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Tactics of infusion therapy in patients with acute destructive pancreatitis: a narrative review

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Тактика инфузионной терапии у больных с острым деструктивным панкреатитом: обзор литературы

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Abstract

INTRODUCTION: Infusion therapy is the main method of correcting pathological changes that occur during the phase of "aseptic" inflammation in acute pancreatitis. **OBJECTIVE:** Summarize current data on infusion therapy regimens in patients with acute destructive pancreatitis, the advisability of using various infusion solutions and options for monitoring the effectiveness of therapy. **MATERIALS AND METHODS:** The study was carried out in accordance with international reporting requirements for reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The search was carried out in the following Internet search engines Pubmed and Cochrane Controlled Clinical Trials Register. To select articles, a literature reference search method was also used. The search strategy did not include restrictions on language, article type, or date. **RESULTS:** The analysis of literature data revealed two approaches to infusion therapy. The initial interest in "aggressive (4 liters per day or more)" infusion therapy regimens in the first 24 hours of the disease has now been replaced by a trend towards less "aggressive" regimens due to the publication of works on the high incidence of various complications (progression of organ dysfunction, local complications). When considering the qualitative composition of infusion therapy, preference should certainly be given to crystalloids. Basic monitoring of infusion therapy should include non-invasive methods: heart rate, blood pressure, diuresis rate. **CONCLUSIONS:** The analysis demonstrated different approaches to the tactics of infusion therapy in this category of patients. further research into the effectiveness and safety

Реферат

АКТУАЛЬНОСТЬ: Инфузионная терапия — основной метод коррекции патологических изменений, которые возникают в фазу «асептического» воспаления при остром панкреатите. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Обобщить актуальные данные о схемах инфузионной терапии у больных с острым деструктивным панкреатитом, целесообразности применения различных инфузионных растворов и вариантов мониторинга эффективности терапии. **МАТЕРИАЛЫ И МЕТОДЫ:** Исследование выполнено в соответствии с международными требованиями отчетности для обзоров (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Поиск осуществлялся в поисковых системах сети Интернет Pubmed и Cochrane Controlled Clinical Trials Register. Для отбора статей также был применен метод поиска по ссылкам литературы. Стратегия поиска не предусматривала ограничений по языку, типу и дате статьи. **РЕЗУЛЬТАТЫ:** Проведенный анализ данных литературы выявил два подхода к инфузионной терапии. Первоначальный интерес к «агрессивным» (4 л/сут и более) схемам инфузионной терапии в первые 24 ч заболевания в настоящее время сменился тенденцией к менее «агрессивным» схемам в связи с появившимися работами о высокой частоте различных осложнений (прогрессирование органной дисфункции, местные осложнения). Рассматривая качественный состав инфузионной терапии, безусловно, предпочтение следует отдавать кристаллоидам. Базовый мониторинг инфузионной терапии должен включать неинвазивные методы: частоту

of infusion therapy, taking into account the varying severity of acute pancreatitis, the possibility of the influence of the qualitative composition of the infusion on the course of this disease and the formation of recommendations for initial and maintenance infusion therapy based on the principles of personalized medicine.

KEYWORDS: acute pancreatitis, infusion therapy, fluid responsiveness, Ringer lactate

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сердечных сокращений, среднее артериальное давление, темп диуреза. **ВЫВОДЫ:** Анализ продемонстрировал различные подходы к тактике инфузионной терапии у данной категории больных. Необходимо дальнейшее исследование вопросов эффективности и безопасности инфузионной терапии с учетом различной степени тяжести острого панкреатита, возможности влияния качественного состава инфузии на течение данного заболевания и формирование рекомендаций стартовой и поддерживающей инфузионной терапии, основанных на принципах персонализированной медицины.

КЛЮЧЕВЫЕ СЛОВА: острый панкреатит, инфузионная терапия, жидкостная реанимация, Рингер лактат

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Introduction

Acute pancreatitis is an inflammatory disease of the pancreas, characterized by a high incidence of complications. According to available data, about 2.5 million cases of the disease are recorded annually worldwide [1]. According to various data a severe form develops in 10–20 %, which leads to death in 15–40 % of cases [2]. It should also be emphasized that the main cause of death in the first week of the disease is the progression of organ dysfunction, which manifests itself already on the first day in 17 % of cases in patients with severe acute destructive pancreatitis [3].

In the absence of specific pharmacological therapy, infusion therapy is currently one of the basic types of therapy for patients in the first 72 hours from the onset of the disease. According to the literature, the effects of the classical approach — "aggressive" infusion therapy — are currently being actively studied and considered. However, despite the frequent mention of this term in both Russian and foreign literature, no author has formulated a clear definition of "aggressive" infusion therapy. It is more likely to focus on indicators of 3–5 ml/kg/h or more in the first 24 hours from the onset of the disease. Since this rate was used in various studies when considering the option of "aggressive" infusion therapy [4]. At the same time, excessive infusion therapy may contribute to further progression of multiple organ failure syndrome against the background of myocardial overload and an increase in interstitial edema of the pulmonary parenchyma with the development of disorders of the oxygenating function of the lungs. There are studies that have shown that "non-aggressive" infusion therapy can have a positive effect on the course and outcome of the disease [5, 6]. The important role of infusion therapy is also determined by the fact that correct infusion allows minimizing disturbances in the respiratory, hemodynamic (volumetric oxygen transport) and tissue components of the oxygen transport system and, consequently, the development of hypoxia/reperfusion syndrome. Hypoxia/reperfusion syndrome induces disturbances in mitochondria, leading under certain conditions to the progression of cell dysfunction or death

[7]. The clinical manifestation of these changes is an increase in organ dysfunction.

Therefore, despite the presence of a large number of publications devoted to the tactics of infusion therapy for acute destructive pancreatitis, discussion continues. They are aimed at determining the volume of infusion, the type of infusion media, as well as the required amount of hemodynamic monitoring in order to ensure effectiveness and safety.

Objective

The target of this review is to summarize current data on infusion therapy regimens in patients with acute destructive pancreatitis, the expedience of using various infusion solutions, and options for monitoring the effectiveness of therapy.

Materials and methods

A review of studies on infusion therapy in patients with acute destructive pancreatitis was conducted. The study was carried out in accordance with international reporting requirements for reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The search was carried out using the Pubmed and Cochrane Controlled Clinical Trials Register search engines. To select articles, a literature reference search method was also used. The search strategy did not include restrictions on language, article type, or date. The following queries were used for the search: "acute pancreatitis" and "infusion therapy", "acute pancreatitis and fluid responsiveness", "acute pancreatitis and Ringer-Lactate".

There were the following criteria for inclusion in the review: full-text publications devoted to the problem of infusion therapy tactics for destructive pancreatitis, hemodynamic monitoring in patients with acute destructive pancreatitis, the influence of various infusion solutions on the effectiveness of infusion therapy in patients with acute destructive pancreatitis.

The exclusion criteria were the following: duplicates, abstracts, abstract publications without a full-text version, publications not related to infusion therapy and hemodynamic monitoring in patients with acute destructive pancreatitis in adults (Figure 1).

Pathophysiological basis for the use of infusion therapy

The main goals of infusion therapy in patients with acute destructive pancreatitis in the phase of aseptic inflammation are to restore the volume of the vascular bed, stabilize hemodynamics and correct pathological changes at the microcirculation level. These disorders arise as a result of the influence of various digestive enzymes against the background of necrosis of pancreatic cells. As a result, there is an increase in the level of various inflammatory mediators that affect the tone of the vascular wall (vasoconstriction at the level of arterioles) and the functional state of its epithelium (increased permeability) [3]. At the same time, activation of the hemostatic system towards hypercoagulation is observed. As a result, massive microthrombosis occurs at the level of microcirculation with a slowdown or cessation of blood flow. All this creates conditions for the development of hypoxia/reperfusion syndrome and the occurrence of organ dysfunction.

Clinical manifestations of changes in vascular permeability are pronounced deposition of fluid in the third space (abdominal cavity, pleural cavities), which is accompanied by tachycardia, hypotension, oliguria and laboratory signs of hemoconcentration.

Hemoconcentration and hematocrit level were among the first indicators that were proposed to assess the severity

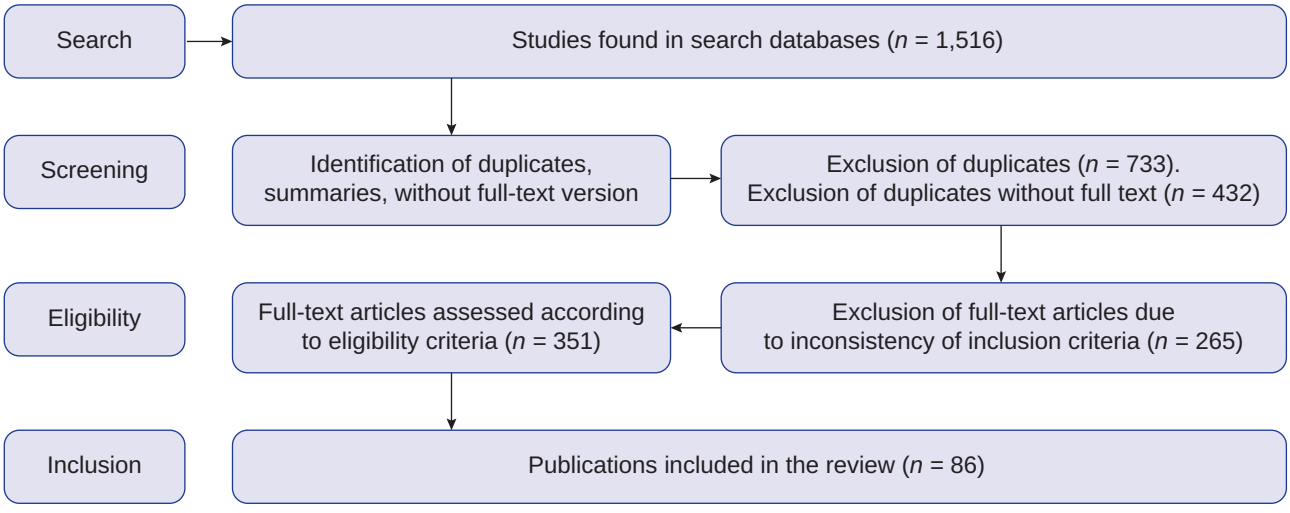

Fig. 1. Block diagram of the literature search algorithm

of the disease and predict the volume of damage to the pancreas [8, 9]. Thus, a number of studies have demonstrated data that a hematocrit level of 44 % or more in the first 24 hours from the onset of the disease contributes to the progression of pancreatic cell necrosis and affects the course of the underlying disease [9, 10]. The indicators that have been used for quite a long time as criteria for assessing infusion therapy are urea and creatinine [11,12]. In patients with acute destructive pancreatitis, against the background of intravascular hypovolemia and hypotension, conditions for the occurrence of disturbances in renal blood flow and filtration function of the kidneys are created. In this case, the increase in urea and creatinine levels indirectly reflect the adequacy of recovery or the level of persisting disorders during infusion.

To objectify the indicators, the KDIGO (Kidney Disease Improving Glodal Outcomes) criteria, which allows to determine the stage of acute kidney injury,should be used. It must be emphasized that the goals of infusion therapy in patients with acute destructive pancreatitis differ significantly from the tasks solved by correcting hypovolemia against the background of acute blood loss. This is due to the occurrence of endothelial damage, increased vascular permeability and the progression of fluid deposition in the interstitium against the background of severe systemic inflammation in patients with acute pancreatitis. The goals of infusion therapy in this category of patients should be considered not only replenishment of the vascular bed, but also correction of the inflammatory response, stabilization of the vascular wall and maintenance of the barrier function of the intestinal wall [13].

Numerous works devoted to the pathogenesis of acute destructive pancreatitis have demonstrated the role of infusion therapy in the treatment of this category of patients. This circumstance has caused an increase in research devoted to the study of the effects and tactics of infusion therapy for destructive pancreatitis. In the 1980s, the first works that studied the effect of infusion therapy on the course of acute pancreatitis in various animal models appeared. The works that demonstrated the positive effects of using both crystalloid and colloid solutions were provided [14–16]. The authors of the studies confirmed the improvement in splanchnic blood flow in general and pancreatic perfusion in particular in work on various laboratory animals (pigs, dogs, rats). Further studies were aimed at solving the problem of infusion therapy tactics in patients with varying severity of the disease and the selection of optimal infusion media.

Who is infusion therapy indicated for?

According to Russian clinical guidelines, it is customary to distinguish three forms of acute pancreatitis: mild, moderate and severe [17, 18]. The key drawback of the basic classification presented in Russian recommendations, adopted in Atlanta [19] in 1992, is that the severity of acute destructive pancreatitis is assessed according to the time of occurrence of complications from the onset of the disease (organ dysfunction or the presence of purulent-septic complications). This approach allows only a retrospective assessment of both the severity of the process and the quality of the treatment provided, including infusion therapy. However this classification of the course of pancreatitis does not provide a solution to one of the key problems — routing (specialized department or intensive care unit). Not only routing but also infusion therapy tactics (volume, rate of administration, monitoring) in patients with mild and in some cases moderate (in the absence of signs organ dysfunction) forms of acute pancreatitis, as the main tool for preventing the appearance and progression of foci of pancreatic tissue necrosis and the development of organ dysfunction. According to current recommendations, there are no differences in volemic load between mild and moderate forms [18]. There is no doubt that the severity of hypovolemia differs significantly in these forms of pancreatitis. This creates the prerequisites for the development of hypervolemia in patients with a mild form; against this background, the risk of complications increases. At the same time, massive infusion therapy should be prescribed to patients with moderate and severe forms of acute destructive pancreatitis. The main goal of infusion therapy is to minimize damage to the pancreas and relieve the manifestations of the systemic inflammatory response. Adequate infusion therapy significantly affects the severity of organ dysfunction and mortality rate in patients with acute pancreatitis [20, 21]. Meanwhile the lack of positive dynamics during therapy correlates with the degree of damage to the gland and serves as an unfavorable marker of the course of the disease [21, 22].

What type of infusion solution is advisable to use?

There is still no clear opinion which solution should be considered as ideal while conducting infusion therapy. There are various studies that have examined the effects of both colloids and crystalloids. Colloids are usually represented by solutions of albumin, hydroxyethyl starch and gelatin-based preparations. Among the crystalloids, the most commonly used are 0.9 % sodium chloride solution (saline) or Ringer's lactate solution.

Based on theoretical premises, colloids should have become the optimal solution for the rapid correction of intravascular hypovolemia and hypotension in patients with acute destructive pancreatitis. Large molecule size of the colloid was supposed to contributed to this effect. As a result, high oncotic pressure and prolonged retention of fluid in the lumen of the vascular bed remained. An additional argument for the use of colloids to crystalloids was the possibility of using them significantly less to achieve a clinical effect. Consequently, the risks of hypervolemia and complications caused by this condition especially in the group of patients with concomitant cardiac pathology were reduced. The first experimental and clinical studies confirmed the positive properties of colloidal solutions. Thus, the experi-

ment revealed a decrease in the volume of pancreatic lesions against the background of intra-aortic administration of colloidal solutions [23], a positive effect on the microvasculature [24] and capillary leak syndrome [25], and a decrease in trypsinogen activity [26]. Thus, the experiment revealed a decrease in damage to the pancreas during intra-aortic administration of colloidal solutions [23], a positive effect on the microvasculature [24] and capillary leak syndrome [25] and a decrease in trypsinogen activity [26]. The authors of clinical studies reported the effect of colloids on the course of the systemic inflammatory response and a lower likelihood of intra-abdominal hypertension syndrome in this category of patients [27]. There were researches have demonstrated the positive effect of colloid infusion compared with crystalloids on the severity of multiple organ failure syndrome, infectious complications and the course of the inflammatory reaction [13]. Nevertheless, further randomized trials comparing the use of colloid and crystalloid solutions demonstrated a higher incidence of complications of infusion therapy, levels of organ dysfunction and mortality with the active use of colloid solutions [28, 29]. In a review by Lewis S.R. et al. (2018) it was noted that the inclusion of colloids in fluid therapy regimens increased the need for renal replacement therapy (relative risk (RR) 1.35; 95 % confidence interval (95 % CI) 1.01–1.80; $p = 0.04$) and increased the risk of death (RR 1.17; 95 % CI 1.01–1.36; $p = 0.03$) [30]. All these published results contributed to a significant reduction in the frequency of use of colloidal solutions in patients with acute destructive pancreatitis. Currently, all modern clinical guidelines recommend to use only crystalloid solutions when creating an infusion therapy program [18, 31–33].

For a long time, the main crystalloid solution used during infusion therapy in patients with acute destructive pancreatitis was saline solution. However, massive infusion of this solution can lead to hyperchloremia, a decrease in pH, an increase in the severity of the systemic inflammatory response [34, 35] and consequently progression of the severity of the disease. Hyperchloremic acidosis also influences on the appearance of renal vasoconstriction with decreased blood flow and the development of acute kidney injury [36, 37]. The effectiveness and feasibility of using Ringer's lactate solution in patients with acute destructive pancreatitis is now also being researched. There are experimental studies that have demonstrated the positive effect of Ringer's lactate solution on the course of systemic inflammation, trypsin activity and the severity of metabolic acidosis [38, 39]. A randomized controlled research comparing lactated Ringer's solution with saline was published in 2018 (there were more than 15,000 patients involved). There was a significant difference in the incidence of acute kidney injury (odds ratio (OR) 0.90; 95 % CI 0.82–0.99; $p = 0.04$) and no difference in 30-day mortality index (10.3 and 11.1 %, $p = 0.06$) [39]. In the last decade, a number of randomized studies which reported a more favorable course of systemic inflammation and disease severity in patients receiving Ringer's lactate solution as the main component of infusion therapy has also been presented [40–42]. At the present time, meta-analyses noting the positive effects of Ringer's lactate solution have been published. Thus, in a meta-analysis by Di Martino M. et al. (15 studies; 1,074 patients) revealed a significantly lower incidence of complications during infusion of Ringer's lactate solution (OR 0.48; 95 % CI 0.29–0.81, $p = 0.006$) [33]. For the last 5 years meta-analyses comparing the clinical efficacy of crystalloids, differences in organ dysfunction, and mortality have reported mixed findings. In the studies there were not any associations in outcome between the findings obtained from solutions or lactated Ringer's [43, 44]. The work of Ocskay K. et al. demonstrated a significantly lower incidence of deaths and the degree of organ dysfunction in the group of patients who used Ringer lactate as the main solution, though [45]. It should be noted that these data were obtained in a group of patients with moderate severity of acute pancreatitis. In this regard, modern recommendations present different views on the advisability of using a certain type of crystalloid. Therefore, a number of clinical recommendations define Ringer lactate as the optimal solution for infusion therapy in patients with acute destructive pancreatitis [31, 32]. This inference is absent in Russian clinical recommendations, as well as in a number of foreign ones [18, 46].

Tactics of infusion therapy

The main issue of discussion when choosing the tactics of infusion therapy in patients with acute destructive pancreatitis is the advisability of using large dosages in the first 24–48 hours from the moment of illness, as well as the rate of fluid administration. Currently, there are two fundamental models of infusion therapy in patients with acute destructive pancreatitis in the first 72 hours of the disease: "aggressive" and "non-aggressive". In studies presented by the Mayo Clinic group, "aggressive" tactics are defined as the application of more than 33 % of the total 72-hour infusion dosage in the first 24 hours from the start of therapy [47]. The Mayo Clinic group presented two retrospective studies [47, 48], which examined the feasibility of using "aggressive" infusion therapy tactics. The first study included 28 patients who received a "non-aggressive" type of therapy and 17 patients who received an "aggressive" type of infusion. A significantly higher mortality rate was found in the group with "non-aggressive" infusion therapy tactics (17 % and 0 %; $p < 0.04$). In the second study, the group with the "non-aggressive" type of infusion had a more intense systemic inflammatory response. Similar data were published by Wall I. et al. [49]. According to the results obtained, the rates of pancreatic damage and mortality were significantly higher than in the group of patients who received an infusion dosage of 194 ml/h in the first 6 hours and 188 ml/h in the next 12 hours than in the group receiving 234 ml/h and 221 ml/h, respectively, in the first 6 hours and the next 12 hours. In 2019, a multicenter retrospective study that

included 1,097 patients was published. They were divided into two groups: a "non-aggressive" infusion group (708 patients, less than 6,000 ml in the first 24 hours) and an "aggressive" infusion group (389 patients, more than 6000 ml in the first 24 hours) [50]. The mean infusion levels in the groups were 3,992 ± 1,097 ml and 8,706 ± 3,011 ml, respectively ($p < 0.001$). The initial analysis demonstrated a significantly longer duration of mechanical ventilation ($p < 0.001$) and mortality ($p < 0.05$) in the group with the "aggressive" type of infusion. However, later the authors identified patients with severe acute destructive pancreatitis criteria according to the Atlanta classification (revision 2012). 201 patients were included in the group with "aggressive" infusion therapy, and 167 patients were included in the group with "non-aggressive" infusion therapy. The analysis in this subgroup of patients did not reveal differences in mortality rates ($p = 0.15$), incidence of purulent-septic complications ($p = 0.77$) and frequency of surgical treatment ($p = 0.76$). Multivariate analysis demonstrated a decrease in mortality rates in the group with the "aggressive" type of infusion (OR 0.56; 95 % CI 0.32–0.98; $p < 0.05$). However, there is evidence that "aggressive" fluid resuscitation may sometimes lead to increased mortality and complication rates in patients with acute pancreatitis. Thus, according to Mao E.Q. et al. [51], there were higher rates of mortality, duration of mechanical ventilation, incidence of intra-abdominal hypertension and sepsis obtained in the group with infusion therapy (10–15 ml/kg/h in the first 72 hours) compared with the group of patients receiving infusion of 5–10 ml/kg/h. The same group of authors published work [52], demonstrating that when the hematocrit level in the patient group reached 35 % in the first 48 hours, the mortality rate was 36 %, and in the comparison group with a lower hematocrit level it was 15.3 %. Eckerwall G. et al. [6] noted a higher incidence of respiratory failure (66 % *vs.* 53 %; $p < 0.001$) in patients who received more than 4,000 ml of infusion in the first 24 hours. In 2019 Bo Y. et al. published a retrospective study, included 179 patients with a clinical picture of moderate to severe acute destructive pancreatitis [53]. The results of the study demonstrated that in the group with "aggressive" infusion (4,000 ml or more in the first 24 hours), acute kidney injury occurred significantly more often (53.12 and 25.64 %, $p = 0.008$), persisted for a longer time ($p = 0.038$), and there was a higher need for renal replacement therapy (47.27 *vs.* 30.65 %, $p = 0.042$). Adverse effects were also reported by other authors, who discovered a high level of mortality and incidence of organ dysfunction against the background of "aggressive" infusion therapy regimens [5, 54, 55]. In 2020, a meta-analysis that included 11 researches (2,685 patients) was published, the main purpose was to evaluate the effect of "aggressive" infusion therapy tactics on disease outcomes [4]. Analysis in subgroups of patients considering the severity of acute pancreatitis was not done due to insufficient data. The authors of this study discovered a higher incidence of acute kidney injury (RR 2.17; 95 % CI 1.66–2.83) and respiratory failure, correction of respiratory failure required artificial ventilation (RR 2.4; 95 % CI 1.63–3.54). There are quite contradictory results of various infusion therapy regimens based on the administered of infusion solution at a certain rate for a given period of time. In view of the above, regimens with a loading dose (bolus) followed by a sequential change in fluid administration have been proposed. Regimen with a loading dose (bolus) followed by a sequential change in fluid administration have been proposed. So, Nasr J.Y. et al. [56] offered a regimen that is used in their clinical practice: bolus injection of 20 ml/kg followed by dosing of 3 ml/kg/h for 24 hours. In 2011, Wu B.U. et al. [57] published a study comparing different infusion regimens using two types of crystalloids. They were Ringer's solution lactate and saline: 20 ml/kg bolus + 3 or 20 ml/kg bolus + 1.5 ml/kg/h and liberal type of infusion therapy (infusion dose and rate were determined by the attending physician based on clinical data). To assess the effectiveness of the regimens, signs of a systemic inflammatory response and dynamics of C-reactive protein levels were monitored over a 24-hour period. There weren't any significant differences found in these indicators.

Some authors have recommended using a fluid bolus of 20 ml/kg over 30–45 minutes followed by a maintenance rate of 2 ml/kg/h for 36 hours [58]. Buxbaum J.L. et al. (2017) compared two infusion regimens: 20 ml/kg bolus + 3 ml/kg/h and 10 ml/kg bolus + 1.5 ml/kg/h [59]. Early normalization of laboratory parameters (hematocrit, creatinine, urea) and indicators of the systemic inflammatory response were revealed in the group with an "aggressive" infusion therapy regimen. Nevertheless, there were no complications that could arise against the background of massive infusion. It should also be emphasized that only moderate acute destructive pancreatitis patients were included in the study. Also, in 2017, there was a publication of a retrospective multicenter study (1,010 patients) [60], which examined the effect of the dosage of initial infusion therapy (the first 4 hours from hospitalization) and the total daily dosage of infusion in the first 24 hours on disease outcomes.

According to the dosage of initial infusion therapy, patients were divided into three groups: up to 500 ml, 500–1,000 ml, more than 1,000 ml. There were no significant differences in mortality rates. Patients, whose infusion was up to 1,000 ml, had the smallest number of local complications (parapancreatic effusion, parapancreatic necrosis and pancreatic necrosis). Significant differences were obtained (OR 0.54; 95 % CI 0.35–0.83, $p < 0.025$) compared with the group of patients receiving an infusion of up to 500 ml. However, assessing the effect of daily infusion, there was a significantly higher number of local complications (OR 2.61; 95 % CI 1.63–4.19, $p < 0.025$) and the need for surgical intervention (OR 6.9; 95 % CI 1.54– 30.99, $p < 0.025$) in the group with a daily infusion of more than 4,300 ml compared with the group receiving no more than 3,200 ml. There were no differences between the groups receiving daily dosage of up to 3,200 ml and 3,200–4,300 ml. In 2022, a prospective randomized study, named the WATERFALL study, was pub-

lished [61]. It compared two infusion regimens: 122 patients received 20 ml/kg over 2 hours followed by an infusion of 3 ml/kg/h and 127 patients received 10 ml/kg in the presence of hypovolemia followed by an infusion of 1.5 ml/kg/h. In case of normovolemia, bolus therapy was not carried out. Assessments were conducted after 12, 24, 48 and 72 hours. Signs of hypervolemia appeared more often in patients with "aggressive" infusion therapy tactics (20.5 and 6 %, respectively), but no consistent indicators of negative outcomes were noted.

Due to the large amount of conflicting data and the lack of prospective randomized trials, recommendations for the rate and dosage of infusion therapy currently vary significantly:

- 5–10 ml/kg/h during the first 12–24 hours [32, 62];
- 250–500 ml/h in the first 24 hours [31];
- 160–500 ml/h ml for signs of hypovolemia or shock and 130–150 ml/h in patients without signs of hypovolemia [63];
- 20 ml/kg in the first 45 minutes; 3 ml/kg/h for the first 12 hours; 1.5 ml/kg/h under the control of hemodynamic parameters [64];
- 30–40 ml/kg/h for 2 hours, followed by correction based on an assessment of volumetric status and hemodynamic disturbances [18].

Hemodynamic monitoring as the basis of patient-centered infusion therapy

The previously presented results from various studies have clearly demonstrated that infusion therapy in patients with acute destructive pancreatitis can have both positive and negative effects. "Aggressive" regimens are relatively well tolerated by patients with moderate acute destructive pancreatitis. In severe forms, owing to severe capillary leakage, massive infusion is often accompanied by the progression of organ dysfunction and the occurrence of complications due to hypervolemia [65]. This is especially pronounced in patients with concomitant pathologies of the cardiovascular and respiratory systems. Thus, apparently, in this category of patients, infusion therapy should be carried out using monitoring that reflects the state of volumetric status, hemodynamics, tissue perfusion and ensures the safety and adequacy of the infusion [66]. According to the data, monitoring parameters used in patients with acute destructive pancreatitis, can be divided into non-invasive, invasive and laboratory data:

- In clinical practice, noninvasive parameters such as heart rate (HR), mean arterial pressure (MAP), and urine output are routinely assessed. High heart rate with low blood pressure and urine output are pathognomonic signs of severe tissue hypoperfusion [67]. Target values to strive for during infusion therapy are heart rate < 120 beats/min, blood pressure — 65–85 mmHg, diuresis rate — more than 50 ml/h. Other easily assessed signs such as the color and temperature of the skin, the symptom of capillary refill should not be neglected [68, 69]. Among non-invasive methods for assessing volume (circulating blood volume) status, the most promising is the use of ultrasound [70]. The main advantages of ultrasound are availability as a bedside method and the ability to evaluate indicators over time. Monitoring of several indicators is used to assess the level of volume. It is the most accessible and simple either to assess the diameter of the inferior vena cava or assess the level of collapse of the internal jugular vein. These indicators are most suitable for initially determining the initial level of volume. To monitor the effectiveness of infusion therapy, it is advisable to evaluate various indicators. The end-diastolic volume of the left ventricle with simultaneous assessment of the contractile function of the left ventricle (ejection fraction, stroke volume) are extremely important. Currently, a significant number of works have been presented demonstrating the possibility of dynamic assessment of hemodynamics and volumetric status in patients with shock [71, 72]. However, ultrasonography (US) is an operator-dependent procedure, the accuracy of measurements depends on the level of proficiency [73].
- Measurement of invasive hemodynamic parameters is available in intensive care units using a central venous catheter and an arterial catheter with pulse waveform assessment. One of the most accessible methods is measuring central venous pressure. Currently, there is an active discussion about the advisability of routine use of this technique to assess the level of circulating blood volume. There is a number of factors that can significantly affect this indicator. Despite the fact that most experts note the low information content of this technique, studies continue to appear. Some researches report the possibility of using this technique in critically ill patients [74, 75]. Based on the data obtained these works indicate more effective treatment of patients in groups which central venous pressure was routinely measured and treatment was adjusted. This technique has certain limitations in patients with acute destructive pancreatitis. It is primarily influenced by the significance of intra-abdominal hypertension [76, 77], which is common in this group of patients. Some authors claim that values of 5 mmHg. and below can be considered a sign of severe hypovolemia [78, 79]. There is no doubt that central venous pressure should not be used as the main method of monitoring. But this technique can be used in clinical practice as a screening to identify pronounced disorders and preliminary assessment of therapy. For long-term and routine assessment of hemodynamic disorders and the effectiveness of therapy, extended hemodynamic monitoring based on transpulmonary thermodilution should be conduct-

ed. It is recommended especially in patients with severe destructive pancreatitis. Such methods include PiCCO (Pulse Index Continuous Cardiac Output) monitoring. The use of this type of monitoring in patients with acute destructive pancreatitis [80, 81] showed a good correlation with the dynamics of cardiac output during infusion. It made possible to timely identify early signs of fluid overload, which had a positive effect on the quality of treatment. This was due to the ability to assess parameters in real time and timely correction of the infusion rate. Although additional studies are certainly required in a larger patient population.

- The main laboratory criteria include lactate level and mixed venous blood saturation [82]. These indicators make it possible to quickly identify violations of tissue perfusion and oxygen delivery. In some studies [83, 84] it was demonstrated that indicators of venous blood saturation and blood lactate content can sufficiently characterize the correspondence of oxygen delivery to oxygen consumption. Therefore, dynamically display the effectiveness of the therapy. Additionally, it is advisable to monitor hematocrit, urea and creatinine levels [65]. These indicators should be assessed initially and after 12–24 hours as markers of restoration of tissue perfusion. Works have been published showing the importance of assessing a number of indicators as a predictor of the severity and likelihood of an unfavorable course of the disease [85]. The most important indicators are hematocrit, urea initially and 24 hours after admission to the hospital. Lin S. et al. in their study presented data that the initial urea level upon admission > 6.1 mmol/l and an increase in this indicator to 8.3 and above indicate severe acute pancreatitis. And the urea level of 13.3 mmol/l and the absence of its decrease in the first 24 hours should be considered as a predictor of death [86]. Lin S. et al. in their study presented data that the initial urea level upon admission > 6.1 mmol/l and an increase in this indicator to 8.3 and above indicate severe acute pancreatitis. And the urea level of 13.3 mmol/l and the absence of its decrease in the first 24 hours should be considered as a predictor of death [86].

Thus, there are many methods for monitoring hemodynamics and assessing the effectiveness of infusion therapy in patients with acute pancreatitis. However, it should be noted that in studies devoted to the problem of the effectiveness of monitoring, the authors did not consider this issue taking into account the severity of the disease. Non-invasive indicators (heart rate, blood pressure, diuresis rate) in combination with laboratory data (hematocrit, urea, creatinine) are promoted as the main control parameters. This amount of monitoring is likely to be optimal for patients with mild disease. Moderate severity and severe disease patients are required methods that allow to evaluate real-time assessment of changes during therapy and make the necessary adjustments. These methods include invasive hemodynamic monitoring. Invasive monitoring is an expensive procedure, which can lead to various complications. Unfortunately, there are no studies that would clearly formulate an algorithm for its use in patients with acute pancreatitis (stage of disease, volume of monitoring, time of onset). This also requires further study of this problem. Ultrasound methods of hemodynamic monitoring in patients with acute pancreatitis as an alternative to invasive monitoring should also be considered with a certain degree of caution. Scientific works devoted to the evaluation of ultrasound as an effective method for assessing hemodynamic parameters in this particular patient population are extremely insufficient. It is known, in patients with acute pancreatitis, fluid is redistributed with the formation of a third "pathological" space. The main work to assess the volume status and the effectiveness of infusion therapy using ultrasound was in patients with acute fluid loss (acute blood loss, trauma, exicosis of various origins). All of the above indicates that it is necessary to create algorithms that would include not only a set of monitored indicators, but would allow them to be selected taking into account the severity of the disease.

Along with monitoring in the first 72 hours from the onset of the disease, it is recommended to use the modern concept of R.O.S.E. infusion therapy. (Resuscitation, Optimization, Stabilization, Evacuation), developed for patients in critical condition. This concept responds the question of how it is necessary to change patient management tactics depending on monitoring data and the course of the disease [66]. In this regard, it is reasonable to use it in patients with acute pancreatitis (Figure 2), which is also characterized by stages and determines the tactics of infusion therapy.

Conclusion

Acute destructive pancreatitis is a pathology, a high level of mortality remains in severe cases. Based on the pathogenesis of the early stage of this disease, fluid extravasation with the development of severe hypovolemia and hypotension develops rapidly. Infusion therapy is considered a key treatment method in the acute phase of destructive pancreatitis. Despite the existence of numerous studies, the issue of qualitative composition, dosages and rate of fluid administration remains controversial. Studies described high incidence of various complications (progression of organ dysfunction, local complications) have appeared. Therefore, the initial interest in "aggressive" (4 l/day or more) infusion therapy regimens in the first 24 hours of the disease has been replaced by a trend toward less "aggressive" regimens. The study of schemes for bolus "aggressive" fluid administration in the first 2–4 hours with subsequent correction of the rate of administration (regarding hemodynamic and laboratory parameters) is also ongoing. Considering the qualitative

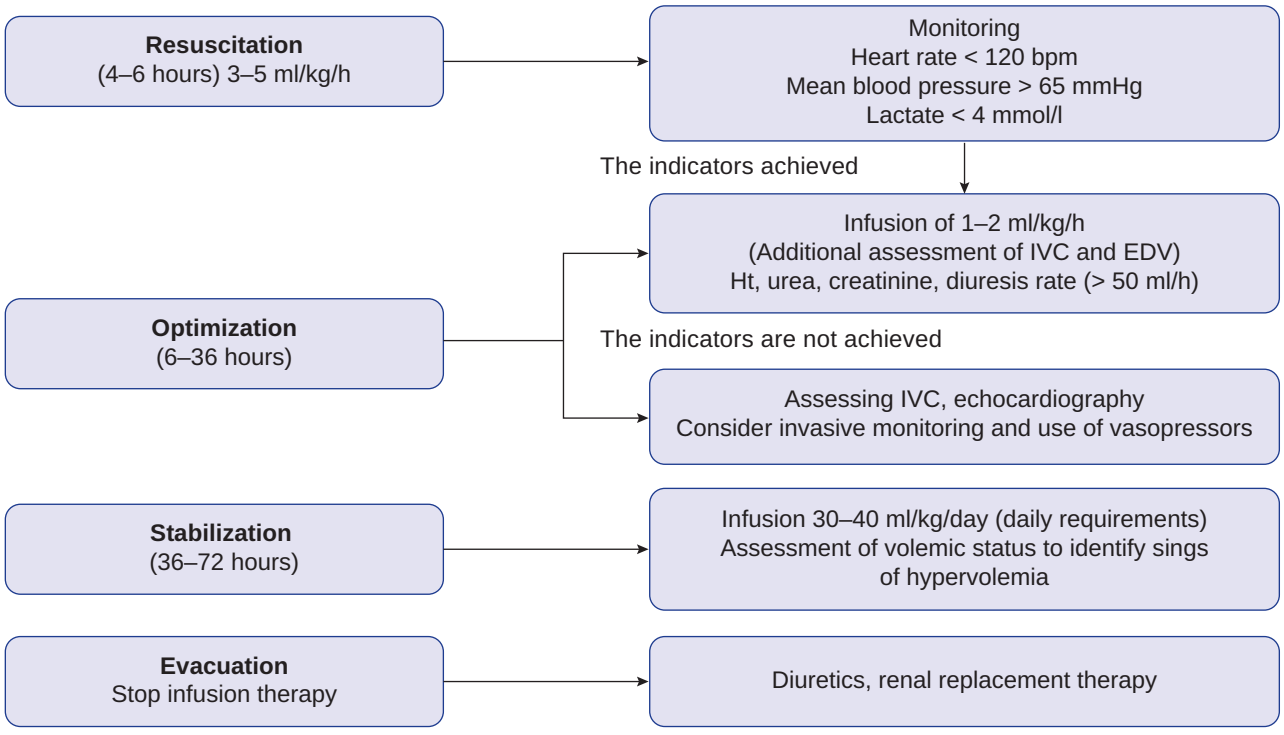

Fig. 2. Algorithm of infusion therapy for acute pancreatitis
EDV — end diastolic volume; IVC — inferior vena cava.

composition of infusion therapy, preference should be given to crystalloids. In foreign studies the drug of choice is Ringer lactate (currently not available in the Russian Federation). Russian clinical guidelines consider isotonic crystalloids as an alternative — 0.9 % sodium chloride solution or complex sodium chloride solution (potassium chloride + calcium chloride + sodium chloride).

Monitoring of infusion therapy should initially include non-invasive methods (heart rate, blood pressure, diuresis rate) and laboratory parameters (hematocrit, urea, creatinine). In the absence of positive dynamics in the first 6–12 hours, it is advisable to additionally use ultrasound to assess the inferior vena cava, end-diastolic volume and invasive hemodynamic monitoring. It is necessary to study the issues of the Diptych of infusion therapy, considering the varying degrees of severity of acute pancreatitis, the possibilities of the qualitative composition of the infusion and the means of starting and maintaining infusion therapy, based on the principles of further personalized medicine.

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