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Optimizing the Treatment of Acute Duct-Destructive Pancreatitis

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ABSTRACT

The search for new methods for treating duct-destructive pancreatitis is a relevant problem. Endogenous intoxication and oxidative stress that accompany acute pancreatitis often progress even after surgery, which forces one to search for additional possibilities of preventing these severe consequences. This research studied the effect of small doses of direct electric current and intravenous ozone therapy in combination with therapeutic omental pancreatic bursoscopy in the treatment and prevention of the infection of necrotic foci of the pancreas. The rate of postoperative complications in patients with infected pancreatic necrosis and the causes of death of patients with infected pancreatic necrosis were studied.

KEYWORDS
Severe acute pancreatitis, pancreatic necrosis, postoperative therapy, small doses of direct electric current, ozone therapy

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Introduction

The incidence of acute pancreatitis and the rate of its severe duct-destructive forms has grown during the last decades (Bradley, 1993; Büchler et al., 2000).

Pancreatitis is often accompanied by cholecystitis and vice versa – cholecystitis can cause pancreatitis (Tenner et al., 2013). Acute pancreatitis is often accompanied by infection (suppurative complications), phlegmon, pancreatic abscess (Sheĭko & Oganezian, 2013) or, in some cases, intraabdominal hemorrhage (Beger & Rau 2007). Another serious complication of pancreatitis is the destruction of the pancreas and lethal peritonitis.

After its acute stage, pancreatitis goes into chronic form. The exacerbation of acute pancreatitis generally is caused by irritant food and alcohol. Chronic pancreatitis can cause diabetes mellitus (VanSonnenberg et al., 1989).

Despite the success of modern surgery, the mortality rate with duct-destructive acute pancreatitis remains high (40-70%) and shows no signs of decreasing (Vinokurov, Savel'ev & Ammosov, 2008; Nydegger et al., 2007; VanSonnenberg et al., 1989). The main cause of death of 30-80% of patients is

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suppurative and septic complications, which are an inflammatory response of the organism to the destructive inflammatory processes in the abdomen and the retroperitoneum (Li et al., 2016).

Basic combined therapy improves the rate of postoperative rehabilitation significantly. However, due to the physiological characteristics of each patient, basic combined therapy is not always effective; cases of endotoxicosis and signs of peritonitis are encountered, which necessitates reoperation with a high mortality rate (Karakayali, 2014). In combination with alternative techniques of postoperative therapy, such as small doses of direct electric current and intravenous ozone therapy, the conventional combined therapy can be more effective (Kaliev et al., 2013).

Literature Review

Acute pancreatitis is a common abdominal pathology caused by defective functioning of the pancreas (Spanier, 2008). A higher morbidity rate is observed regardless of the level of development of countries (Connor et al., 2005; VanSonnenberg et al., 1989; Tinto et al., 2002; Schwartz et al., 2013; Lindkvist et al., 2004), with a potential of increasing incidence (Yousaf, McCallion & Diamond, 2003). The disease becomes severe in 20% of cases, (Zerem, 2014), each third of which causes infected pancreatic necrosis (Banks, et al. 2013). Without modern surgical intervention, the mortality rate of patients with infected pancreatic necrosis is close to 100% (Spanier, Dijkgraaf, & Bruno 2008; Herath & Kulatunga, 2016).

Clinical and laboratory studies, as well as imaging evaluation, are used to diagnose severe acute pancreatitis (SAP) (Besselink et al., 2009). Thanks to considerable investment in the development of new diagnostic techniques, various scoring systems exist that enable diagnosing the severity of acute pancreatitis. Laboratory express tests are characterized by simplicity of use and quick obtainment of results (Ferreira et al., 2001; Larvin & Mcmahon, 1989; Ranson, 1979; Knaus et al., 1985; Wu et al., 2008; Papachristou et al., 2010). General severity systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) (Knaus et al., 1991; Knaus et al., 1985), and Simplified Acute Physiology Score (SAPS) (Papachristou et al., 2010) are used to determine the standard mortality ratio (SMR), and are a key element in intensive care units (ICU) benchmarking. APACHE assesses the morbidity rate and determines the severity of the disease or the effectiveness of treatment (Knaus et al., 1991). General clinical and biochemical blood tests are used to determine the state of the patient's organism during therapy, which include the middle molecular weight of blood (Nikolskaya, Danilchenko & Memetova, 2013), activity of lipid peroxidation (Forman et al., 2015), content of diene conjugates (Halliwell & Chirico, 1993), antioxidant protection system (Dröge, 2002), etc.

Imaging evaluation determine the stage of development of the pathology and provide data that are required for successful surgery. Contrast-enhanced computed tomography (CECT) is currently the standard imaging modality in the setting of SAP. The drawback of this technique is the difficulty of determining the presence or absence of necrosis within four days of development of severe acute pancreatitis in most patients, especially with the formation of fluid-predominant collections (Banks & Freeman, 2006). Ultrasound examination is characterized by mobility and the ability to use it in cases when a patient is non-transportable to perform computed tomography (Maher et al., 2004). The disadvantage of this technique is frequent association with ileus making visualization of the pancreas difficult (Bennett & Balthazar, 1998). A more accurate diagnosis of severe acute pancreatitis is possible using endoscopic ultrasound (EUS), which raises the diagnostic accuracy to 83-97% (Chak et al., 1999). However, in common with transabdominal ultrasound, the major disadvantage of EUS is that it does not provide any information regarding the viability of pancreatic tissue (Maher et al., 2004).

An alternative to CECT is magnetic resonance imaging (MRI), a diagnostic technique that is becoming increasingly popular in both medical practice and SAP studies (Schwartz et al., 2013). The advantage of this technique is the smaller thickness of the examined layer, when compared to CECT, and the possibility of obtaining a three-dimensional image (Pankhurst et al., 2003). The disadvantage of this technique, besides the ones that are also true for CECT, is the cost of the equipment and its maintenance.

Hospital admissions for acute pancreatitis increase with age, the median age of the first attack is in the sixth decade of life. The gender comparison of the hospital admission rate shows the prevalence of men (Lankisch et al., 2002; Lindkvist et al., 2004), although the men-to-women ratio tends to even out with age (Tinto et al., 2002). Depending on the stage of the pathology, severe acute pancreatitis, mild acute pancreatitis, acute fluid collections, pancreatic necrosis, and other minor forms are distinguished (Bradley, 1993). In terms of the incidence of pancreatic and retroperitoneal necrosis, interstitial pancreatitis, sterile pancreatic necrosis, and infected pancreatic necrosis are distinguished (Boyko et al., 2002).

The difference incidence of pancreatic and retroperitoneal necrosis and the fact of their infection predetermine the variety of surgical tactics (Voskanyan et al., 2013).

The crucial component of the combined treatment of infected pancreatic necrosis is the lancing of suppurative foci and, when possible, removal of dead tissues (Sheĭko & Oganezian, 2013). However, the development of effective means of accelerated rejection or removal of necrotic sections of the pancreas after surgery as the main cause of suppurative infection is still an unsolved problem (Vinokurov, Savel'ev & Ammosov, 2008). SAP has local postoperative complications (pancreatic abscess, retroperitoneal phlegmon, arrosive hemorrhage, and fistulas), and systemic complications (postoperative pneumonia, myocardial infarction, acute kidney failure, pulmonary embolism, and ventral hernia) (VanSonnenberg et al., 1989). The postoperative mortality rate remains high (Karakayali, 2014), which is why the search for effective postoperative therapy of SAP is very relevant. Ozone treatment is important in terms of accelerating colon anastomosis recovery by reducing oxidative stress

and proinflammatory cytokines (Ersoz et al., 2016). The possibility of using small doses of direct electric current for therapeutic purposes (Tokar et al., 2013), including in integrated treatment of patients with sterile pancreatonecrosis (Kaliev et al., 2013) was demonstrated.

Aim of the Study

The aim of this study was to improve the effectiveness of the combined treatment of duct-destructive acute pancreatitis by using small doses of direct electric current (DEC) and ozone therapy.

Research questions

The overarching research question of this study was as follows:

What effect do small doses of electric current and intravenous ozone therapy have on pancreatic necrosis treatment? How do small doses of direct electric current, ozone therapy, and omental pancreatic bursoscopy affect the microflora of the foci of postoperative inflammation?

Methods

This research is based on the results of a retrospective and prospective examination and treatment of 286 patients with various forms of acute duct-destructive pancreatitis.

One hundred seventy four (61%) of the 286 patients were included into the control group, in which the retrospective analysis (for 1997-2007) included the results of conventional treatment according to archive materials.

The prospective analysis included the results of treatment of 112 patients, whose treatment used small doses of DEC, ozone therapy, and dynamic laparoscopic debridement of the omental bursa (main group). The age of patients ranged from 18 to 72 years; the average age was 48.2±3.6 years. The main group included 74 men (66.1%) and 38 women (33.9%); the control group included 115 men (66.1%) and 59 women (33.9%).

In most cases (52.8%), patients were admitted to the hospital within 24-72 hours after the onset of the disease, while the other 113 patients (39.5%) – 72 hours and later.

Table 1 shows that the prevalent form of pancreatic disorder in both groups was large focal and subtotal necrosis.

In accordance with the international classification of acute pancreatitis (Bradley, 1993), the main group included 34 (31%) cases of sterile pancreatic necrosis and 78 cases (63%) of infected pancreatic necrosis, while the control group included 55 cases (32%) and 119 cases (68%), respectively.

Table 1. Distribution of patients by forms of pancreatic disorder

Form of pancreatic necrosis	*Main group* (n=112)		*Control group* (n=174)		*Total* (n=286)	
	abs.	%	abs.	%	abs.	%
Acute small focal pancreatic necrosis	14	12.5	22	12.6	36	12.6
Acute large focal pancreatic necrosis	45	40.2	66	38.0	111	38.8
Acute subtotal pancreatic necrosis	35	31.2	57	32.8	92	32.2
Total pancreatic necrosis	18	16.1	29	16.6	47	16.4

The distribution of patients by sings of systemic inflammatory response syndrome (SIRS) is presented in Table 2.

Table 2 shows that both groups had a large number of patients with SIRS IV – 188 (65.7%) and SIRS III – 47 (16.4%). The incidence of septic shock in patients was significantly lower – 13 cases (4.6%).

Table 2. Distribution of patients by SIRS signs

SIRS type	*Number of patients*					
	Main group n=112		Control group n=174		Total n=286	
	abs.	%	abs.	%	abs.	%
SIRS III	19	17.0	28	16.1	47	16.4
SIRS IV	77	68.7	111	63.8	188	65.7
Severe sepsis	12	10.7	26	14.9	38	13.3
Septic shock	4	3.6	9	5.2	13	4.6

The first surgery for all patients in both groups was open. It included: midline laparotomy, lancing of the omental bursa with removal of effusion, probe decompression of the gastrointestinal tract, sanitation of the omental bursa with ozonized solutions, and penetrating drainage of the omental bursa.

The compared groups differed in the final stage of surgery – patients in the main group were installed a sleeve for future laparobursosanitation.

Dynamic bursa sanitation in both groups began 10-12 days after surgery, which coincided with the beginning of discharge of pancreatic sequesters.

The technique of using DEC and ozone therapy: the positive electrode is installed at the lumbar across the entire projection of the pancreas, while the negative electrode is installed at the front surface of the abdomen near the navel. The amperage of the current was 20-25 μA, while the density of the current at the anode was 0.05-0.1 mA/cm^2. The DEC procedure was carried out daily for 8-10 hours per day, starting with the first postoperative day, for one-two weeks.

Ozone therapy used physiological saline with 1-6 μg/ml ozone concentration and an OTRI onozator. Intravenous infusion was carried out immediately after the solution was prepared. The amount of infused solution was 200 ml; the infusion time was 15 minutes. Ozone sanitation of the omental bursa was

carried out daily, starting with the first postoperative day. No complications were detected during the procedure.

General clinical and biochemical blood checks were carried out in accordance with accepted methods; the leukocyte index of intoxication (Ostrovskiĭ et al., 2003) and the middle molecular weight was determined through screening (Gabrielyan et al., 2011). The intensity of lipid peroxidation was determined from the content of diene conjugates (Volchegorsky et al., 2000); secondary products of lipid peroxidation were determined from the content of malondialdehyde with a common thiobarbituric acid assay using an SF-26 spectrophotometer (Russia) (Bertin-Maghit et al., 2000). The system of antioxidant protection was determined by the content of the catalase and superoxide dismutase. The activity of the catalase was determined from the rate of hydrogen peroxide decomposition in a reaction medium (Pereslegina, 1989).

Ultrasound of the abdomen was carried out using Combisoni 320-5 machines manufactured by Kretstechnik AD (Austria) and AlokaSSD – 1400 (Japan).

The endoscopic examination of the gastrointestinal tract used Olympus GIF – 30 fibrogastroscopes. Computed tomography was carried out using a Philips Brilliance 16-slice scanner.

All obtained values were subjected to variation-statistical processing with the calculation of the mean value (X), standard error (Sx), standard deviation (fx), confidence factor of mean value differences (t), probability of error by Student's distribution (p), correlation coefficients (r), and significance (td). Statistical calculations were done in Microsoft Excel.

Results

Of the 286 patients, 89 (32%) were diagnosed with duct-destructive acute pancreatitis in the form of sterile pancreatic necrosis.

Sterile pancreatic necrosis and its complications were diagnosed based on the data from medical history, objective examinations, clinical and laboratory signs, ultrasound, and computed tomography.

All 89 patients were prescribed conventional basic combined therapy after hospital admission and diagnosis. The basis of the medication therapy was anti-enzymatic, cytostatic, and antibacterial therapy with massive infusion therapy and forced diuresis.

Besides the conventional combined medication therapy, 34 patients were treated with intravenous ozone therapy and small doses of DEC from the first day; these patients constituted the main group.

The research found that the inclusion of small doses of DEC and ozone therapy into the treatment was tolerated well by patients as was not accompanied by unpleasant subjective sensations.

The improvement of the patients' clinical state was accompanied by a significant reduction of the level of endogenous intoxication. Main group patients had a significantly lower level of leukocytosis, ESR and neutrophil count, leukocyte index of intoxication, and medium molecular weight after five-seven days; the significant reduction of these indexes in the control group occurred two-three days later. This difference also concerned the rise of the relative lymphocyte count, which indicated the stimulation of the general response and resilience of the organism, which was greater in main group patients.

The study of blood amylase, urine amylase, trypsin, lipase, and phospholipase A found a significantly greater drop in these levels in a shorter time in the main group when compared to the control group. The transaminase activity increased significantly. AST was 104.1±15.2 mU/l and ALT was 121.2±17.1 mU/l in both groups; it normalized on day five (AST 45.2±5.3 mU/l, ALT to 47.6±6.3 mU/l) in the main group and on day 9-11 (AST 47.2±6.1 mU/l, ALT to 48.2±8.3 mU/l) in the control group. The thymol turbidity test was normal.

Changes in the main physiological indexes, expressed in integral scales, allowed assessing the effectiveness of the conventional combined therapy with small doses of DEC and intravenous ozone therapy.

According to APACHE II, the improvement of physiological indicators was significant already on day three after the beginning of the conventional combined therapy with small doses of DEC and intravenous ozone therapy; when using only the conventional therapy, this effect of treatment was found only on day seven (Figure 1).

Conventional therapy was clinically effective for 38 (69%) patients in the control group and 29 (85.3%) of patients in the control group (CT images show a reduction in the level of fluid and the absence of necrosis growth areas). The therapy was ineffective for 17 control group patients and five main group patients; endotoxicosis progressed; signs of peritonitis emerged. For this reason, these patients underwent surgery on day 4-10 of hospital treatment.

The scope of surgery in both all patients (17 control group patients and five main group patients) in case of enzymatic peritonitis was similar: laparoscopy, laparoscopic cholecystectomy according to signs, and sanitation and drainage of the abdomen. Patients underwent conventional combined therapy in the postoperative period. Main group patients continued using small doses of DEC in combination with intravenous ozone therapy.

Only seven (41.2%) of control group patients that were treated in the postoperative period only with conventional combined therapy managed to achieve a significant clinical effect. The average duration of hospital treatment was 17.06±0.93 bed days.

In the other 10 (58.8%) of control group patients, sterile necrosis transitioned into the infected form. These patients underwent open surgery – laparotomy, omental pancreatic bursoscopy, lumbotomy, penetrating drainage of the omental bursa, and debridement.

A distinct clinical effect was found in four (80%) main group patients. Sterile necrosis transitioned into the infected form in only one (20%) patient.

The research also analyzed the results of treatment of 197 patients with infected pancreatic necrosis, 78 of which constituted the main group, while 119 – the control group.

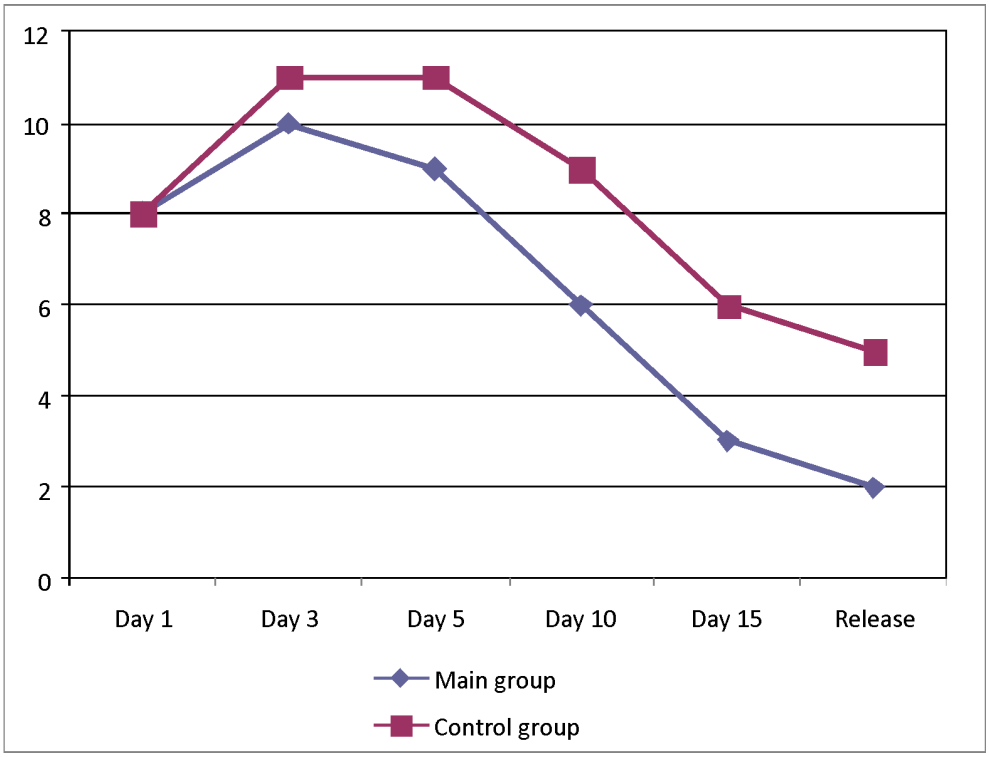

Figure 1. Dynamic of APACHE II indexes in the main and control group

The comparative assessment of the final results of patient treatment was carried out by the following parameters: no microbial content in the omental bursa, rate of postoperative complications, average duration of patients' hospitalization, and mortality rate.

After the first bursa sanitation, the microbial content remained above critical in 60% of main group patients and 65% of control group patients; after the second bursa sanitation – in 35% of main group patients and 44% of control

group patients; after the third bursa sanitation – in 8% of main group patients and 16% of control group patients.

Table 3 shows the intraabdominal complications in were discovered in 43.6% of control group patients and in 32% of main group patients. The rate of extraabdominal complications differed in the compared groups (19.3% in the control group and 14.1% in the main group).

One of the advantages of endoscopic sanitation of the omental bursa is the absence of postoperative hernias and a satisfactory cosmetic effect. The minimally invasive sanitation of the omental bursa in combination with small doses of DEC and ozone therapy in the combined treatment of infected pancreatic necrosis significantly reduced the duration of the patients' hospitalization.

Table 3. Rate of postoperative complications in patients with infected pancreatic necrosis in the main and control groups

Postoperative complications		*Main group* (n = 78)		*Control group* (n = 119)	
		abs.	%	abs.	%
Intraabdominal	Pancreatic abscess	10	12.8	23	19,3
	Retroperitoneal phlegmon	10	12.8	19	15,9
	Arrosive hemorrhage	3	3.8	5	4,2
	Gastric fistula	-	-	-	-
	Intestinal fistula	1	1.3	3	2,5
	Pancreatic fistula	1	1.3	2	1,7
Total		25	32	52	43.6
Extra-abdominal	Postoperative pneumonia	4	5.1	6	5,0
	Myocardial infarction	5	6.4	7	6,0
	Acute kidney failure	1	1.3	1	0,8
	Pulmonary embolism	1	1.3	1	0,8
	Ventral hernia	-	-	8	6,7
Total		11	14.1	23	19.3

The hospitalization duration was 35.4±1.48 bed days in the main group and 53.3±1.9 bed days in the control group, i.e. it was 1.5 times greater in the control group. The research also found a drop in the postoperative mortality rate: 16 (20.5%) main group patients and 41 (34.4%) of control group patients. The structure of the mortality rate differed. For instance, abdominal sepsis caused 15.9% of deaths in the control group and 7.7% - in the main group (Table 4).

Table 4. Causes of death of patients with infected pancreatic necrosis

Causes of death	*Number of deceased patients*	
	Control group	Main group
	n-41	n-16
Progression of enzymatic-toxic shock	10 (8.4%)	4 (5.1%)
Progression of endotoxicosis, abdominal sepsis	19 (15.9%)	6 (7.7%)
Arrosive hemorrhage	4 (3.4%)	2 (2.6%)
High small intestine fistula	2 (1.7%)	-
Pulmonary embolism	1 (0.8%)	1(1.3%)
Myocardial infarction	5 (4.2%)	3 (3.8%)
Total number of deceased patients	41 (34.4%)	16 (20%)

Discussion and Conclusion

There are various techniques for detecting the development of SAP; effective detection requires using a combination of techniques, depending on the stage and complication of the pathology (Büchler et al., 2000; Mikolasevic et al., 2016).

Combined treatment of sterile pancreatic necrosis with small doses of direct electric current and intravenous ozone therapy facilitates the rapid improvement of the patients' overall state, accelerates the normalization of clinical and laboratory indexes, and prevents sterile pancreatic sclerosis from transitioning into the infected form by three times. Therefore, preventive treatment of infected necrotic pancreatic foci is a promising method (Ersoz et al., 2016).

The combination of small doses of direct electric current, ozone therapy, and omental pancreatic bursoscopy in the combined treatment of infected pancreatic necrosis accelerates the drop in the microbial content of the suppurative focus, reduces the rate of intra- and extraabdominal complications by 1.4 times, reduces the mortality rate by 1.7 times, and reduces the duration of hospitalization by 1.4 times. Therefore, it is an effective means of treatment of duct-destructive forms of acute pancreatitis (Kaliev et al., 2013).

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Banks, P. A., & Freeman, M. L. (2006). Practice Guidelines in Acute Pancreatitis. *The American Journal of Gastroenterology 101(10)*, 23–79.

Banks, P. A., Bollen, Th. L., Dervenis, Ch., Gooszen, H. G., Johnson, C. D., Sarr, M. G., Tsiotos, G. G., & Vege, Santhi S. (2013). Classi Fi Cation of Acute Pancreatitis — 2012. *Gut, 62(1)*, 102-11.

Beger, Hans G., & Rau Bettina M. (2007). Severe Acute Pancreatitis. *Clinical Course and Management, 13*(38), 5043–5051.

Bennett, G. L., & Balthazar, E. J. (1998). *Imaging of Acute and Chronic Pancreatitis in Hepatobiliary and Pancreatic Radiology*. In G.S. Gazelle, S. Sai, P.R. Mueller (Eds.). New York: Thieme, 1238 p.

Bertin-Maghit, M., Goudable, J., Dalmas, E., Steghens, J. P., Bouchard. C., Gueugniaud, P. Y., Petit. P., & Delafosse, B. (2000). Time Course of Oxidative Stress after Major Burns. *Intensive Care Medicine 26(6)*, 800–803.

Besselink, M. G., VanSantvoort, H. C., Boermeester, M. A., Nieuweohuijs, V. B., VanGoor, H., Dejong, C. H, C., Schaapherder, A. F., & Gooszen, H. G. (2009). Timing and Impact of Infections in Acute Pancreatitis. *British Journal of Surgery 96*(3), 267–273.

Boyko, V. V., Krivoruchko, I. A., Shevchenko, R. S., Smachilo, R. M., & Pesotsky, O. N. (2002). Acute Pacreatitis. *Pathophysiology and Treatment, 7,* 47-52.

Bradley, E. L. (1993). Clinically Based Classification System for Acute Pancreatitis. *Arch Surg, 128,* 111-121.

Büchler, M. W., Gloor, B., Müller Ch. A., Friess, H., Seiler, Ch. A., & Waldemar, Uhl. (2000). Acute Necrotizing Pancreatitis: Treatment Strategy according to the Status of Infection. *Annals of Surgery, 232(5)*, 619–626.

Chak, A., Hawes R. H., Cooper, G. S., Hoffman, B., Catalano, M. F, Wong, R. C. K., Herbener, Th. E., & Sivak M. V. (1999). Prospective Assessment of the Utility of EUS in the Evaluation of Gallstone Pancreatitis. *Gastrointestinal Endoscopy 49(5)*, 599–604.

Connor, S., Raraty, M. G. T., Howes. N., Evans, J., Ghaneh, P., Sutton, R., & Neoptolemos, J. P. (2005). Surgery in the Treatment of Acute Pancreatitis. *Scandinavian Journal of Surgery, 94(6)*, 135–142.

Dröge, W. (2002). Free Radicals in the Physiological Control of Cell Function. *Physiological Reviews 82(1),* 47–95.

Ersoz, N., Ozler, M., Topal, T., Uysal, B., Poyrazoglu, Y., Simsek, K., Gocgeldi, E., & Korkmaz, A. (2016). The Effect of Ozone Treatment on Experimental Colon Anastomosis in Rats. *European Surgery 48(2)*, 122–128.

Ferreira, F. L., Bota, D. P., Bross, A., Mélot, Ch., & Vincent, J. L. (2001). Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients. *Jama 286(14)*, 1754–1758.

Forman, H. J., Augusto, O., Brigelius-Flohe, R., Dennery, Ph. A., Kalyanaraman, B., Ischiropoulos, H., Mann, G. E., Radi, R., Roberts, L. J., & Vina, J. (2015). Even Free Radicals Should Follow Some Rules. *Free Radical Biology and Medicine 78*, 233–235.

Gabrielyan, N. I., Savostyanova, O. A., Gorskaya, Ye. M., & Poptsov, V. I. (2011). The Significance of Postoperative Measurement of the Middle Molecular Weight as a Predictor of Suppurative Septic Infections in Cardiac Surgery Patients. *Epidemiology and Infectious Diseases, 1*, 20–25.

Halliwell, B., & Chirico, S. (1993). Lipid Peroxidation. *The American Journal of Clinical Nutrition, 57(5)*, 715–724.

Herath, H. M., & Kulatunga, A. (2016). Acute Pancreatitis Complicated with Deep Vein Thrombosis and Pulmonary Embolism. *Journal of Medical Case Reports, 10,* 253-267.

Kaliev, A. A., Zhakiev, B. S., Eleulov, G. A., & Konakbaeva, N. K. (2013). Concomitant Use of Intravenous Ozone Therapy and Small Doses of Direct Current in the Integrated Treatment of Patient with Sterile Pancreatic Necrosis. *Proceedings of the Russian Academy of Medical Sciences/Russian Academy of Medical Sciences*, *1(2)*, 16–18.

Karakayali, F. Y. (2014). Surgical and Interventional Management of Complications Caused by Acute Pancreatitis. *World Journal of Gastroenterology, 20(37)*, 134-142.

Knaus, W. A, Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). A Severity of Disease Classification System. *Critical Care Medicine, 13(10)*, 818–829.

Knaus, W. A., Wagner, D. P., Draper, E. A., Zimmerman, J. E., Bergner, M., Bastos, P. G., Sirio, C. A, Murphy, D. J., Lotring, T., & Damiano, A. (1991). Prognostic System. Risk Prediction of Hospital Mortality for Critically Hospitalized Adults. *Chest Journal, 100(6),* 1619–1636.

Lankisch, P. G., Assmus, C., Maisonneuve, P., & Lowenfels, A. B. (2002). A Study in a Defined German Population. *Pancreatology, 2(5),* 469–477.

Larvin, M. & Mcmahon M. J. (1989). Score for Assessment and Monitoring of Acute Pancreatitis. *The Lancet, 334*, 201–205.

Li, Q., Bai Z., Xueyan Z., Chendlin P., Wenpeng C., Wang Y., Jing S., Wenguo C., & Wenpeng, M. (2016). Treatment of Necrotizing Acute Pancreatitis with Peritoneal Lavage and Dialysis by a New Simpli Fi Ed Technique Insert Catheters. *Medicine, 95(23),* 214–226.

Lindkvist, B., Appelros, S., Manjer, J., & Borgström, A. (2004). Trends in Incidence of Acute Pancreatitis in a Swedish Population: Is There Really an Increase? *Clinical Gastroenterology and Hepatology 2*(9), 831–837.

Maher, M. M., Lucey, B. C., Gervais, D. A., & Mueller, P. R. (2004). Acute Pancreatitis: The Role of Imaging and Interventional Radiology. *Cardiovascular and Interventional Radiology, 27*, 208–225.

Mikolasevic, I., Milic, S., Orli,c L., Poropat, G., Jakopcic, I., Franjic, N., Klanac, A., Kristo, N., & Stimac, D. (2016). European Journal of Internal Medicine Metabolic Syndrome and Acute Pancreatitis. *European Journal of Internal Medicine*., *12(2)*, 245-252.

Nikolskaya, V. A., Danilchenko, Yu. D., & Memetova Z. N. (2013). The Biochemical Aspect of the Role of Middle Molecular Mass in the Organism. *Scientific Notes of the Community of the V.I. Vernadsky Tavrida National University, 5,* 145-152.

Nydegger, A., Heine, R. G., Ranuh, R., Gegati-levy, R., Crameri, J., & Oliver, M. R. (2007). Changing Incidence of Acute Pancreatitis. *Gastroenterology 22*: 1313–1316.

Ostrovskiĭ, V. K., Alimov, R. R., Mashchenko, A. V., Semenova, O. P., & Kurapova, M. I. (2003). Normal Parameters of Leukocyte Index of Intoxication. *Clinical Laboratory Diagnostics*, *1*, 45–46.

Pankhurst, Q. A., Connolly, J., Jones, S. K., & Dobson J. (2003). Applications of Magnetic Nanoparticles in Biomedicine. *Journal of Physics, 36*, 167–181.

Papachristou, G. I., Muddana, V., Yadav, D., Connell, M. O., & Sanders, M. K. (2010). Comparison of BISAP , Ranson's, APACHE-II , and CTSI Scores in Predicting Organ Failure, Complications, and Mortality in Acute Pancreatitis. *The American Journal of Gastroenterology 105*, 435–441.

Pereslegina, I. A. (1989). The Activity of Antioxidant Enzymes in the Saliva of Healthy Children. *Laboratory Studies*, *11*, 20–23.

Ranson, J. H. (1979). The Timing of Biliary Surgery in Acute Pancreatitis. *Annals of Surgery 189(5),* 654.

Schwartz, J., Winters, J. L., Padmanabhan, A., Balogun, R. A., Delaney, M., Linenberger, M. L., Szczepiorkowski, Z. M., Williams, M. E., Wu Yanyun, & Shaz, B. H. (2013). Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis. *Journal of Clinical Apheresis 28(3),* 145–284.

Sheĭko, V. D., & Oganezian A. H. (2013). The Optimization of Surgical Tactics in Local Accumulations of Liquid in Patients with Severe Acute Pancreatitis. *Ministry of Healthcare of Ukraine, Scientific Community of Surgeons of Ukraine, 12*, 22–24.

Spanier, B. W., Dijkgraaf, M. G., & Bruno M. J. (2008). Epidemiology, Aetiology and Outcome of Acute and Chronic Pancreatitis. *Best Practice & Research Clinical Gastroenterology* 22*(1)*, 45–63.

Tenner, S., Baillie, J., DeWitt, J., & Vege, S. S. (2013). American College of Gastroenterology Guideline. *Am J Gastroenterol*, *108(9),* 140–152.

Tinto, A., Lloyd D. A. J., Kang, J.-Y., Majeed, A., Ellis, C., Williamson, R. C., & Maxwell, J. D. (2002). Acute and Chronic Pancreatitis-Diseases on the Rise. *Alimentary Pharmacology & Therapeutics, 16(12)*, 97–105.

Tokar, J. L., Barth, B. A., Banerjee, S., Chauhan, Sh. S., Gottlieb, K. T, Konda, V., Maple, J. T., Murad, F. M., Pfau, P. R., & Pleskow, D. K. (2013). Electrosurgical Generators. *Gastrointestinal Endoscopy, 78(2)*, 197–208.

VanSonnenberg, E., Wittich, G. R., Casola, G., Brannigan, T. C., Karnel, F., Stabile, B. E., Varney, R. R., & Christensen, R. R. (1989). Percutaneous Drainage of Infected and Noninfected Pancreatic Pseudocysts. *Radiology, 170(3),* 757–761.

Vinokurov, M. M., Savel'ev, V. V., & Ammosov, V. G. (2008). Advantages and Disadvantages of Various Surgical Tactics in Treatment of Infected Pancreatic Necrosis. *Surgery*, *11*, 23–26.

Volchegorsky, I. A., Dolgushin, I. I., Kolesnikov, O. L., & Tseylikman, V. E. (2000). *Experimental Modeling and Laboratory Assessment of the Organism's Adaptation Responses*. Chelyabinsk: Mir, 167 p.

Voskanyan, S. E., Kotenko, K. V., Korsakov, I. N., & Naydenov, E. V. (2013). Prediction of the Acute Pancreatitis after Surgery on the Pancreas. *Experimental & Clinical Gastroenterology*, *9*, 61–68.

Wu, B. U., Johannes, R. S., Xiaowu S., Ying T., Conwell, D. L, & Banks, P. A. (2008). The Early Prediction of Mortality in Acute Pancreatitis. *Gut* 57*(12),* 1698–1703.

Yousaf, M., McCallion, K., & Diamond, T. (2003). Management of Severe Acute Pancreatitis. *British Journal of Surgery 90*(4), 407–420.

Zerem, E. (2014). Treatment of Severe Acute Pancreatitis and Its Complications. *World Journal of Gastroenterology* 20(38), 13879–13892.