 contribute to the rapid and abrupt onset of systemic symptoms during OP. Thomson J.-E. _ _ _ et al in a study of IL -17 in predicting the severity of AP found that the average concentration of IL-17A on days 7, 9, 11 and 13 in patients with mild and severe AP did not show statistically significant differences between groups (51).

Hanna Sternby et al in a comprehensive study of IL 1β, IL -6, IL -8, IL -10, IL -12, IFN -γ and TNF -α, differences between severity groups, the predictive ability of biomarkers and association with the severe course of the disease were analyzed, which established a clear change in IL -1β, IL -8, IL -10 and IL -6 during the first 48 hours after the onset of OP.

At the same time, IL-1β and IL-6 were associated with a severe course of the disease, however, the prognostic ability of the studied biomarkers is low (29). Also, a synchronous study of the early dynamics of pro-inflammatory cytokines IL -6, IL -8, IL -18 and TNF -α on days 1, 2 and 14 in 60 patients substantiated the use of these markers as prognostic factors for the development of organ failure in patients with the first attack. OP (37).

Thus, the study of the role of pro- and anti-inflammatory cytokines in OP plays a certain role in the pathogenesis of the development and course of this disease. This area of scientific research is certainly one of the promising areas for solving this problem and requires further development, and therefore the study of the cytokine profile, its relationship, changes in various courses and treatment remains an urgent problem.

REFERENCES

Abdullayev, R. B., & Makhmudova, L. I. (2021). Features of chemical elements in various forms of irritable bowel syndrome. Annals of the Romanian Society for Cell Biology, 25(2), 2993-3000. Retrieved from www.scopus.com

Acute pancreatitis: Clinical guidelines - Ministry of Health of the Russian Federation, revision 2020 - p.66.

Alekesheva, L. Z., Abdullaeva, M. A., Inoyatov, A. S., Jabborova, O. I., Nigmatullaeva, M. A., Kudratova, M. O., & Navruzova, U. O. (2021). Ways to solve the incidence of covid-19 as a global problem. Annals of the Romanian Society for Cell Biology, 25(4), 1873-1880. Retrieved from www.scopus.com

Aliev, S. A. Infected pancreatic necrosis: State of the problem and alternative approaches to surgical treatment. Literature review / S. A. Aliev, N. Yu. Bayramov, E. S. Aliev // Bulletin of Surgical Gastroenterology.- 2015. - No. 1 - 2. - S. 75 - 83

Bakhtin, V. A. Experience in the treatment of infected pancreatic necrosis / V. A. Bakhtin, V. M. Rusinov, V. A. Yanchenko // Abstracts of the V Interregional Scientific and Practical Conference "Actual Issues of Abdominal Surgery". - Tomsk. - 2016. - S. 12 - 14.

Banks, P.A.; Bollen, TL; Dervenis, C.; Gooszen, HG; Johnson, CD; Sarr, M.G.; Tsiotos, GG; Vege, SS Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. gut 2013, 62, 102–111. [Google Scholar] [CrossRef]

Baranovsky, A.Yu. Indicators of morbidity and mortality from diseases of the digestive system in the Northwestern Federal District of Russia and measures taken to reduce them / A.Yu. Baranovsky, A.M. Belyaev, E.A. Kondrashina // Russian Journal of Gastroenterology, Hepatology, Coloproctology. - 2019. - T. 29. - No. 1. - P. 36–46.

Chen, P.; Huang, L.; Sun, Y.; Yuan, Y. Upregulation of PIAS1 protects against sodium taurocholate-induced severe acute pancreatitis associated with acute lung injury. Cytokine 2011, 54, 305–314. [Google Scholar] [CrossRef] [PubMed]

Criddle, DN Reactive oxygen species, Ca 2+ stores and acute pancreatitis; a step closer to therapy? Cell Calcium 2016, 60, 180–189. [Google Scholar] [CrossRef] [Green Version]

Daly C, Rollins B.J. Monocyte chemoattractant protein-1 (CCL2) in inflammatory disease and adaptive immunity: therapeutic

opportunities and controversies. Microcirculation 2003 ; 10 :247–57. [PubMed] [Google Scholar]

Davlatov S. S., Khamdamov B. Z., & Teshaev Sh. J. (2021) Neuropathic form of diabetic foot syndrome: etiology, pathogenesis, classifications and treatment (literature review). Journal of Natural Remedies. Vol. 22, No. 1(2), – P. 147-156.

Dibirov, M. D. Features of the prevention and treatment of liver and kidney dysfunction in acute pancreatitis / M. D. Dibirov, M. V. Kostyuchenko, Yu. I. Ramazanova, R. M. Gabibov, R. R. Nukhov, A. A. Ashimova // Ukrainian Journal of Surgery. - Kyiv. - 2011. - No. 2 (11). - P. 40 - 44.

Dugernier, TL; Laterre, P.F.; Wittebole, X.; Roeseler, J.; Latinne, D.; Reynaert, MS; Pugin, J. Compartmentalization of the inflammatory response during acute pancreatitis: Correlation with local and systemic complications. Am. J. Respir. Crit. Care Med. 2003, 168, 148–157. [Google Scholar] [CrossRef] [PubMed]

El Ashmawy, N.E.; Khedr, N.F.; El Bahrawy, H. A.; Hamada, OB Suppression of inducible nitric oxide synthase and tumor necrosis factor-alpha level by lycopene is comparable to methylprednisolone in acute pancreatitis. Dig. LiverDis. 2018, 50, 601–607. [Google Scholar] [CrossRef] [PubMed]

Gorsky V.A., Agapov M.A., Kovalchuk L.V., Ovanesyan E.R., Khoreva M.V., Nikonova A.S. Syndrome of systemic inflammatory response in acute pancreatitis: features of molecular pathophysiology and possible ways of correction // Clinical Medicine - STM ∫ 2010 - 2 - p. 39 -44

Gostishchev V.K., Glushko V.A. Pancreatic necrosis and its complications, basic principles of surgical tactics. Surgery. 2003; 3:50–4.

Gurusamy, K.S.; Nagendran, M.; Davidson, BR Early versus delayed laparoscopic cholecystectomy for acute gallstone pancreatitis. Cochrane Database Syst. Rev. 2013. [Google Scholar] [Cross Ref]

Hanna Sternby Hartman, Henrik Thorlacius, Sara Regner. The Initial Course of IL1 β, IL-6, IL-8, IL-10, IL-12, IFN- γ and TNF-α with Regard to Severity Grade in Acute Pancreatitis// Biomolecules. 2021 Apr 17;11(4):591. doi: 10.3390/biom11040591.

IL-6 and CRP are superior in early differentiation between mild and non-mild acute pancreatitis / H. Sternby, H. Hartman, D. Johansen, H. Thorlacius, S. Regnér / Pancreatology. - 2017. - Vol. 17, No. 4. - P. 550-554;

Inoue M, Ino Y, Gibo J, et al. The role of monocyte chemoattractant protein-1 in experimental chronic pancreatitis model induced by dibutyltin dichloride in rats. Pancreas 2002; 25 : e64–70. [PubMed] [Google Scholar]

Interleukin-12 as a predictor of outcome in patients with severe acute pancreatitis / P. Gregorić, K. Doklestić, S. Stanković, A. Sijacki, A. Karamarković, D. Radenković, N. Ivancević, D. Bajec // Hepatogastroenterology. - 2014. - Vol. 61, No. 129. - P.208-211.

Jiang, C.F.; Shiau, YC; Ng, KW; Tan, SW Serum interleukin-6, tumor necrosis factor alpha and C-reactive protein in early prediction of severity of acute pancreatitis. J. Chin. Med Assoc. 2004, 67, 442–446. [Google Scholar] [PubMed]

Khaidarov F.N., Khamdamov B.Z., Musoev

T.Ya., Khamdamov A.B. Diagnostic significance of determining the level of procalcitonin and lactoferrin in the blood in destructive forms of acute calculous cholecystitis // Tibbiyotda yangi kun. - Bukhara, 2021. - No. 6 (38). - S. 282-289.

Khamdamov B. Z., Khamroev U. P. The Effectiveness of the Therapeutic and Diagnostic Algorithm of Complex Surgical Treatment of Diffuse Toxic Goiter. // American Journal of Medicine and Medical Sciences, 2022.12(12).- P.1361-1366 DOI:10.5923/j.ajmms.20221212.39

Khamdamov B.Z., Davlatov S.S., Khaidarov F.N., Khamdamov I.B. Optimization of surgical treatment of acute calculous cholecystitis complicated by purulent cholangitis // Doctor akhborotnomasi. - Samarkand, 2021. - No. 3 (100). - S. 116-119.

Khamdamov B.Z., Khamroev U.P. Development and comperative evaluation of the effectiveness of the diagnostic and treatment algorithm for complex surgical treatment of diffuse toxic goiter // Journal of educational and scientific medicine. - Tashkent, 2022. - Issue 3 (2). -P 84-89.

Khamdamov B.Z., Khamroev U.P., Khamdamov I.B. Assessment of efficiency of surgical treatment of the diffusion toxic craw // Europe's Journal of Psychology., 202 1. 17(3) - P. 123-127.

Khamdamov B.Z., Mirkhodzhaev I.A., Khaidarov F.N., Khamdamov I.B. A differentiated approach to the surgical treatment of acute calculous cholecystitis complicated by purulent cholangitis // Bulletin of the Tashkent Medical Academy. - Tashkent, 2021. - No. 4. - C. 167-169.

Khamdamov B.Z., Musoev T.Ya., Khaidarov F.N., Khamdamov A.B. Cytokine profile of blood in destructive forms of acute calculous cholecystitis // International Scientific and Practical Conference Horizons of modern surgery. - Samarkand, 2021. - S. 475-480.

Khamdamov B.Z., Nuraliev N.A., Khamdamov I.B. Experimental development of methods for the treatment of wound infection. Biology wa tibbiot muammolari. Samarkand, 2020. - No. 1 (116). –S.194-199.

Khamdamov B.Z. Indicators of immunocitocine status in purulent-necrotic lesions of the lover extremities in patients with diabetes mellitus. American Journal of Medicine and Medical Sciences, 2020 10 (7): 473-478 DOI: 10.5923/j.20201001.08

Khamdamov B.Z., Nuraliev NA Pathogenetic approach in complex treatment of diabetic foot syndrome with critical lower limb ischemia. American Journal of Medicine and Medical Sciences, 2020 10 (1) 17-24 DOI: 10.5923/j.20201001.05.

Khamraev U.P. Comparative Characteristics of Surgical Methods of Treatment of Diffuse Toxic Goiter // Journal of educational and scientific medicine. – Tashkent, 2023. – Issue 1 (2). -P 92-100.

Khamraev U.P. Results of surgical treatment of patients with diffuse toxic goitre // New day in medicine. - Bukhoro, 2022. - No. 11 (49). - C. 51-57.

Khamraev U.P., Khamdamov B.Z. Features of Changes In Endothelial System Parameters In Patients With Diffuse Toxic Goiter // Journal of education & Scientific medicine. - Tashkent, 2022.- P. 62-67.

Khanna, A. K.; Meher, S.; Prakash, S.; Tiwary, S.K.; Singh, U.; Srivastava, A.; Dixit, V. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. Hpb Surg. 2013. [Google Scholar] [CrossRef]

Li, Y.; Bai, J.; He, B.; Wang, N.; Wang, H.; Liu, D. Weak association between the interleukin-8 rs4073 polymorphism and acute pancreatitis: A cumulative meta-analysis. BMC Med. Genet. 2019, 20, 129. [Google Scholar] [CrossRef] [PubMed][Green Version]

Malmstr o m, Marie Louise; Hansen, Mark Berner, Andersen, Anders Mollere et al. Cytokines and Organ Failure in Acute Pancreatitis: Inflammatory Response in Acute Pancreatitis Pancreas 41(2) :p 271-277, March 2012. DOI: 10.1097/MPA.0b013e3182240552

National clinical guidelines. Acute pancreatitis. / S. F. Bagnenko, D. A. Blagovestnov, V. A. Vishnevsky, E. A. Galperin, V. R. Goltsov, M. V. Danilov, M. D. Dibirov, T. G. Dyuzheva, I I. Zatevakhin, V. G. Ivshin, M. P. Korolev, V. A. Kubyshkin, N. A. Maistrenko, Yu. S. Polushin, M. I. Prudkov, S. A. Sovtsov, M. I Filimonov, M. Sh. Tsitsiashvili, A. V. Shabunin. - Moscow. - 2015. - S. 47.

Order No. 83 of the Moscow Department of Health "On the unified tactics for the diagnosis and treatment of acute surgical diseases of the abdominal organs in medical institutions of the Moscow Department of Health." Moscow. - 2017. - S. 32

Oripova, F. S., Ikhtiyarova, G. A., Shukurlaev, K., & Khamdamova, M. T. (2021). New methods of correction of inflammatory diseases of the genitalia (clinical and experimental study). Annals of the Romanian Society for Cell Biology, 25(4), 1865-1872. Retrieved from www.scopus.com

Pastor, C. M.; Morel, D. R.; Vonlaufen, A.; Schiffer, E.; Lescuyer, P.; Frossard, JL Delayed production of IL-18 in lungs and pancreas of rats with acute pancreatitis. pancreatology 2010, 10, 752–757. [Google Scholar] [Cross Ref]

Predictive Capacity of Biomarkers for Severe Acute Pancreatitis / H. Sternby, H. Hartman, D. Johansen, H. Thorlacius, S. Regnér //. EUR Surg Res. - 2016. - Vol. 56, nos. 3-4. - P. 154-163.

Saluja, A.; Dudeja, V.; Dawra, R.; Sah, R. P. Early Intra-Acinar Events in Pathogenesis of Pancreatitis. gastroenterology 2019, 156, 1979–1993. [Google Scholar] [CrossRef]

Sarr, MG Minimal access necrosectomy : the newest advance of many in the treament of necrotising pancreatitis / MG Sarr // Journal Online First. - 2017. - P. - 314

Shakhrizod EB Infected pancreatic necrosis as a problem of modern pancreatology. Bulletin of emergency medicine. 2016; 1:102–6.

Simbirtsev A.S. Cytokines. Classification and biological functions // Cytokines and inflammation. 2004. V. 3. No. 2. P. 16–22.,

Zavgorodnyaya E.G. Cytokines and their place in the diagnosis and treatment of a number of ENT organs. Bulletin of Otorhinolaryngology. 2008. No. 3. S. 74–76.

Singh, VK An assessment of the severit of interstitial pancreatitis / VK Singh, TL

Bollen, BU Wu // Clinic Gastroenterology Hepatology. - 2011. - Vol. 9. - P. 98 - 103.

Soyalp, M.; Yalcin, M.; Oter, V.; Ozgonul, A. Investigation of procalcitonin, IL-6, oxidative stress index (OSI) plasma and tissue levels in experimental mild and severe pancreatitis in rats. Bratisl. Lek. Listy 2017, 118, 137–141. [Google Scholar] [Cross Ref] [PubMed] [Green Version]

Staubli, SM Laboratory markers predicting severity of acute pancreatitis / SM Staubli, D. Oertli, CA Nebiker // Crit Rev Clin Lab Sci. - 2015. - Vol. 52, No. 6. - P. 273-283;

Thomson J.- E. Brand M., Fonteh P. The role of IL17-A in the second hit of acute pancreatitis // Open Archive I: https://doi.org/10.1016/j.hpb.2019.10.1526

Topical issues of pancreatic surgery / A.Sh. Revishvili [et al.] // Surgery. Journal them. N.I. Pirogov. – 2018. – No. 9. – P. 5–14

Unresolved issues in the treatment of acute destructive pancreatitis / D.V. Kulikov [et al.] // Bulletin of Experimental and Clinical Surgery. - 2019. - T. 12. - No. 2. - P. 134–140.

Vlasov A.P., Trofimov V.A., Al- Kubaisi Sh.S., Anaskin S.G., Malakhova O.S., Morozova M.M., Muratova T.A., Vasiliev V.V., Vlasova T.I., Kuzmin A.N. Factors of progression of acute pancreatitis. Modern problems of science and education. 2018; 5. URL: http:// www. science - education. ru / ru / article / view ? id =28045

Yu, JH; Kim, H. Oxidative stress and inflammatory signaling in cerulein pancreatitis. World J. Gastroenterol. 2014, 20, 17324–17329. [Google Scholar] [Cross Ref] [PubMed]

Zhang, B.; Li, S.L.; Xie, H.L.; Fan, JW; Gu, CW; Kang, C.; Teng, MJ Effects of silencing the DUSP1 gene using lentiviral vector-mediated siRNA on the release of proinflammatory cytokines through regulation of the MAPK signaling pathway in mice with acute pancreatitis. Int. J. Mol. Med. 2018, 41, 2213–2224. [Google Scholar] [Cross Ref] [PubMed] [Green Version]