# Balanced solutions in infusion therapy for acute pancreatitis: practice-proven efficacy

**Treatment for acute pancreatitis is undeniably a pressing and complex issue of abdominal surgery. Incidence of acute pancreatitis in different countries ranges between 4.9 and 73.4 cases per 100,000 population. Based on expert estimates, the destructive forms develop in 20-30% of hospitalized patients, while the case fatality rate makes up 40-80% with no significant reduction over the past decades.**

In Ukraine, incidence of acute pancreatitis achieves 67-69.5 cases per 100,000 population, and there is a tendency to increase of this indicator. The overall case fatality rate for acute pancreatitis varies from 4 to 15%, while for the necrotic form it is as high as 24-60%; postoperative case fatality rate reaches 70% [1, 2].

Acute pancreatitis is an inflammatory-necrotic disease of the pancreas, provoked by self-digestion of pancreatocytes by their own activated enzymes, with subsequent association of aseptic or bacterial inflammation, as well as damage of surrounding organs and systems in the retroperitoneal space.

According to current concept of pathogenesis of acute pancreatitis, its trigger mechanism comprises a local surge of free radical activity in acinar cells of the pancreatic gland with subsequent activation of enzyme secretion and development of local inflammation, a systemic inflammatory response with rapid formation of multiple organ failure [3].

The activated pancreatic enzymes exert both local and general effects by entering the systemic circulation, abdominal cavity and retroperitoneal space. Activation of the kallikrein-kinin system and the associated changes in the thrombin and plasmin systems constitute an important segment of pathogenesis of acute pancreatitis. These processes provoke formation of secondary aggression factors – bradykinin, histamine, and serotonin. Activation of kinins is accompanied by impairment of microcirculation (vasodilation, blood stasis), increase in vascular permeability, progression of local and systemic exudation that result in plasma loss. The latter leads to unavoidable contraction of circulating blood volume (CBV), centralization of blood circulation and deterioration of tissue perfusion, occurrence of ischemia and functional impairment of organs and systems [4].

Distinctive features of generalized inflammatory response are reduction in systemic vascular tone and damage of vascular endothelium away from the primary focus, with local platelet activation at the site of injury. The potent cytotoxic effect of inflammatory mediators at early stages of the disease leads to development of pancreatogenic shock and multiple organ disorders that determine severity of patient's condition [4].

A key component of treatment for acute pancreatitis is the need to take account of stadiality of the disease course when choosing a therapeutic tactic. In most cases, patients are hospitalized in the toxemia phase. At this stage, the primary tasks are anti-enzyme therapy, correction of hypovolemia and microcirculatory disorders, restoration of fluid and electrolyte balance, prevention of functional insufficiency of the intestine and infectious complications.

Endotoxicosis is one of the key segments of pathogenesis of acute pancreatitis. For this reason, the critical relevance in the treatment for this pathology is assigned to intensive infusion therapy. Tasks of the infusion therapy include restoration of circulatory dynamics, fluid resuscitation, correction of electrolyte disorders. The maximum effect is achieved if infusion therapy is initiated during the first 12-24 hours after the disease onset [5].

**Since endotoxicosis and multiple organ failure are the main causes of severity of the patient's condition and fatal outcome, the infusion therapy is still a foundation of comprehensive intensive therapy for acute destructive pancreatitis.**

The literature sources contain an extensive evidence of high efficacy of Rheosorbilact and Latren (Yuria-Pharm, Ukraine) in the treatment of patients with acute pancreatitis and pancreatic necrosis [6–9].

Rheosorbilact belongs to crystalloid plasma substitutes. This is a combination drug product, with balanced ionic composition, which contains a buffer and an energy source. Rheosorbilact is a 6% (isotonic) solution of sorbitol. In addition to the hexatomic alcohol, this formulation contains: sodium lactate, sodium chloride, calcium chloride, potassium chloride, magnesium chloride. Owing to its composition, Rheosorbilact possesses a variety of positive properties. In particular, it exhibits an antishock, detoxication, alkalizing and rheological effects.

The main pharmacologically active substances of the drug product are sorbitol and sodium lactate. After intravenous administration, sorbitol gets rapidly involved into the general metabolism. In the liver, sorbitol is first converted to fructose, which is subsequently converted into glucose, and then into glycogen. A certain amount of sorbitol is used to satisfy urgent energy needs, the rest is deposited as a stock in the form of glycogen. Isotonic solution of sorbitol has a disaggregation effect and thus improves microcirculation and perfusion of tissues.

Sodium lactate is another important component of Rheosorbilact. Correction of metabolic acidosis with sodium lactate, in contrast to bicarbonate solution, decelerates as sodium lactate is included in the metabolism, but no sharp fluctuations in pH occur. Action of sodium lactate is manifested in 20-30 minutes after administration.

Many clinicians traditionally believe that solutions containing lactate are contraindicated in acidosis, because lactate is an acid. It is worth reminding that lactic acid is an acid, and lactate *per se* is an alkali. **Therefore, administration of solutions containing lactate will never lead to lactate acidosis.** In such solutions lactate is present in the form of a sodium salt and is bound by an alkali, thus being a potential bicarbonate, but not a source of H+. This statement has been confirmed in clinical practice, since overdosing with lactate-containing Rheosorbilact solution leads to alkalosis phenomena that quickly resolve unassisted, provided that administration of the drug product is immediately stopped [10].

The rest of components of Rheosorbilact solution are involved in restoration of fluid and electrolyte balance.

Osmolality of Rheosorbilact is 900 mOsmol/kg, which is 3 times higher than plasma osmolality. Osmoreceptors are highly responsive to the increase in blood plasma concentration of osmotically active substances, which triggers changes in concentration of vasopressin. Increase in vasopressin concentration is known to activate the hypothalamic-pituitary-adrenal system, increasing the production of adrenocorticotropic hormone and, as a result, adrenaline and noradrenaline, which leads to an increase in arterial pressure (AP) as a result of increase in vascular tone and exerts significant effect on the hemodynamic parameters [11]. Besides, increase in plasma osmolality leads to activation of the sympathetic nervous system and, consequently, to increase in AP, increase in blood volume due to contraction of the spleen, and more intense adrenaline rushes from the adrenal medulla [12].

Multiple studies have shown a pronounced effect of Rheosorbilact on the hemodynamic parameters:

- it rapidly normalizes hemodynamic parameters in patients with pancreatic necrosis (A.V. Kapshitar, 2012);
- it is effective as an agent for rapid restoration of CBV in hypovolemia of various etiology (A.V. Starikov, P.V. Gerasimenko 2006);
- it ensures positive hemodynamic effect within 2-3 hours: it promotes the shift of blood circulation from hypokinetic type to aukinetic type as a result of redistribution of the extracellular fluid into the vascular bed and does not produce any negative effect on the systolic-diastolic function of the left ventricle myocardium (Kim En Ding, 2012);

it leads to a significant increase in preload and cardiac output in children with low cardiac output syndrome (M.A. Georgiiants et al. 2007).

**Mechanism of detoxication action of Rheosorbilact [3, 13]**

1. Owing to its hyperosmolarity, Rheosorbilact causes inflow of fluid from the interstitial space into the vascular bed, thereby enhancing microcirculation and tissue perfusion (M.A. Georgiiants et al., 2007).
2. Relocation of the fluid from the interstitial sector into the intravascular space leads to an increase in circulating blood volume due to an increase in plasma volume, which is accompanied by hemodilution. As a result of this process, the interstitial space is drained and released from toxic factors (N.I. Gumenyuk, S.I. Kirkilevsky, 2004).
3. Owing to the diuretic effect, toxins and metabolites are eliminated from the body (O.F. Vozgonov et al., 2003).
4. Rheosorbilact eliminates metabolic acidosis and electrolyte disorders. It possesses more potent alkalizing ability than Ringer's lactate solution owing to high content of sodium lactate (M.A. Georgiiants et al., 2007).

Another drug product intended for intensive treatment for acute pancreatitis is Latren, a complex solution for infusion. It contains pentoxifylline and a balanced iso-osmolar electrolyte solution, Ringer's lactate solution. Based on recommendations of the American College of Gastroenterology, ACG, (2013) and Adapted clinical guideline "Acute Pancreatitis" (State expert center of the Ministry of Health of Ukraine, 2016), Ringer's lactate solution is recommended for primary infusion therapy for acute pancreatitis (GRADE 1B evidence quality, strong recommendation) [14, 15]. According to results of foreign studies (Le Campion E.R., 2013), in addition to typical effect of tissue microcirculation enhancement, pentoxifylline produces anti-inflammatory effect in acute pancreatitis, namely, it reduces levels of tumor necrosis factor TNF-α, interleukins 6 and 9. It has been proven (Vege S.S., 2015) that pentoxifylline shortens the hospital stay of patients with acute pancreatitis.

As a consequence of inflammatory-destructive changes in the pancreas and as a result of increase in pressure in pancreatic tissue and ductal system, as well as in response to involvement of the nerve trunks, a pronounced pain syndrome develops. In acute pancreatitis, pain is highly intense; it is localized in the epigastric region and irradiates in the lower back region (belt-like pain). The pronounced pain syndrome negatively affects the subjective sensations, general and psychological state of the patient. Therefore, rapid relief of pain by combining drug products with different pharmacodynamic effects according to multimodal analgesia principle is extremely important in the treatment for acute pancreatitis.

The concept of multimodal analgesia implies simultaneous use of two or more analgesics that possess different mechanisms of action and enable to adequately relieve pain with a minimum of adverse effects unlike high doses of one analgesic in the setting of monotherapy (Kehlet H. et al., 1993).

According to recommendations of the American Society of Anesthesiologists, ASA, (2012), multimodal analgesia includes drugs that exert action on the nociceptive pathways in the spinal cord (paracetamol – Infulgan®), weak opioids (Nalbuphine), nonsteroidal anti-inflammatory drugs (NSAIDs), N-methyl-D-aspartate receptor antagonists (ketamine, magnesium disulfate, dextromethorphan), α-2-δ-calcium channels antagonists (gabapentin and pregabalin), cyclooxygenase (COX) inhibitors, and corticosteroids (dexamethasone, betamethasone). Recommendations of the ASA and the American Pain Association, APS, (2016) specify that patients with severe pain syndrome should receive NSAIDs and paracetamol (Infulgan®) night and day.

Paracetamol is the safest non-opioid analgesic of systemic action intended for use in surgery. The available form for parenteral administration (Infulgan) enables to use this drug product in the system of multimodal analgesia.

In the event when, due to intense pain, it is impossible to avoid administration of opioids, it is expedient to use drug product Nalbuphine. Nalbuphine is indicated in patients with pain syndrome of high and medium intensity of various etiologies. The main advantages of this opioid analgesic are: it causes nausea and vomiting less frequently; it produces no effect on arterial pressure, heart rate and cardiac output; it is characterized by rapid onset of action and prolonged effect; analgesic potential of Nalbuphine is equal to that of morphine, but it does not cause respiratory depression; it has a low narcogenic potential.

In 33-70% of cases of pancreatic necrosis, infection of destruction foci takes place. This occurs mainly due to translocation of intestinal microflora. The main pathogens include: *Escherichia coli, Klebsiella spp., Enterobacter spp., Proteus spp., Pseudomonas aeruginosa, Bacteroides spp., Clostridium spp.* and enterococci. Dependence of frequency of infected pancreatic necrosis on duration of the disease has been traced: these forms are detected in 24% of patients during the 1st week, in 36% – during the 2nd week, in 71% – during the 3rd week and in 47% of patients – during the 4th week of the disease. Upon completion of the 5 week period, risk of ingress of infection is minimal. Development of infection within the first 3 weeks of the disease raises the risk of an adverse outcome. The share of infectious complications in the structure of death causes in patients with destructive pancreatitis ranges from 20 to 85.7% [16].

One of important tasks in the treatment for destructive pancreatitis is the prevention of development of infectious complications. For this purpose, it is advisable to use antibacterial drugs at the early stages of treatment..

The spectrum of action of antibiotics should include Gram-negative and Gram-positive aerobic and anaerobic microorganisms. When choosing an antibacterial agent, it is necessary to consider the ability of the agent to penetrate pancreatic tissue. Of all the classes of modern antibiotics, fluoroquinolones, carbapenems, and nitroimidazole derivatives create the highest concentrations in pancreatic tissues, which exceed the minimum inhibitory concentration for most pathogens in pancreatic necrosis. In view of this fact, the use of combined drug product Grandazole, containing levofloxacin 500 mg and ornidazole 100 mg, is justified.

To illustrate efficacious use of the above listed drug products in the treatment for acute pancreatitis and pancreatic necrosis, we give a description of several clinical cases.

## Case report No. 1

Male patient V., 66 years old, was urgently admitted to the surgical department of Odessa Regional Clinical Hospital with complaints of weakness, dizziness, epigastric pain and pain in the right hypochondrium, nausea, vomiting.

**Anamnesis morbi.** The patients considers himself to be ill for the last day, when against the background of well-being, after a dietary error, the above-mentioned complaints appeared and began to augment.

**From the anamnesis vita.** In 1999, the patient had acute ischemic-type cerebral circulation disorder in the left medial cerebral artery district. The patient underwent surgery for acute appendicitis, Schmorl's nodule. The patient denies presence of tuberculosis, HIV infection, sexually transmitted diseases, hepatitis, and blood transfusion events.

**Physical examination evidence at admission.** Intoxicated; hemodynamic indices are stable (AP – 130/80 mmHg, heart rate – 78 beats/min).

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During palpation, the abdomen is soft, painful in the epigastrium and right hypochondrium. Korte's, Mayo-Robson's and Voskresensky symptom are positive. Peristalsis is auscultated; no peritoneal signs have been detected. Bowel and bladder function is not disturbed.

Results of rectal examination: without organic pathology; feces on the glove are of brown color.

Results of computed tomography of the abdominal organs: signs of edematous cephalic pancreatitis, without exudation.

**Diagnosis.** Based on the anamnesis data and results of the examination, the patient was diagnosed with acute non-biliary non-infected edematous pancreatitis.

**Secondary diagnosis.** Cerebral atherosclerosis, chronic cerebrovascular insufficiency stage II-III, condition after acute ischemic-type cerebral circulation disorder in the left medial cerebral artery district.

**Prescribed in-patient treatment:**

- Rheosorbilact – 400 ml IV drip once daily
- Grandazole – 200 ml IV drip once daily
- Latren – 400 ml IV drip once daily
- Infulgan – 100 ml IV drip four times daily
- NaCl 0.9% – 200 ml + papaverine 2.0 + No-Spa 2.0 IV drip once daily.

In the course of the treatment, high rates of pain and intoxication syndromes relief were noted. As early as on the 1st day of treatment, persistent relief of pain syndrome was observed, and on the 3rd day the patient no longer needed inpatient treatment because the clinical and laboratory parameters had improved.

The performed therapy was well tolerated; no allergic reactions and adverse effects of the administered drug products were observed. The patient was discharged in good condition to continue treatment in the outpatient setting at the place of residence.

## Case report No. 2

Male patient B., 41 years old, was urgently admitted to surgical department of Kharkov Regional Clinical Hospital with complaints of severe belt-like pain in the upper abdomen with irradiation in the back, nausea, vomiting, general weakness, malaise.

**Anamnesis morbi.** The above complaints appeared about 5 days ago after a dietary error. That was the second hospital admission for the patient. Three weeks ago, the patient underwent inpatient treatment for acute pancreatic necrosis. The patient underwent sanitation and drainage of the abdominal cavity.

**Physical examination evidence at admission.** The general condition is severe. The patient is fully conscious. Skin coatings and visible mucous membranes are pale. Body temperature – 38.9 °C. AP – 140/70 mm Hg., heart rate – 110 beats/min. The abdomen is swollen and is involved in the act of breathing; during palpation the abdomen is tense, acute in the upper sections and in the projection zone of the pancreas, where the infiltrate without clear boundaries is palpable. Blumberg's sign is weakly positive. During auscultation, the intensity of peristaltic waves is slightly weakened; the splashing sound is not detected. Hepatic dullness is preserved, dulling in the area of the flanks is determined. Hernial bulgings are absent. The lumbar region is painless on palpation, Pasternatsky symptom is negative on both sides.

Results of rectal examination: rectal walls are painless, elastic, pathological protrusions are absent, sphincter tone is preserved; traces of feces on the glove are of normal color.

Laboratory findings: RBC – $3.16x10^{12}$/L, hemoglobin – 86 g/l, WBC count – $13.6x10^{9}$/L (neutrophils – 90.4%, lymphocytes – 7.2%, monocytes – 1.5%, eosinophils – 0.5%, basophils – 0.4%). Blood glucose – 6.2 mmol/L, blood amylase – 1,149.5 U/L. Other biochemical indicators – within normal range.

Abdominal organs X-ray: no abnormal masses, no signs of intestinal obstruction (Kloiber's cups), and no free gas detected.

Abdominal cavity ultrasound imaging: hepatomegaly, signs of chronic diffuse pathology of the liver parenchyma, space-occupying lesion of the liver chronic pancreatitis in the phase of exacerbation, diffuse pathology of the renal parenchyma with events of chronic bilateral pyelonephritis, ascites.

Esophagogastroduodenoscopy – signs of erosive-papular antral gastropathy, cicatricial deformity of the duodenal bulb, congestive duodenopathy, duodenogastric reflux, diaphragmatic hernia.

**Diagnosis.** Based on results of the examination, the patient was diagnosed with acute pancreatic necrosis with symptoms of enzymatic peritonitis, endotoxic shock.

**Secondary diagnosis.** Cirrhosis of the liver in the subcompensation stage, with syndromes of hepatocellular insufficiency and portal hypertension. Ascites. Chronic gastroduodenitis. Diaphragmatic hernia. Duodenal ulcer with cicatricial deformity of the bulb. Chronic bilateral pyelonephritis.

On the day of admission, the patient underwent surgery (video laparoscopy, sanitation and drainage of the abdominal cavity). Level of α-amylase of exudate of the abdominal cavity (collected intraoperatively) – 14,602.3 U/L.

**Treatment prescribed for the postoperative period:**

- Rheosorbilact – 600 ml IV
- Latren – 200 ml IV twice daily
- Grandazole – 200 ml IV twice daily
- Proximum – 40 mg IV
- Gordox – 100 ths. + NaCl 0.9% – 200 ml IV twice daily
- Yu-Trip – 1 vial + glucose 5% – 200 ml IV
- Yunorm – 4 mg twice daily
- Infulgan – 100 ml IV
- Nalbuphine – 10 mg IM in case of intense pain
- Infesol – 500 ml IV
- Ringer's solution – 200 ml IV twice daily
- Glucose 5% – 400 ml + KCl 7.5%15ml + insulin 6 units.

The patient was discharged on the 9th day after the surgery in satisfactory condition.

## Case report 3

Female patient B., 50 years old, was admitted to surgical department of Prilutsk Central City Hospital with complaints of abdominal pain, nausea, multiple vomiting, and heartburn.

**Anamnesis morbi.** Abdominal pain for about six months, gradual intensification of pain. The patient believes that emergence of complaints is associated with stress.

**From the anamnesis vitae.** The patient denies presence of chronic diseases and does not confirm presence of allergic reactions.

**Physical examination evidence at admission.** General condition of moderate severity. AP – 100/60 mm Hg. Heart rate – 80 beats/min. The abdomen is moderately swollen and is involved in the act of breathing, soft on palpation, slightly tender in the epigastrium and right hypochondrium; symptoms of peritoneal irritation are negative, peristalsis is satisfactory. Pasternatsky symptom is negative on both sides. Bowel and bladder function is not disturbed.

**Provisional diagnosis.** Active gastric ulcer? Acute pancreatitis.

On the 2nd day of hospital stay, the patient's condition got worse, signs of intoxication, pain syndrome augmented. Due to deterioration of condition, the patient was transferred to the intensive care unit, where she remained for 7 days.

Abdominal organs ultrasound imaging: signs of pancreatitis.

The patient underwent laparocentesis; about 100 ml of hemorrhagic fluid was obtained.

**Diagnosis.** On the basis of complaints, anamnesis evidence and results of the examination, the patient was diagnosed with acute pancreatitis and pancreatic necrosis.

**The patient underwent treatment as follows:**

- Grandazole – 200 ml IV
- Infulgan – 100 ml IV
- Rheosorbilact – 400 ml IV
- Latren – 400 ml IV
- Ringer's lactate – 800 ml IV
- Trisol – 800 ml IV
- Glucose – 5% 1000 ml IV
- Omeprazole – 40 mg IV
- Oktra – 0.1 mg SC four times daily
- Furosemide – 2 ml IV
- Flenox – 0.4 ml IV
- Sorbilact – 200 ml IV
- Volutenz – 500 ml IV
- Infezol – 250 ml twice daily
- Dikloberl – 3 ml IV once daily.

In the course of the treatment, the patient's condition gradually improved, intoxication and pain syndromes were arrested. The patient was discharged in 3 weeks after admission.

**The described clinical cases have demonstrated high efficacy and good tolerance of combination of drug products Rheosorbilact and Latren in treatment of patients with acute pancreatitis, pancreatic necrosis, complicated peritonitis and endotoxic shock, even in the presence of severe concomitant pathology.**

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