The first data on international multicenter clinical study RheoSTAT-CP0698 on the efficacy and safety of Rheosorbilact® infusion in therapy of pneumonia

Y.I. Feshchenko1, S. Beridze2, Dinh Thi Hoa3, V.Y. Molodtsov4, M.I. Gumeniuk1, N. Gogoreliani5, H.I. Sattarov6, N. Emukhvari7, G. Lupu8, Y.M. Mostovoi9, L.M. Kuryk1, Nguyen Thi Thu Anh10

1. National Institute of Phthisiopulmonology named after F.G. Yanovsky of the NAMS of Ukraine, Kyiv, Ukraine
2. JSC “EVEX Medical Corporation” / Batumi State University named after Sh. Rustaveli, Georgia
3. 198 Hospital, Hanoi, Vietnam
4. City Hospital № 1, Mykolaiv, Ukraine
5. JSC “EVEX Medical Corporation” / Kutaisi Referral Hospital, Georgia
6. Republican Scientific Center of Emergency Medical Aid, Tashkent, Uzbekistan
7. “Israel Georgian Medical Research Clinic HELSI Core LLC” LTD, Tbilisi, Georgia
8. Municipal Clinical Hospital “Sfinta Treime”, Chisinau, Moldova
9. Vinnytsia National Medical University / City Clinical Hospital № 1, Vinnytsia, Ukraine
10. Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam

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ABSTRACT. Adequate and effective treatment of severe pneumonia is especially relevant in present situation. The most problematic issue is infusion therapy. The current evidence and guidelines recommend balanced crystalloid infusion for patients with severe pneumonia and sepsis. The composition of Rheosorbilact® provides significant benefits in patients
with severe infections, including respiratory infections. According to the results of the randomized open blinded end-point RheoSTAT-CP0698 study, administration of Rheosorbilact® to patients with pneumonia (intravenous infusion at a dose of 200-400 ml/day for 3 days) effectively improves the clinical condition, reduces the manifestations of (multi-) organ failure and endogenous intoxication. Small-volume infusion therapy promotes rapid normalization of circulating blood volume, stabilization of hemodynamics, acid-base, electrolyte and gas composition of the blood, significantly improves saturation and reduces tachypnea. The positive effect of therapy on renal function and inflammation has also been established. This therapy had a favorable safety profile (e.g., it did not lead to fluid overload, pulmonary edema, pleural effusion or other serious side effects, and was not associated with a clinically significant increase in endogenous serum lactate level). The RheoSTAT-CP0698 study substantiates the feasibility of using Rheosorbilact® in the complex treatment of pneumonia.

**KEY WORDS:** pneumonia, infusion therapy, efficacy, safety, Rheosorbilact.

**Разные данные международного многоцентрового клинического исследования RheoSTAT-CP0698 по эффективности и безопасности инфузионного раствора Реосорбилакт® в комплексной терапии пневмонии**

Ю.И. Фещенко1, С. Беридзе2, Динь Тхи Хоа3, В.Е. Молодцов4, Н.И. Гуменюк1, Н. Гогорелиани5, Х.И. Саттаров6, Н. Эмухвари7, Г. Лупу8, Ю.Н. Мостовой9, Л.М. Курк1, Нгуен Тхи Тху Ань10
1. Национальный институт фтизиатрии и пульмонологии им. Ф.Г. Яновского НАМН Украины, г. Киев, Украина
2. ОАО «EVEX Medical Corporation» / Батумский государственный университет им. Ш. Руставели, Грузия
3. Госпиталь № 198, г. Ханой, Вьетнам
4. Городская больница № 1, г. Николаев, Украина
5. ОАО «EVEX Medical Corporation» / Реферальная больница г. Кутаиси, Грузия
6. Республиканский научный центр экстренной медицинской помощи, г. Ташкент, Узбекистан
7. «Израильско-грузинская клиника медицинских исследований HELSI Core LLC» LTD, г. Тбилиси, Грузия
8. Муниципальная клиническая больница «Святая Троица», г. Кишинев, Молдавия
9. Винницкий национальный медицинский университет / Городская клиническая больница № 1, г. Винница, Украина
10. Тхайбиньский университет медицины и фармации, г. Тхайбинь, Вьетнам

**Конфликт интересов: отсутствует**

**РЕЗЮМЕ.** Адекватное и эффективное лечение пневмонии тяжелого течения ныне особенно актуально. Наиболее проблемными являются вопросы инфузионной терапии. Имеющаяся доказательная база и современные рекомендации отдают предпочтение сбалансированным кристаллоидным инфузионным растворам в качестве патогенетической терапии тяжелой пневмонии и сепсиса. Состав Реосорбилакта обеспечивает существенные преимущества при тяжелых инфекциях, в том числе инфекциях дыхательных путей. Как свидетельствуют результаты открытого с ослепленной оценкой рандомизированного контролируемого исследования RheoSTAT-CP0698, введение пациентам с пневмонией Реосорбилакта путем внутривенной инфузии в дозе 200-400 мл/сут в течение 3 дней значительно улучшает клиническое состояние, уменьшает проявления (поли-) органных недостаточности и эндогенной интоксикации. Малообъемная инфузионная терапия Реосорбилактом способствует быстрой нормализации объема циркулирующей крови, стабилизации показателей гемодинамики, кислотно-щелочного, электролитного и газового состава крови, существенно улучшает сатурацию и уменьшает тахипноэ. Установлено положительное влияние терапии на показатели воспаления и функции почек. Введение препарата в таком режиме имеет благоприятный профиль безопасности: не приводит к перегрузке жидкостью, отеку легких, плевральному выпоту или другим серьезным побочным эффектам, а также не вызывает клинически значимого повышения эндогенного лактата крови. Исследование RheoSTAT-CP0698 обосновывает целесообразность применения препарата Реосорбилакт® в комплексной терапии пневмонии.

**КЛЮЧЕВЫЕ СЛОВА:** пневмония, инфузионная терапия, эффективность, безопасность, Реосорбилакт.
Introduction

Despite significant advance in diagnosis and treatment, the mortality rate due to pneumonia has not changed significantly over the past 30 years [1]. 5 to 15 % of hospitalized patients die within 30 days [2], and mortality rate in intensive care units (ICU) reaches 17-48 % [3]. Adequate and effective treatment of severe pneumonia is especially relevant in present conditions, and the most challenging issue is infusion therapy. For the most part, fever and more intense perspiration are successfully managed by oral fluid administration. However, it is not always possible in critical patients, which leads to hypovolemia. In addition, in response to bacterial exo- and endotoxins, as well as under the influence of endogenous cytokines and histamine, vasoplegic vasodilation associated with hypotension and septic shock occurs as pneumonia is the most common cause of sepsis [4]. According to a recent multicenter study, sepsis and septic shock complicate the course in a third of patients hospitalized due to pneumonia [5]. Systemic hypovolemia is also associated with the “capillary leakage” phenomenon caused by endothelial dysfunction and increased vascular permeability due to damaged glycocalyx. Endothelial glycocalyx is a matrix of membrane-bound glycoproteins and proteoglycans on the inner surface of endotheliocytes of 0.2 to 8 µm, retaining 700 to 1500 ml of intravascular fluid like a sponge [6]. The capillary glycocalyx layer acts as a semipermeable barrier that prevents penetration of large molecules, in particular albumin, through the gaps between endothelium. It is the glycocalyx that is responsible for establishing the hydrostatic pressure-resistant onotic gradient. According to revision of the Starling principle, considering the endothelial glycocalyx model, an increase in plasma oncotic pressure results in fluid filtration from the intravascular to interstitial space, but does not cause fluid return back to the vessel [7]. Water from the extracellular matrix mostly returns to the intravascular space through the lymphatic system [8]. In severe infections and sepsis, tumor necrosis factor causes activation of nuclear factor-κB and endothelial damage, and lipopolysaccharides damage the glycocalyx by the mechanism of oxidative stress [9, 10]. Glycocalyx may be damaged by a number of chronic diseases, in particular by diabetes mellitus [11], and comorbidity is known to be one of the extrapulmonary factors that determine the severity of pneumonia.

As a result, the liquid part of the blood is moved to the interstitial extracellular space. At this stage, a vicious circle is triggered: oxygen transport in the lungs is disrupted, causing or deepening respiratory distress; hypovolemia and hypoperfusion of organs and tissues increases, causing or aggravating multiple organ failure [7, 12, 13]. In addition, intracellular edema disrupts a number of biochemical processes, such as glucose metabolism, cardiomyocyte contractility, inflammatory reactions, endogenous antimicrobial activity of plasma, etc. [7].

Under these conditions, intravenous infusion therapy is a basic pathogenetic treatment. Guidelines mainly focus on the etioprotective treatment of pneumonia, while the issues of pathogenetic therapy are only covered conceptually. Infusions are indicated to be combined with early respiratory support and strict monitoring of clinical and laboratory parameters, such as mean blood pressure, central venous pressure (CVP) and central venous blood saturation in ICU settings.

In septic hypotension, short-term initial liquid resuscitation is recommended with the predominant use of balanced crystalloid solutions and early administration of low or medium doses of vasopressors – epinephrine at initial dose of 0.2-0.5 µg/kg/min, in case of heart failure – norepinephrine or dobutamine [14]. This principle, known as “early goal-directed therapy” (EGDT), was introduced into clinical practice as early as 2001, after E. Rivers et al. demonstrated that optimizing hemodynamics in patients with septic shock (including 39 % with pneumonia) reduces hospital mortality by 16 % [15]. The following criteria for EGDT initiation were proposed:

1) inability to maintain an average blood pressure ≥65 mm Hg without administration of vasopressors;
2) serum lactate level ≥2 mmol/l (18 mg/dl) in the absence of hypovolemia;
3) quick SOFA score ≥2, i.e. the presence of at least two of the following signs: respiratory rate ≥22/min, systolic blood pressure <100 mm Hg, Glasgow Coma Scale score ≤14 [16].

After stabilization of hemodynamic parameters, i.e. reaching the mean blood pressure of 65 to 90 mm Hg or in the absence of shock, it is recommended to use a restrictive type of infusion therapy [14]. After all, excessive infusion volume can increase pulmonary edema and hypoxemia, is associated with an increase in the time spent in ICU or on mechanical ventilation, and a significantly higher risk of death [17-19]. It has also been shown that the volume of intravenous fluids administered by infusion is independently associated with the degree of glycocalyx degradation, which indicates the possibility of iatrogenic endothelial damage due to improper infusion therapy strategy [10]. Investigators hypothesize that intravenous fluid can cause direct damage and exfoliation of the endothelium, regardless of fluid balance [10]. In the presence of inflammatory mediators, sudden stretching of blood vessels caused by liquid boluses stimulates endothelial expression of metalloproteinases and promotes activation of cathepsin L and endothelial heparanase, which cause glycocalyx exfoliation. Infusion of isotonic solutions promotes the activation of circulating white blood cells and their release of elastase, which can also damage the glycocalyx [10]. In addition, fluid overload causes intra-abdominal hypertension with the compression of internal organs leading to their dysfunction [18, 20], as well as slows down the recovery of renal function or increases the risk of acute renal impairment [21-23]. All negative impacts are summarized in table 1 [7,12,13].

How shall clinicians balance benefits and risks? How to choose an adequate infusion solution? What is the evidence for the strategy and tactics of infusion therapy in patients with severe pneumonia? These questions support the feasibility of our study, which was aimed at finding evidence for infusion therapy in severe pneumonia.

Materials and methods

An electronic search in the PubMed, MEDLINE and Cochrane Library databases over the past 20 years was conducted using a sensitive strategy without language restrictions for the following keywords: “pneumonia”, “sepsis”, “septic shock”, “acute respiratory distress syndrome”, “hypoxemia”, “mortality”, “early targeted therapy”, “liquid therapy”, “liquid resuscitation”, “restrictive type of infusion therapy”, “choice of infusion solution”, “randomized controlled study”, “review”, “meta-analysis”. For data on sepsis, septic...
Table 1. Consequences of fluid overload in infusion therapy

| Systems               | Manifestations                                                                 |
|-----------------------|-------------------------------------------------------------------------------|
| Central nervous system| Cognitive impairment, delirium, hypoperfusion and brain edema, increased intracranial pressure, compartment syndrome |
| Respiratory system    | Pulmonary edema, pleural effusion, impaired elasticity of the lungs and chest wall, hypoxemia, hypercapnia, decreased lung volume, prolonged time spent on mechanical ventilation or more difficult weaning from mechanical ventilation |
| Cardiovascular system | Myocardial edema, impaired conduction, contractility, diastolic dysfunction, increased central venous pressure, decreased stroke volume, cardiac output and left ventricular ejection fraction, pericardial effusion |
| Gastrointestinal tract| Intestinal edema, ascites, malabsorption, decreased intestinal contractility, obstruction, increased intestinal wall permeability, bacterial translocation |
| Liver                 | Congestion, impaired synthetic function, increased cholestasis, decreased cytochrome P450 activity, compartment syndrome |
| Kidneys               | Interstitial edema, increased venous pressure and vascular resistance, slow blood flow, salt and water retention, increased uremia, decreased glomerular filtration rate, compartment syndrome |

shock, and acute respiratory distress syndrome, the proportion of patients with pneumonia was determined and only those studies where at least a third of patients had pneumonia were included.

The results of the recently completed international multicenter open-label blinded end-point randomized controlled phase III-IV RheoSTAT-CP0698 study (RCS) were also reviewed based on a report provided by “Yuria-Pharm”. The study was conducted from 1 September 2017 until 28 February 2020 by a contract research organization in accordance with the Good Clinical Practice (ICH GCP), ethical standards of the Helsinki Declaration of the World Medical Association and national standards, and included in the Cochrane Library [24], one of the most authoritative evidence-based medicine electronic databases, which indicates a high level of evidence. Overall, the RheoSTAT-CP0698 RCS included 628 patients with sepsis, peritonitis, burn disease, and pneumonia who were treated in 44 clinical centers in 7 countries. The RheoSTAT-CP0698 pneumonia sub-study involved 150 patients from 12 clinical centers in 6 countries – Ukraine, Moldova, Georgia, Uzbekistan, Kazakhstan and Vietnam.

Essential inclusion criteria for the RheoSTAT-CP0698 pneumonia sub-study were: age 18-60 years, confirmed Georgia, Uzbekistan, Kazakhstan and Vietnam.

Overall, the RheoSTAT-CP0698 RCS included 628 patients with sepsis, peritonitis, burn disease, and pneumonia who were treated in 44 clinical centers in 7 countries. The RheoSTAT-CP0698 pneumonia sub-study involved 150 patients from 12 clinical centers in 6 countries – Ukraine, Moldova, Georgia, Uzbekistan, Kazakhstan and Vietnam.

Essential inclusion criteria for the RheoSTAT-CP0698 pneumonia sub-study were: age 18-60 years, confirmed community-acquired pneumonia with PSI/PORT risk class IV or higher, provided that the period from the initiation of antibacterial therapy did not exceed 48 hours; signed informed consent to participate in the study; initial quick SOFA score ≥2; blood pH <7.45, blood potassium <5.1 mmol/l and blood sodium <145 mmol/l.

The average age of the study participants was 41.3 years (62 % male), including 33 % with concomitant diseases (12 % – arterial hypertension, 21 % – others). Patients were randomized to the treatment group (n=78) and control group (n=72). Subjects of the treatment group received Rheosorbilact® infusion solution for 3 days by intravenous infusion at a dose of 200-400 ml/day. On day 3, their efficacy criteria were evaluated, and after 14±2 days, safety and disease outcomes were monitored (fig. 1).

It is worth noting a thorough and objective evaluation of the efficacy and safety of the study drug, which was carried out on the basis of numerous evaluation scales and clinical and laboratory values indicated in table 2.

Results and discussion

There are two main classes of infusion agents – colloids and crystalloids. Colloids include albumin, hydroxyethyl starch, and gelatin. Due to onctotic activity, colloids should theoretically slow down capillary leakage. However, in patients with severe infection, this effect is quite short-term due to glycocalyx damage [8, 13]. Compared to crystalloids, colloids have a slightly longer intravascular space elimination half-life, although capillary leakage affects both classes [25]. Other hypothetical benefits of colloids include an anti-inflammatory effect and the ability to absorb nitric oxide, but this only applies to albumin [26]. There are no major RCS that prove a clear difference in mortality between crystalloid or colloid infusion therapy in pneumonia or sepsis. The SAFE RCS was quite large and included critically ill adults comparing 0.9 % sodium chloride solution and albumin as liquid resuscitation agents. Despite the absence of a significant difference in 28-day mortality in the general group, better results were reported with albumin in patients with severe sepsis and

Fig. 1. RheoSTAT-CP0698 pneumonia study design scheme
### Table 2. Criteria for evaluating efficacy and safety in the RheoSTAT-CP0698 pneumonia study

**Efficacy was evaluated by comparing baseline values during hospitalization and values on day 3 of therapy**

**Key parameter:** change in total SOFA score  
**Secondary parameters:**  
- Change in total APACHE II, SAPS II, MODS and CURB-65 scores  
- Change in the PSI/PORT pneumonia severity index  
- Assessment of pleural cavity ultrasound changes: amount of fluid, type of effusion, pleural thickness  
- Assessment of endogenous intoxication based on:  
  - biochemical markers: serum concentrations of glucose, sodium, potassium, urea, creatinine, total bilirubin, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, procalcitonin, albumin fraction, base excess, standard bicarbonate and lactate;  
  - immunological criteria: assay content of white blood cells, lymphocytes, platelets with calculation of leukocyte, nuclear and hematochemical intoxication indices (II), neutrophils and lymphocytes ratio, C-reactive protein concentration, immunoglobulins, interleukins 1 and 2, complement components 3 and 4;  
  - clinical signs (adynamia, apathy, weakness, memory disorders, sleep disorders, irritability, anorexia), electrocardiogram, central hemodynamics parameters and assessment of consciousness using the Glasgow scale  

**Safety evaluation**  
- Overall frequency of adverse events (AEs)  
- Frequency of serious AEs  
- Frequency of study drug-related AEs  
- Frequency of pleural effusion according to ultrasonography  
- Frequency of AEs leading to the patient’s withdrawal from the study  
- Frequency of AEs not previously described in the instructions for use of the study drug  
- Frequency of multiple organ failure  
- Overall survival of patients (%) during follow-up (day 14±2)

Acute respiratory distress syndrome, but worse in patients with severe traumatic brain injury [27, 28]. Hydroxyethyl starch solutions are associated with acute kidney injury in critically ill individuals, making them to be recognized as dangerous in the United States and Europe [29, 30]. Recent international guidelines for the management of sepsis do not recommend the use of colloids as a starting solution for liquid resuscitation due to lack of benefits and excessive costs [31].

Among the crystalloids, non-buffer solutions (isotonic sodium chloride solution) and buffer multi-electrolyte solutions can be distinguished, the latter differing in their composition, chloride concentration, pH and osmolarity, but being closer to plasma than isotonic sodium chloride solution. Resuscitation using 0.9 % sodium chloride solution is associated with the occurrence of hyperchloremic metabolic acidosis, acute kidney injury and dangerous vital organ dysfunction [32-35]. Despite this, isotonic sodium chloride solution remains the most commonly used crystalloid solution [36], which is also most often used as a solvent for intravenous administration of various drugs [33]. Two recent RCS, SALT-ED and SMART, indicate clear advantages of balanced buffer solutions over isotonic sodium chloride solution. Although there were no differences in short-term mortality, administration of 0.9 % sodium chloride solution was associated with a higher risk of acute kidney injury, including death, the need for dialysis, or long-term renal impairment [34, 35].

Special attention should be given to infusion solutions containing polyatomic alcohols, primarily sorbitol, which has a number of advantages:

1) due to its slow conversion to monosaccharides, it is utilized better than glucose, and does not cause carbohydrate overload;

2) after administration, it is quickly incorporated into the general metabolism (80 % is utilized by the liver, 5 % is deposited in brain tissues, myocardium and skeletal muscles, the rest is excreted in the urine or used for urgent energy needs);

3) eliminates intestinal spasm caused by acetylcholine, stimulates peristalsis without acute increasing, which substantiates its use in the postoperative period;

4) in hypertonic concentration, has a significant anti-edematous action, in particular promotes the reverse development of pulmonary edema, is characterized by an osmotic diuretic effect, which is important in oligoanuria and acute kidney injury;

5) due to powerful cholecystokinetic and choleretic action, facilitates restoration of normal digestive function, has a proven therapeutic effect in acute and chronic hepatitis and toxic liver injury;

6) in isotonic concentration, acts as a disaggregating, improving microcirculation and tissue perfusion.

Among sorbitol-containing products, it is worth noting Rheosorbilact®, a complex polyfunctional infusion product manufactured by “Yuria-Pharm” (Ukraine). In addition to sorbitol, it contains other important electrolytes – potassium, calcium and magnesium, but the chloride content of as much as 112.7 mmol/l reduces the risk of hyperchloremic acidosis. Another important component of Rheosorbilact® is sodium lactate, which provides an alkalinizing effect, increases the reserve and titrated alkalinity of the blood, corrects metabolic acidosis, which often complicates severe infections, sepsis, peritonitis, intestinal obstruction, renal failure, burns, shock, chronic hypoxia, etc. It has a positive effect on the cardiac function, regeneration and respiratory function of the blood, stimulates the functions of the mononuclear phagocyte system, has a detoxification effect, increases diuresis, improves kidney and liver function. The concentration of sodium lactate in Rheosorbilact® is 5-6 times higher (160-180 mmol/l) than in most solutions for infusion, which provides a powerful therapeutic effect.
The presence of two agents with a synergistic detoxification effect and the ability to correct the acid-base and water-electrolyte balance puts this medicinal product on a par with the most powerful detoxification agents [37].

The successful use of Rheosorbilact® for detoxification and normalization of blood rheology in patients with severe purulent-inflammatory diseases such as peritonitis [38], destructive pancreatitis [39], diabetic foot syndrome [40] suggests an improvement in clinical outcomes of pneumonia. In addition, one of the clinical studies found that the administration of Rheosorbilact® in patients with pneumonia contributes to early normalization of body temperature, disappearance of astheno-vegetative syndrome manifestations and reduction the average length of stay in hospital, stabilization of the acid-base status and coagulogram values [41].

In addition, Rheosorbilact® has been studied in the RheoSTAT-CP0698 RCS, which provides a high level of evidence in patients with pneumonia. According to the study results, administration of Rheosorbilact® by intravenous infusion at a dose of 200-400 ml/day effectively improves the clinical condition, reduces the manifestations of (multi-)organ failure and endogenous intoxication in most of the analysed indications. On day 3 of therapy, most patients had normalized

| Parameters, units | At baseline | On day 3 | P |
|-------------------|------------|----------|---|
| SOFA              | 73 2 2-3   | 73 1 0-1 | <0.001 |
| APACHE II         | 73 9 7-12 | 73 3 2-6  | <0.001 |
| SAPS II           | 73 24 20-27 | 73 13 12-18 | <0.001 |
| MODS              | 73 3 2-5  | 73 2 0-4  | <0.001 |
| CURB-65           | 73 2 1-3  | 73 0 0-0  | <0.001 |
| PS/PORT           | 73 100 94-106 | 73 4 31-60 | <0.001 |
| Body temperature, °C | 73 40.1 38.7-40.1 | 73 36.8 36.6-36.9 | <0.001 |
| Heart rate, bpm   | 73 103 90-126 | 73 78 70-84  | <0.001 |
| Systolic blood pressure, mm Hg | 73 88 85-120 | 73 120 115-125 | <0.001 |
| Diastolic blood pressure, mm Hg | 73 59 50-80  | 73 75 70-80 | <0.001 |
| CVP, mm H₂O       | 73 52 41-54 | 73 61 54-68  | <0.05 |
| Respiratory rate in 1 min | 73 31 31-32  | 73 20 19-22  | <0.001 |
| Saturation, %     | 67 93 90-96.5 | 45 98 96-98 | <0.001 |
| Urea, mmol/l      | 78 7.6 5.1-9.2 | 78 4.2 3.6-5.0 | <0.001 |
| Creatinine, mmol/l | 78 86.0 71.0-102.0 | 78 52.4 42.5-70.1 | <0.001 |
| Total bilirubin, µmol/l | 78 12.0 9.0-14.9 | 78 8.0 6.0-10.2 | <0.001 |
| ALAT, IU/l        | 78 24.0 20.0-43.0 | 78 20.0 20.0-45.0 | <0.001 |
| ASAT, IU/l        | 78 25.0 21.3-38.0 | 78 25.0 22.0-40.0 | <0.001 |
| Lactate dehydrogenase, U/l | 78 30.0 223-463 | 78 300 206-396 | <0.001 |
| Alkaline phosphatase, U/l | 78 82 66-101 | 78 80 62-97 | <0.001 |
| Gamma-glutamyltransferase, U/l | 77 29.0 20.0-50.0 | 78 35.0 20.0-68.0 | <0.001 |
| Albumin fraction, % | 30 60.2 57.5-62.4 | 29 60.1 58.1-61.8 | <0.05 |
| Glucose, mmol/l   | 78 6.1 4.8-14.0 | 76 5.3 4.6-8.3  | <0.001 |
| C-reactive protein, mg/l | 77 16.5 35.3-43.4 | 77 8.0 2.0-24.0 | <0.001 |
| Procalcitonin, ng/ml | 31 0.05 0.04-0.39 | 33 0.04 0.02-0.40 | <0.001 |
| Platelets, ×10⁹/l | 73 210 194-273 | 73 242 202-287 | <0.001 |
| White blood cells, ×10⁹/l | 73 9.20 6.48-11.00 | 73 6.80 4.97-8.00 | <0.001 |
| Nuclear II        | 22 0.07 0.05-0.08 | 23 0.06 0.03-0.08 | <0.001 |
| Leukocytic II     | 22 4.22 2.57-4.29 | 22 2.45 1.95-2.50 | <0.001 |
| Hematological II  | 22 4.00 2.70-4.00 | 22 2.40 2.33-2.42 | <0.001 |
| Neutrophil/lymphocyte index | 22 4.00 3.36-4.44 | 22 3.50 2.50-3.50 | <0.001 |
| Blood pH          | 73 7.41 7.38-7.44 | 73 7.40 7.37-7.44 | <0.001 |
| Pao₂, mm Hg       | 73 35.6 33.1-39.9 | 73 36.6 32.4-40.2 | <0.001 |
| Pao₂, mm Hg       | 73 70.3 61.8-80.4 | 73 80.6 679-86.9 | <0.001 |
| Base excess, mmol/l | 73 -0.70 -2.20-0.26 | 73 -1.40 -4.0-1.20 | <0.001 |
| Standard bicarbonate, mmol/l | 73 23.5 22.4-24.5 | 73 23.0 21.1-25.0 | <0.001 |
| Lactate, mmol/l   | 36 1.14 0.98-1.68 | 33 1.60 1.18-1.90 | <0.001 |

Notes: * data provided by “Yuria-Pharm” in the RheoSTAT-CP0698 RCS results report; n – number of observations; Me (IQR) – the median (interquartile range).
body temperature, respiratory rate, blood saturation and gas composition, renal function, which significantly improved the score of all the scales used in the study for assessment of the severity of pneumonia and critical conditions (table 3).

Small-volume infusion therapy with Rheosorbiact® provides an increase in the circulating blood volume, which is indicated by a significant increase in CVP, and stabilization of blood pressure and heart rate. On the other hand, after a 3-day course of infusions, CVP values did not increase to critically high levels (table 3), which, according to study data, are associated with an unfavorable prognosis and a higher risk of death [42]. This therapy allowed to reduce the total volume of infusion required to achieve a therapeutic effect without the risk of hyperhydration and fluid overload, which is especially important in older patients with comorbidity or in critical conditions that have a particularly unfavorable prognosis in pneumonia [1, 7, 12, 13].

The administration of Rheosorbiact®, in complex therapy contributed to a significant decrease in the level of leukocytes, leukocyte and hematological II and normalization of the neutrophil/lymphocyte ratio, which indicates the ability to reduce the manifestations of infection-related endogenous intoxication. A significant decrease in C-reactive protein and a certain improvement in acid-base balance indicators were observed (table 3).

As for the safety profile, a total of 296 adverse events were reported in the treatment group in 43.6 % of patients, which was not statistically different from the control group (304 AEs in 50.0 % of patients). Most of the abnormalities were not clinically significant, and no serious adverse effects were reported during the study. No new safety signals have been received for the study drug. According to the analysis results, Rheosorbiact® has a favorable safety profile.

Exogenous lactate in the composition of Rheosorbiact® does not affect the level of endogenous lactate (table 3), elevation of which is associated with an unfavorable prognosis in sepsis and pneumonia [16, 43]. This proves the safety of the solution administered to patients with pneumonia. It should be noted that on day 3 of therapy, subjects of the treatment group showed a decrease in the percentage of laboratory abnormalities in the function of elimination organs, blood glucose and electrolyte levels, including clinically significant ones (fig. 2).

No cases of pulmonary edema or pleural effusion were detected in patients of the treatment group after infusion therapy (table 4).

Conclusions

The current evidence and guidelines recommend the balanced crystalloid infusion as a pathogenetic therapy for severe pneumonia and sepsis. The composition of

![Fig. 2. Percentage of abnormalities in the function of elimination organs, blood glucose and electrolytes before and after a 3-day treatment with Rheosorbiact®](image)

| Group                      | Appearance of effusion |
|---------------------------|------------------------|
| Treatment (n=53)          | Yes                    |
|                           | 0 (0.00 %) [0.00-6.72] |
|                           | No                     |
|                           | 53 (100.00 %) [93.28-100.00] |
| Control (n=52)            | Yes                    |
|                           | 3 (5.77 %) [1.21-15.95] |
|                           | No                     |
|                           | 49 (94.23 %) [84.05-98.79] |

Intergroup value p=0.118

Table 4. Number of patients with reported fluid confirmed by ultrasound (safety population)

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Rheosorbilact® provides significant benefits in patients with severe infections, including respiratory infections. According to the results of the open blinded end-point RheoSTAT-CP0698 RCS, administration of Rheosorbilact® to patients with pneumonia (intravenous infusion at a dose of 200-400 ml/day for 3 days) effectively improves the clinical condition, reduces the manifestations of (multi-)organ failure and endogenous intoxication. Small-volume infusion therapy by Rheosorbilact promotes rapid normalization of blood volume circulating, stabilization of hemodynamics, acid-base, electrolyte and gas composition of the blood, significantly improves saturation and reduces tachypnea. The positive effect of therapy on renal function and inflammation has also been established. This therapy had a favorable safety profile (e.g., it did not lead to fluid overload, pulmonary edema, pleural effusion or other serious side effects, and was not associated with a clinically significant increasing the blood levels of endogenous lactate). The RheoSTAT-CP0698 study substantiates the feasibility of using Rheosorbilact® in the complex treatment of pneumonia.
1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect. Dis.* 2018 Nov; 18 (11): 1191-1210. doi: 10.1016/S1473-3099(18)30510-4.

2. Chalmers J., Campbell J., Elborough G., Hawkey P., Madhava H., Slack M. Community-acquired pneumonia in the United Kingdom: a call to action. *Pneumonia* (London). 2017 Oct; 9: 15.

3. Phua J., Dean N.C., Guo Q., Kuan W.S., Lim H.F., Lim T.K. Severe community-acquired pneumonia: timely management measures in the first 24 hours. *Crit. Care.* 2016; 20 (1): 237. Published 2016 Aug 28. doi: 10.1186/s13054-016-1414-2.

4. Angus D.C., Linde-Zwirble W.T., Lidsky J., Clermont G., Carcillo J., Pinsky M.R. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit. Care Med.* 2001; 29: 1503-1510. doi: 10.1097/00003246-200107000-00002.

5. Montull B., Menendez R., Torres A., Reyes S., Mendez R., Zalacain R. et al. Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia. *PLoS One.* 2016; 11: e0145929. doi: 10.1371/journal.pone.0145929.

6. Woodcock T.E., Woodcock T.M. Revised Starling equation and the glycosylaxyl model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br. J. Anaesth.* 2012; 108 (3): 384-394.

7. Chang R., Holcomb J. Choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock. *Shock.* 2016 Jul; 46 (1): 17-26. doi: 10.1097/01.SHK.0000480000.000577.

8. Best M.W., Jaber S.F. Fluid management in septic shock: a review of physiology, goal-directed therapy, fluid dose, and selection. *Curr. Anaesthesiol. Rep.* 2019; 9: 151-157. https://doi.org/10.1007/s40140-019-00350-3.

9. Liang Y., Li X., Yang L., Sun Y., Li Z., Ma X. Elevated levels of plasma TNFα are associated with microvascular endothelial dysfunction in patients with sepsis through activating the NF-κB and p38 mitogen-activated protein kinase in endothelial cells. *Shock.* 2014; 41 (4): 275-281.

10. Hinnensteel J.A., Uchimido R., Tyler P.D., Burke R.C., Zhang F. et al. Intraabdominal fluid resuscitation is associated with septic endothelial glycosylaxyl degradation. *Crit. Care.* 2019; 23 (259). https://doi.org/10.1186/s13054-019-2534-2.

11. Nieuwdorp M., Mooij H.L., Kroon J., Ataseer B., Spaan J.A., Ince C., Holleman F., Diamant M., Meine R.J., Hoekstra J.B. et al. Endothelial glycosylaxyl damage coincides with microalbuminuria in type 1 diabetes. *Diabetes.* 2006; 55 (4): 1127-1132.

12. Malbran M.L.N.G., Van Regenmortel N., Saugel B., De Tavernier B., Van Gaal P.J., Malbran M.L. et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Ann. Intensive Care.* 2018 May 22; 8 (1): 66. doi: 10.1186/s13613-016-0402-x.

13. Marik P., Bellomo R. A rational approach to fluid therapy in sepsis. *Br. J. Anaesth.* 2016; 116 (3): 339.

14. Adaptation of liver transplantation, zasnovana na dokazah. Nekogosipalna pneumonija u dobroj osobi: etiologija, patogeneza, klasifikacija, diagnostika, antimikrobierna terapija i profilakcija. Ukladajte: Fensko Z. I., Belopolskaya G.K., Golubovskaya O.A. et al. – K: NAM Ukraini, 1994. – 94s.

15. Rivers E., Nguyen B., Havstad S., Ressler J., Muzzin A., Knoblich B. et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N. Engl. J. Med.* 2001; 345: 1586-1597. doi: 10.1056/NEJMoa010307.

16. Singer M., Deutschman C., Seymour C., Shankar-Hari M., Annane D., Bauer M. et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2014; 315: 801-10.

17. Koonangnesomboon W., Khwannimit B. Impact of positive fluid balance on mortality and length of stay in septic shock patients. *Indian J. Crit. Care Med.* 2015 Dec; 19 (12): 708-13.

18. Cordemans C., De Laet I., Van Regenmortel N., Schoonehdyt K., Dits H., Huber W. et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypoperfusion, capillary leak, and fluid balance. *Ann. Intensive Care.* 2012; 2: 51.

19. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syn- drome (ARDS) Clinical Trials Network. Wiedermann H.P., Wheeler A.P., Bernard G.R. et al. Comparison of two fluid-management strategies in acute lung injury. *N. Engl. J. Med.* 2006; 354: 2564-73.

20. Malbran M.L., Marik P.E., Witters I., Cordemans C., Kirkpatrick A.W., Roberts D.J. et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anesthesiol. Intensive Ther.* 2014; 46: 161-80.

21. Heung M., Wolfgram D.F., Kommarreddy M., Hu Y., Song PX., Ojo A.O. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. *Nephrol. Dial. Transplant.* 2012; 27: 956-61.
22. Bouchard J., Soroko S.B., Chertow G.M., Himmelfarb J., Ikizler T.A., Pag- 

nini E.P. et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury Kidney Int 2009; 76: 422-7.

23. Stein A., de Souza LV, Beletini C.R., Menegazzor WR, Viegas J.R., Costa Pereira E.M. et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study Crit. Care. 2012; 16: 899.

24. Efficacy and Safety of Rhoesorbilact® Solution for Infusion, in a Complex Therapy of Pneumonia. NCT03824457. Cochrane Central Register of Con- 

rolled Trials (CENTRAL) 2019. Issue 3. Available at: https://clinicaltrials.gov/ 

show/NCT03824457

25. Hahn R., Lyons G. The half-life of infusion fluids: an educational review. Eur. J. Anaesthesiol. 2016; 33 (5): 475-82.

26. Caioni P., Tognoni G., Masson S., Fumagalli R., Pesenti A., Romero M. et al. Albumin replacement in patients with severe sepsis or septic shock. N. Engl. J. Med. 2014; 370 (15): 1412-21.

27. Finfer S., Bellomo R., Boyce N., French J., Myburgh J., Norton R. et al. A compar- 

ison of albumin and saline for fluid resuscitation in the intensive care unit. N. Engl. J. Med. 2004; 350 (22): 2247-56.

28. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health, Myburgh J., Cooper D., Finfer S., Bellomo R., Norton R., Bishop N., Kao L S., Vailance S. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N. Engl. J. Med. 2007 Aug 30; 357 (9): 874-84. doi: 10.1056/NEJMoa076514.

29. Myburgh J., Finfer S., Bellomo R., Billiot L., Cass A., Gattas D. et al. Hydrox- 
yethyl starch 130/0.4 versus Ringer’s acetate in severe sepsis. N. Engl. J. Med. 2012; 367 (20): 1901-11.

30. Perner A., Haase N., Guttormsen A., Tenhunen J., Klemenzson G., Åneman A. et al. Hydroxyethyl starch 130/0.42 versus Ringer’s acetate in severe sepsis. N. Engl. J. Med. 2011; 365 (9): 724-34.

31. Rhodes A., Evans L.E., Alhazzawi W., Levy M.M., Antonelli M., Ferrer R. et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit. Care Med. 2017; 45 (3): 486-552.

32. MacDonald N., Pearse R. Are we close to the ideal intravenous fluid? N. Engl. J. Med. 2012; 367 (2): 124-54.

33. Magee C.A., Bastin M.L.T., Laine M.E., Bissell B.D., Howington G.T., Moran P. et al. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: a prospective, open-label, sequential period pilot study. Crit. Care Med. 2018; 46 (8): 1217-23.

34. Self W.H., Semler M.W., Wanderer J.P., Wang L., Byrne D.W., Collins S.P. et al. Balanced crystalloids versus saline in noncritically ill adults. N. Engl. J. Med. 2018; 378 (9): 819-28.

35. Semler M.W., Self W.H., Wanderer J.P., Ehrenfeld J.M., Wang L., Byrne D.W. et al. Balanced crystalloids versus saline in critically ill adults. N. Engl. J. Med. 2018; 378 (9): 829-39.

36. Dalton C. Why did sterile salt water become the IV fluid of choice? Br. J. Anaesth. 2014; 113 (1): 159-78.

37. Magee C.A., Bastin M.L.T., Laine M.E., Bissell B.D., Howington G.T., Moran P. et al. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: a prospective, open-label, sequential period pilot study. Crit. Care Med. 2018; 46 (8): 1217-23.

38. Khamidov D.B., Kosimov Z.K., Kosimov D.D., Kiyamov S.E. Rheosorbilact complex polyfunctional solution in intensive care of endogenous intoxica- 

tion in patients with acute peritonitis. Scientific and Practical Journal TIPPMK. 2002; 16: 94-96.

39. Aliev N.A., Bobiev A.B., Khamidov D.B., Buriev T.N., Kurbanov D.A. et al. Effectiveness of treatment with Rheosorbilact in patients with diabetic foot syndrome. Critical Care Medicine. 2015; 64 (1): 57-59.

40. Pronichev V., Styazhkina S., Mikhailov A. Efficiency of treatment with Rheo- 
sorbilact in patients with acute kidney injury. Ukr. пульмонологічний журнал. 2012; 16: R99.

41. Aliev N.A., Bobiev A.B., Khamidov D.B., Buriev T.N., Kurbanov D.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N. Engl. J. Med. 2012; 367 (2): 124-34.

42. Khamidov D.B., Kosimov Z.K., Kosimov D.D., Khamidov D.B., Buriev T.N., Kurbanov D.A. et al. Albumin replacement in patients with severe sepsis or septic shock. N. Engl. J. Med. 2014; 370 (15): 1412-21.

43. Demirel B. Lactate levels and pneumonia severity index are good predic- 
tors of in-hospital mortality in pneumonia. Clin. Respi. J. 2018 Mar; 12 (3): 991-995.