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New directions of scientific research and clinical practice in the field of extracorporeal hemocorrection in patients with multiple organ dysfunction: a review

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Abstract

INTRODUCTION: Due to the COVID-19 (infectious disease caused by the SARS-CoV-2 virus) pandemic, we had to take a completely different approach to the nature of critical conditions. The pandemic also made us reconsider many views about it. Moreover, that contributed to the development of new practical approaches for treatment and prevention, including the ones in the field of extracorporeal hemocorrection. **OBJECTIVE:** Methods for purification of blood and plasma began to be considered as an independent link for the treatment of organ disorders or as a part of extracorporeal support for the life support of the body. **MATERIALS AND METHODS:** The article consists of three sections: a description of the role of extracorporeal hemocorrection methods in intensive care, their classification and main characteristics; the concept of sequential targeted extracorporeal therapy for a treatable symptom in sepsis; extracorporeal hemocorrection as part of the concept of extracorporeal life support. This article uses literary sources published from January 1, 2022 to July 1, 2023. Materials related to COVID-19 and other specific pathologies (poisoning, acute liver failure, itching, systemic diseases, etc.), requiring separate discussion, are intentionally excluded. **RESULTS:** Technologies in extracorporeal hemocorrection provide support and/or replacement of organ functions; restoration of body resistance and balance between inflammatory and anti-inflammatory response; restoration of body tolerance (metabolism and regeneration). Nevertheless, despite the convincing

Новые направления научных исследований и клинической практики в области экстракорпоральной гемокоррекции у пациентов с полиорганной дисфункцией: обзор литературы

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Реферат

АКТУАЛЬНОСТЬ: Эпидемия COVID-19 (инфекционное заболевание, вызываемое вирусом SARS-CoV-2) заставила совершенно по-иному взглянуть на природу критических состояний, переосмыслить многие взгляды и способствовала разработке новых практических подходов к лечению и профилактике, в т. ч. и в области экстракорпоральной гемокоррекции. Методы очистки крови и плазмы стали рассматриваться как самостоятельное звено терапии органных расстройств или как часть экстракорпоральной поддержки жизнеобеспечения организма. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Обозначение новых направлений, конечных точек и методологии научных исследований, а также практических подходов в области экстракорпоральной гемокоррекции. **МАТЕРИАЛЫ И МЕТОДЫ:** Статья состоит из трех разделов: описание роли методов экстракорпоральной гемокоррекции в интенсивной терапии, их классификация и основные характеристики; концепция последовательной таргетной экстракорпоральной терапии излечимого признака при сепсисе; экстракорпоральная гемокоррекция как часть концепции экстракорпоральной поддержки жизнеобеспечения. В данной статье использованы литературные источники, опубликованные с 1 января 2022 г. по 1 июля 2023 г. Намеренно исключены материалы, связанные с COVID-19 и другими специфическими патологиями (отравления, острая печеночная недостаточность, зуд, системные заболевания и т.д.), требующие отдельного

pathophysiological rationale for the use of these methods in critical conditions, evidence of its effectiveness is limited. Current trends indicate that future research should be primarily aimed at finding biomarkers that can simultaneously designate specific biological processes; characterize different subgroups of patients; allow targeted choice for the method of therapy. The modulation of biomarkers under the influence of this therapy can show its effectiveness for this particular subgroup of patients at this stage of the disease. **CONCLUSIONS:** Methods of extracorporeal blood purification should be aimed at prevailing biological processes, at this stage of pathogenesis, and, accordingly, evaluated by the effectiveness of the impact on these processes.

KEYWORDS: Hemoperfusion, Shock, Septic, Hemofiltration, Critical care, Hemoadsorption

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обсуждения. **РЕЗУЛЬТАТЫ:** Технологии экстракорпоральной гемокоррекции обеспечивают поддержку и/или замещение функций органов; реставрацию резистентности организма и баланса между воспалительной и противовоспалительной реакцией; восстановление толерантности организма (метаболизм и регенерация), но, несмотря на убедительное патофизиологическое обоснование применения данных методов при критических состояниях, доказательства эффективности ограничены. Современные тенденции указывают на то, что будущие исследования должны быть в первую очередь нацелены на поиск биомаркеров, которые могли бы обозначать специфические биологические процессы. Эти маркеры должны давать характеристику различным подгруппам пациентов, позволять сделать выбор метода терапии целенаправленным, и их изменения должны служить оценкой эффективности применяемой терапии у данной конкретной подгруппы пациентов на данной стадии болезни. **ВЫВОДЫ:** Методы экстракорпоральной очистки крови должны быть нацелены на превалирующие на данном этапе патогенеза биологические процессы и, соответственно, оцениваться по эффективности воздействия на эти процессы.

КЛЮЧЕВЫЕ СЛОВА: гемоперфузия, септический шок, гемофильтрация, интенсивная терапия, гемоадсорбция

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Great disasters have always produced great abundance.
They make people want to live.
G.G. Marquez

Introduction

The beginning of the third decade of the 21st century was characterized by a global catastrophe for humanity in the form of the COVID-19 epidemic (the infectious disease caused by the SARS-CoV-2 virus), which forced us to take a completely different look to the nature of critical conditions, rethink many views and contributed to the development of new practical approaches to treatment and prevention [1–3]. It became clear that the body's physiological response to exposure is extremely individual, can be characterized by several options and combinations, has dynamic variability, and the recognized clinical syndromes represent a mixture of biological heterogeneous conditions. In this regard, modern concepts of diagnosis and treatment, based on clinical signs, and not on the biological processes that cause them, do not fully reflect the complexity of critical conditions; the technologies used cannot be assessed by evidence-based methods and often do not show their effectiveness, despite their full theoretical validity [4].

The first blood purification procedure was bloodletting, popular in the 19th century [5]. Extracorporeal blood purification has been studied and developed since the creation of the artificial kidney by Willem Johan Kolff in 1945, and it was among the early methods of extracorporeal life support and was at the origins of critical care medicine. Despite such a long period of development, the presence of numerous technologies and widespread use in intensive care units for various clinical conditions, at the moment extracorporeal hemocorrection (EH) does not have clear indications, evidence of its effectiveness and it is not included in clinical recommendations.

The lack of new knowledge about the nature of the development and correction of multiple organ failure, the deadlock in the treatment of sepsis and number of other clinical conditions, as well as changes that affected both the fundamental and practical foundations of intensive care, could not lead to the formation of new views and strategies in the field of EH, which will be discussed in this review.

Objective

The aim of this study is to describe new directions of scientific research and clinical practice in the field of extracorporeal hemocorrection in patients with multiple organ dysfunction.

Materials and methods

This article consists of three parts: a description of the role of extracorporeal hemocorrection methods in intensive care, their classification and main characteristics; the concept of sequential target extracorporeal therapy for a treatable symptom in sepsis; extracorporeal hemocorrection as part of the concept of extracorporeal life support. The work uses the most interesting, in the opinion of the authors, literary sources published from January 01, 2022 to July 01, 2023 (including books, clinical studies, randomized clinical trials, meta-analyses, reviews and regular reviews), which discuss promising scientific directions of evidence-based research; and specific EH technologies are proposed for implementation.

Materials related to COVID-19 and other specific pathologies (poisoning, acute liver failure, itching, systemic diseases, etc.), requiring separate discussion, were intentionally excluded from the analysis.

Extracorporeal hemocorrection in intensive care

The development of organ dysfunction is directly related to a progressive clinical and biological syndrome that occurs under the influence of a high pathogenic and/or toxic load, characterized by hyperinflammation and/or immune paralysis refractory to therapy, accompanied by endotheliopathy and damage to the coagulation system [6]. Intensive therapy involves supporting and/or replacing organ functions; restoration of the body's resistance and balance between the inflammatory and anti-inflammatory response; restoration of the body's tolerance (metabolism and regeneration), in order to prevent and prevent multiple organ failure. All these areas of intensive care correspond to the technology of extracorporeal life support and direct EH methods [7].

EH can be performed by direct hemoperfusion or plasma purification. The possibilities of various options for procedures depending on the molecular weight of the substances being eliminated are shown in Fig. 1. Extracorporeal blood purification can be achieved using diffusion (hemodialysis), convection (hemofiltration), or a combination of both (hemodiafiltration). The third mechanism is based on the adsorption of dissolved substances by the sorbent [7].

Classification and nomenclature

In the Russian Federation, the nomenclature currently used is approved by Order of the Ministry of Health and Social Development of the Russian Federation dated October 13, 2017 N 804n. (valid from 01/01/2018, as amended by Order of the Ministry of Health of Russia dated March 5, 2020 N 148n (including as amended, entered into force on 04/18/2020, as amended for 2023) [8].

In 2022, a draft of a new Order of the Ministry of Health of the Russian Federation "On approval of the range of medical services" was published (prepared by the Ministry

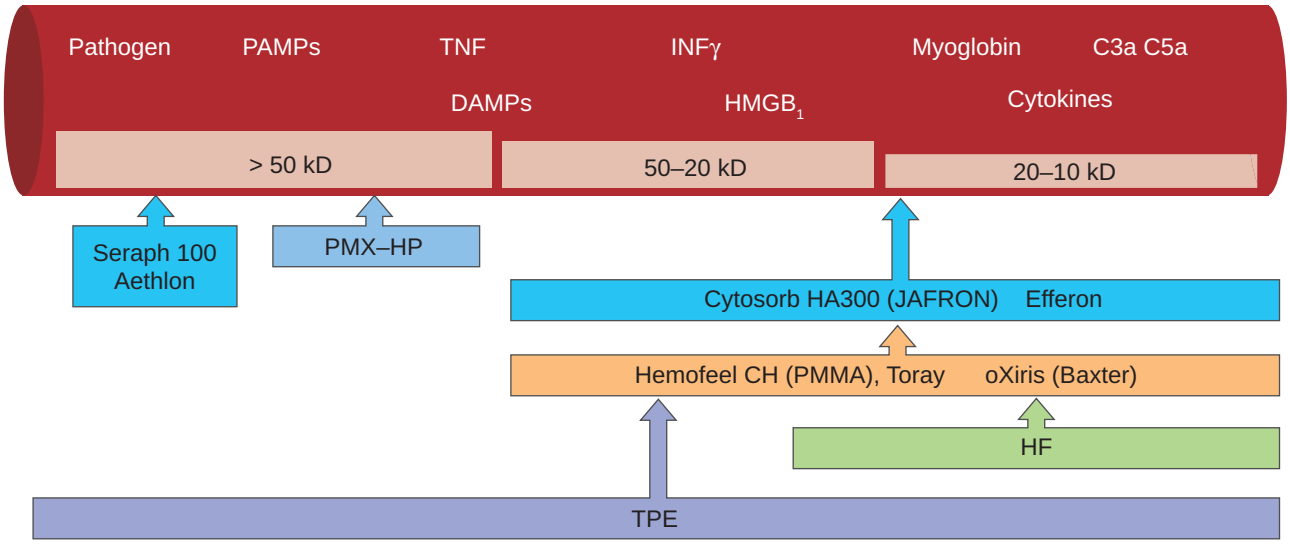

Fig. 1. The modified scheme of sequential extracorporeal hemocorrection with the designation of the relationship between the molecular weight of substances dissolved in the blood and the possibilities of extracorporeal blood purification methods

Pathogen — microorganism; PAMPs — pathogen-associated molecular patterns; TNF — tumor necrosis factor; DAMPs — damage-associated molecular patterns; HMGB1 — high-mobility group protein B1 or amphoterin; kD — kilodalton; PMX-HP — polymyxin-B hemoperfusion.

of Health of Russia on 04/07/2022) [9]. In this document, EH included in section 05 (other diagnostic and therapeutic manipulations and procedures; type of action in section 05 DIA blood) is planned to be divided into two types:

- 05.DIA. 18 — extracorporeal hemocorrection associated with the receipt and/or processing of blood plasma and its fractions:
  - 001.006 plasmapheresis;
  - 002.006 plasma exchange;
  - 003.006 lipid filtration;
  - 004.006 cascade plasma filtration;
  - 005.006 selective plasma filtration;
- 05.DIA.19 — extracorporeal hemocorrection associated with perfusion of whole blood through a sorbent:
  - 001.006 hemosorption;
  - 002.006 selective hemosorption;
  - 003.006 selective hemosorption of cytokines;
  - 004.006 elective hemosorption of lipopolysaccharides;
  - 009.006 plasma sorption;
  - 010.006 selective plasma sorption.

Hemofiltration

The principle of hemofiltration is the convective removal of water and solutes, including mediators, from the bloodstream using a synthetic membrane with a threshold value of ~50–60 kDa (kilodaltons), which are also used in renal replacement therapy (RRT).

Over the past year and a half, no new revolutionary data have been obtained to improve various modalities of RRT. The use of mass exchange devices with membranes with increased sorption properties and/or high permeability (more than 30–60 kDa) showed a significant decrease in the level of cytokines, stabilization of hemodynamics, a decrease in the dose of vasopressors, an increase in PaO_2/FiO_2 (the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen) and reducing the severity of organ dysfunction [10, 11].

The oXiris filter (Baxter, Meyzieu, France) contains a modified AN69 membrane associated with a positively charged polyethylenimine polymer capable of absorbing both endotoxin and several different septic mediators from the bloodstream while simultaneously providing the effects of RRT. Due to low or very low quality of evidence, it is not yet possible to reliably evaluate the effectiveness of oXiris filters. In addition, there was no significant difference in 90-day mortality, ICU mortality, or length of hospital stay [12]. As stated by Li et al. [13], obtaining reliable results is hampered by the heterogeneity of patients and various additional conditions that create background noise.

A study by Kishikawa et al. [10] analyzed the effect of a polymethyl methacrylate and polysulfone membrane on the adsorption of 48 different cytokines in human plasma. Seventy-nine percent (38/48) of cytokines were more efficiently adsorbed onto the PMMA membrane than onto the polysulfone membrane, indicating the high cytokine adsorption capacity of the membrane. Adsorption rates tend to be higher for lower molecular weight cytokines, and a significant correlation has been observed between cytokine molecular weight and adsorption rates. Electron microscopy revealed that the PMMA hollow fiber membrane has a uniform internal structure from the inner to the outer layers of the membrane and nanopores within the membrane, which possibly facilitate the adsorption of proteins with a certain molecular weight range.

Hemoadsorption (hemoperfusion)

Hemoperfusion (HP) involves the adhesion of substances circulating in the blood to the surface of a membrane capable of trapping them. There are no established indications, as well as evidence-based randomized clinical trials, yet, however, there are several biological and pathophysiological rational indications that are quite actively discussed in the literature [14–16]. As stated above, only the problems of multiple organ dysfunction and sepsis will be discussed here.

Sepsis and septic shock

Selective sorption of endotoxin (lipopolysaccharide (LPS)

The most widely studied and used therapy for endotoxin elimination in the treatment of sepsis and septic shock (SS) is polymyxin hemoperfusion (PHP) (Toraymixin, Toray Industries, Tokyo, Japan). In 2023, a post-hoc analysis of two previously completed studies, JSEPTIC-DIC (1911 patients) and EUPHRATES (286 patients), was published to determine the subgroup of patients most likely to benefit from PMX-HP. It was revealed that in a group of patients with sepsis and high endotoxin activity (endotoxin activity assay (EAA) more than 0.6), coagulopathy (prothrombin time and normalized international ratio > 1.4) and hyperlactatemia (lactate > 3 mmol/l), PMX-HP contributed to an increase in 28-daily survival rate 68 %, compared with control 52 %; treatment effect of PMX-HP, +16 % [95% CI +2.2 % to +30 %], p = 0.02. Japanese authors demonstrated that selective RMS-HP may be most beneficial for patients with SOFA scores of 7–12 (28-day mortality was significantly lower than in the control group) [17].

A new trial called TIGRIS (Clinical Trials.gov identifier: NCT03901807) is currently being conducted in 150 patients with endotoxemic SS (EAA ≥ 0.60 and < 0.90). At the time of writing, according to Spectral Medical (Toronto, Canada), 64 patients were included in the study group [18].

At the Hitachi General Hospital Medical Center, a retrospective multicenter study "Studying the optimal timing of starting PMX-HP" (with an assessment of the effect on the need for catecholamines) was launched (the PMX-OPTIC study, 600 patients). The purpose of this study is to examine the maximum dose of vasopressor administered before and after the initiation of direct RMS-HP and examine its relationship with patient outcomes [19].

Non-selective hemoperfusion

A cartridge containing a synthetic resin consisting of microspheres of polystyrene and divinylbenzene (Cytosorb, Cytosorbents Corporation, Monmouth Junction, NJ, USA; Aferetica s.r.l., Bologna, Italy) with a significant adsorption surface (~40,000 m^2), capable of adsorbing hydrophobic pro- and anti-inflammatory drugs mediators with a molecular weight of 5 to 60 kDa, represents an evolution of coupled plasma filtration and adsorption, since it uses the same binding resin that is located in microtubules [16, 20].

Two randomized controlled trials of the Cytosorb device were published in 2022 (one of them focused on COVID-19 and was therefore not included in the discussion). They studied HP during cardiac surgery for infective endocarditis with a device integrated into the cardiopulmonary bypass circuit. There were 142 patients randomized to Cytosorb versus 146 to usual care, and there was no difference in the primary outcome SOFA score or any other clinical outcome, including mortality (21 % vs. 22 %), compared with 73 % in the control group [16, 21–23].

A systematic review and meta-analysis by Dr. Becker S. et al., published in 2023 [23] was aimed to evaluate the effects of Cytosorb in all previously described conditions. The primary endpoint was recorded mortality. In addition, length of ICU stay, norepinephrine requirements, IL-6 and lactate levels were compared. Mortality rate was not significantly different between the Cytosorb group and the control group for all studies pooled (odds ratio (OR 1.07 [0.88, 1.31]) and in the subgroups (OR 0.98 [0.74, 1.31]): operations with cardiopulmonary bypass (RR 0.91 [0.64, 1.31]); 1.29]), severe disease (RR 0.95 [0.59, 1.55]) and COVID-19 (RR 1.58 [0.50, 4.94]). Patients with cardiac arrest showed a significant survival advantage compared with untreated patients from the control group (HR 1.22 [1.02, 1.46]). Results for ICU mortality, in-hospital mortality, or 30-day mortality were similar. The length of stay in the intensive care unit between Cytosorb and the control group was not significantly different for all studies combined or for subgroups with different diagnoses. There was no significant difference in norepinephrine dose (μg/kg/min) or mean arterial pressure at baseline. SOFA, SAPS-2 (Simplified Acute Physiological Score), and APACHE-2 (Acute Physiological Score and Chronic Health Evaluation), none of these scores showed significant differences between the Cytosorb and control groups. C-reactive protein levels did not differ significantly at baseline or at the first measurement after treatment. This meta-analysis, including data from 34 studies (1297 patients treated with Cytosorb compared with 1314 control patients) showed no significant changes with Cytosorb [16, 22–24].

HP cartridges (Jafron Medical, Zhuhai, China) made of styrene-divinylbenzene copolymer contain macroporous adsorbent resin beads and are non-selective adsorption devices. The device was designed for use in clinical situations characterized by elevated cytokine levels. The resin pore size distribution ranges from 500 to 60 kDa and allows the removal of molecules from 10 to 60 kDa. Cartridges have been studied in randomized clinical trials in combination with conventional treatment for SS and have been shown to benefit hemodynamics, markers of lung injury, duration of mechanical ventilation and continuous renal replacement therapy, reduced length of stay in the intensive care unit, and effective reduction of cytokine levels; one trial found a significant effect on mortality [24, 25].

The HP procedure using the Seraph 100 Microbind Affinity Blood Filter (ExThera, Martinez, CA) has been ap-

proved by the USA Food and Drug Administration (FDA) with Emergency Use Authorization for the treatment of severe COVID-19. This device contains ultra-high molecular weight adsorption beads that in vitro remove SARS-CoV-2 virus, bind toxins, bacteria and antithrombin III, removing them from the bloodstream. Recently, Eden G. et al. [26] demonstrated rapid resolution of bacteremia in a group of patients with chronic renal failure who underwent RRT.

In 2022, a randomized controlled multicenter study LASSO (Lipopolysaccharide adsorption in septic shock) was conducted in the Russian Federation to evaluate the use of multimodal LPS hemosorbent (Efferon LPS). It was found that the use of the device was accompanied by a statistically significant improvement in hemodynamics and gas exchange, a decrease in the severity of organ dysfunction and markers of systemic inflammation, a faster resolution of SS, a decrease in the need for RRT and the length of hospital stay. At the same time, there were no significant differences in 28-day mortality: 47.4 % compared to 55 % in the control group [27]. Active distribution of this product in clinics of the Russian Federation contributed to the conduct and registration of a number of studies devoted to the study of the effectiveness and safety of the technique in the treatment of rhabdomyolysis [28], acute pancreatitis [29] and in obstetric practice [30]. The results demonstrated that combined with RRT or isolated early use of HP as part of complex intensive therapy for toxic rhabdomyolysis complicated by the development of acute kidney injury is accompanied by an earlier and significant decrease in the levels of laboratory markers and frequency, compared with standard treatment, as well as shorter treatment periods in ICU and in hospital [29, 30].

Experimental devices

The Aethlon Hemopurifier (USA) is an investigational device for eliminating life-threatening glycosylated viruses that are resistant to other therapies and has not yet received FDA approval. The company currently has an open, FDA-approved expanded access protocol for the treatment of Ebola patients in the USA and an approval of Health Canada (the Ministry of Health of Canada). Hemopurifier has the potential to destroy many viruses that are pathogenic to humans, including hepatitis C virus, human immunodeficiency virus, SARS-CoV-2 and Ebola [31].

Plasma processing methods

Therapeutic apheresis involves removing plasma (plasmapheresis) or blood cells (cytapheresis) from the patient's blood. Therapeutic plasma exchange (TPE) serves to remove pathogenic substances and/or to introduce large quantities of plasma components, the absence of which is considered responsible for dysfunction (eg., ADAMTS 13 (metalloproteinase of the peptidase protein family) for patients with thrombotic thrombocytopenic purpura). Ideally, a substance that is best suited for removal by TPE should have a high molecular weight, a low volume of distribution, a long half-life, and a low turnover rate. Under stationary conditions, 3–5 sessions with an exchange of 1–1.5 volumes of plasma are sufficient to remove most molecules to a level below 90 %. However, if substances are predominantly in the bloodstream (eg., immunoglobulin M), even a single session with a large turnover may be satisfactory and can remove 86 to 92 % [32].

Theoretically, any condition caused by a known or suspected circulating factor could benefit from its elimination. Diseases and syndromes such as sepsis, hemophagocytic lymphohistiocytosis, cytokine release syndrome, and pancreatitis share the phenotypic features of systemic hyperinflammation with endothelial dysfunction and coagulopathy. Excessive release of damage-associated molecular moieties (DAMPs), cell-free DNA (deoxyribonucleic acid) and neutrophil extracellular traps, together with a decrease in protective plasma factors, are involved in many pathophysiological processes.

In sepsis, TPE may modulate biological endpoints related to inflammation, coagulation, microcirculation, and endothelial function. It has been shown that restoring the balance between decreased ADAMTS 13 activity and increased VWF to a normal ratio can improve microvascular perfusion and blood flow. Likewise, TPE can replace consumed anticoagulant proteins such as protein C.

The use of TPE in the treatment of heparin-induced thrombocytopenia, sepsis-mediated disseminated intravascular coagulopathy has been repeatedly reported. A recent prospective study found improvements in platelet count, coagulation function, and even survival after pulmonary embolism, consistent with observations in patients with organ failure, disseminated intravascular coagulation, meningococcal septicemia, Capnocytophaga canimorsus infection, and scorpion stings [33].

A randomized clinical trial of 40 patients [36] demonstrated a trend toward better survival and reduced severity of multiorgan dysfunction in patients treated with a single session of TPE removing > 3000 mL of plasma compared with controls receiving RRT alone; as expected, reductions in sepsis biomarkers and replenishment of plasma-supplied factors, including protein C, protein S, and ADAMTS 13, were observed in the TPE group but not in the control group.

A panel of 18 experts articulated the advantages of this method, as well as challenges for future research, based on the belief that plasma exchange could be beneficial when used in correcting homeostasis disturbances in SS [34].

Economic costs associated with extracorporeal hemocorrection

The article "Clinico-economic assessment of the use of selective sorption methods of extracorporeal hemocorrection in patients of the intensive care unit" [35] shows that the use of EH in the intensive care program for patients with sepsis, although accompanied by an increase in direct and indirect

financial costs, in the medium term leads to saving of budget funds. According to the authors of the article, which is based on an analysis of 38 patients from the LASSO study, the use of the Efferon LPS column has the least burden on the budget.

The study, "Cost-Effectiveness of Polymyxin B Hemoperfusion for Septic Shock: An Observational Study Using the Japanese National Administrative Database for 2018–2021", based on an analysis of 19238 patients with a SOFA severity score of 7–12, also demonstrated a positive result in prolonging life expectancy adjusted for quality of life, as well as an increase in budget costs (by 6935 euros). Due to the fact that in Japan, the treatment of patients with SS is paid for by the insurance company in the amount of 38,462 euros, thus, the use of RMH-HP fits well within the budgetary allocations and is considered effective [36].

Clinical guidelines

In 2022, the Federation of Anesthesiologists and Resuscitators and the Association of Anesthesiologists and Resuscitators of the Russian Federation, with the participation of various public medical organizations, developed and submitted for consideration to the Ministry of Health two draft clinical recommendations: "Sepsis in adults", "Septic shock in adults". It should be noted that in contrast to the 2021 recommendations of the Surviving Sepsis Campaign, where extracorporeal cleansing methods are not recommended for routine use due to the lack of evidence, both Russian documents define groups of patients, severity of condition, laboratory parameters, methods and characteristics of procedures for possible use to replace renal function and influence the systemic inflammatory response [37, 38].

The concept of sequential targeted extracorporeal therapy for sepsis

The events that develop during sepsis are associated with a number of biological processes. Invasion of microbial hosts; formation of a focus of infection; opsonization by bacterial products (eg. LPS); recognition of pathogens leading to an immune response; cellular and humoral effects of circulating pathogens and pathogen products; immune dysregulation and endocrine effects of cytokines; damage to the endothelium and organs leads to the development of multiple organ dysfunction, and in the absence of correction, to multiple organ failure [6].

Each of these biological processes may be a potential target for a specific extracorporeal therapy: selective removal of pathogens from the bloodstream using affinity cartridges; selective elimination of endotoxin by PMX-HP; non-selective removal of cytokines by cartridges with sorbents or using adsorbent membranes; extracorporeal organ support using various methods (CO_2 removal, membrane oxygenation), kidney support (hemofiltration, hemodialysis or ultrafiltration) [6] (Figure 1).

The work of Claudio Ronco and John Kellum et al. [6] is not the first of their strong recommendations to shift the emphasis of scientific and practical research and the choice of trial endpoints towards a step-by-step assessment of the effectiveness of each of the EH methods used, rather than mortality. This approach, according to experts, will bring EH into the world of evidence-based medicine and develop current recommendations.

The concept of selecting methods of extracorporeal hemocorrection based on cause-and-effect relationships

The choice of EH methods should not be aimed at correcting heterogeneous clinical syndromes, but should be carried out taking into account cause-and-effect relationships: a provoking factor causing a shift in physiological disorders (causality factor); a specific physiological disorder ("treatable symptom, condition"), characterized by biomarkers that determine a predictable response to a specific therapy. These predictors allow us to identify a subgroup of patients and select the technology most suitable for influencing a specific treatable symptom [1].

Research shows that different triggers and the damage they cause can start the activation of identical molecular signaling pathways. The same biomarker can change as a result of several different causes, and molecular signals caused by different triggers can trigger different patterns of systemic response. The biological processes that characterize the disease mechanism may be common to various clinical conditions, regardless of cause. The concept of a treatable condition (a physiological state and its corresponding biomarkers) implies that the chosen therapy is directly related to a positive effect on an understood physiological mechanism [1].

Endotoxemia and, accordingly, the level of endotoxin activity in the blood, is one of the treatable conditions that can be diagnosed and quantified.

Assessing the degree of endotoxemia

Endotoxin, being a classical pathogen-associated molecule (PAM), activates the release of cytokines and other biologically active components. Therefore, clinicians need an accurate laboratory diagnostic tool to detect endotoxin in order to initiate specific treatment in a timely manner. Quantitative methods for measuring endotoxin levels in blood have been known for over 50 years [39] and are based on the use of an endotoxin assay using amebocyte lysate from the horseshoe crab Limulus polyphemus. This method has some serious limitations, one of the most important being the low specificity for LPS [40].

The endotoxin activity test is a rapid whole blood test (40 minutes). The test to assess the activity of endotoxin is based on the biological reaction of neutrophils in the patient's blood to the immunological complex of endotoxin and exogenous antibodies; LPS of gram-negative bacteria participates

in the reaction, and there are no cross-reactions with elements of the cell membrane of gram-positive bacteria and other microorganisms. When used with other diagnostic tests, the test is performed to exclude the presence of gram-negative bacterial infections; it can help assessing the risk of detection and progression of sepsis in patients in the intensive care unit. EAA levels below 0.4 represent a low risk of developing severe sepsis and in most cases confirm the absence of severe gram-negative infection. Values in the range of 0.4–0.59 are considered average and correspond to an increased risk of sepsis. EAA levels of 0.6 or more represent a high risk of mortality and SS [40].

Endotoxin activity levels greater than 0.65 have been found to indicate increased 28-day mortality and the presence of other clinical signs of severe infection. The assessment of EAA as predictors of 28-day mortality is of greater importance than the level of procalcitonin, which can be used as a criterion for the initiation of specific treatment, including the earlier introduction of selective adsorption of LPS into the treatment complex. [40]

The significance of determining this biomarker is shown in the multicenter randomized observational study EUPHAS2-G50 published by a group of European authors and its subsequent additional analysis. In critically ill patients with SS and EAA ≥ 0.6 treated with PMX-HP, EAA decreased and SOFA score improved within 120 hours. In those with high EAA resolved within 48 hours, vasopressor dose reduction was more rapid and the need for RRT was lower compared with patients with EAA T48 ≥ 0.6 [41].

In the Russian Federation, determination of endotoxin activity is available in 28 laboratories in different regions, including 11 clinics in Moscow. However, most studies do not use any assessment of endotoxemia at all or use an amoebocyte lysate test from the horseshoe crab Limulus polyphemus [27].

In the described clinical observation from the Russian Scientific Center for Surgery named after. ak. B.V. Petrovsky [42] demonstrated that the use of EAA, as an additional diagnostic tool and as a "treatable sign" that is a target for therapy, in a patient with progressive multiple organ dysfunction against the background of sepsis refractory to antibiotic therapy, allowed for a timely response on the emergence of new foci of infection and effectively use extracorporeal therapy methods to prevent the occurrence of SS.

Extracorporeal hemocorrection as part of the concept of extracorporeal life support

The course of multiple organ disorders must be considered not only as dysfunction/damage caused by pathogens and/or mechanisms of immune resistance, but also from the position of tolerance to the disease as a key regulator of the progression of the process [34, 35].

Functionally, disease tolerance is a product of tissue damage control mechanisms. Damage control mechanisms counteract the stress associated with infection, help maintain homeostasis, and as such establish disease tolerance and limit disease severity. This is a protective strategy that, by restructuring immune and parenchymal metabolism, promoting adaptive homeostasis, allows vital organs to withstand the functional limitations associated with severe disorders. EH as part of extracorporeal life support or temporary replacement of the function of various organ systems fits well into the new strategy aimed at preserving and restoring the physiological mechanisms used by tissues and organs to limit damage and dysfunction [43] (Figure 2).

The protective strategy of the body is formed by maintaining homeostasis (tolerance) by supporting/replacing organ function and ensuring resistance function: sanitization of the source of infection, antibiotic therapy, sequential EH. The ultimate goal of an extracorporeal life support strategy is to preserve metabolism, tissue regeneration, and restore organ function [43].

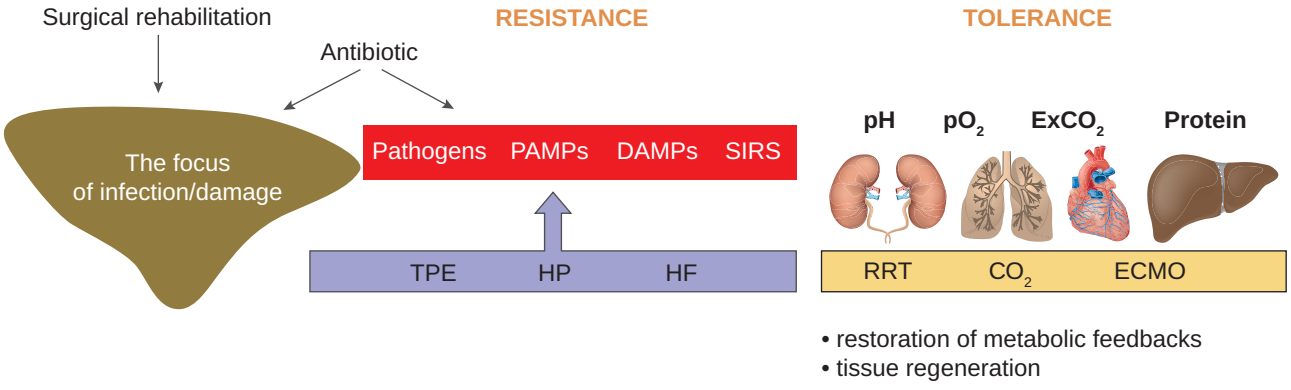

Fig. 2. The place of extracorporeal hemocorrection in the complex of extracorporeal life support, taking into account the effect on protective mechanisms

Pathogens — microorganisms; PAMPs — pathogen-associated molecular patterns; DAMPs — damage-associated molecular patterns; HP — hemoperfusion; PE — plasma exchange; HF — hemofiltration; RRT — renal replacement therapy; CO_2 — extracorporeal carbon dioxide removal; ECMO — extracorporeal membrane oxygenation; pH — pH value; pO_2 — partial pressure of oxygen; $ExCO_2$ — carbon dioxide released; Protein — protein metabolism.

Conclusion

The study of extracorporeal life support strategies and, in particular, EH reflects a progressive understanding of the philosophy of interaction between the environment and human, micro- and macroorganisms-hosts. Despite the compelling pathophysiological rationale for the use of EH in critical illness, evidence of effectiveness is currently limited and based on clinical experience.

One of the fundamental issues underlying the concept of removing harmful mediators from the bloodstream is the consideration that their removal alone may not be beneficial, since even a significant increase in levels may be an evolutionary protective compensatory strategy of the body for a given disease state. Also, de novo response of cytokine production or redistribution from the third spaces can vary greatly and influence plasma cytokine levels and modulate their levels in organs and tissues depending on the underlying disease and the extent of extracorporeal removal [6].

In contrast to signaling molecules, seeded microorganisms and their toxins (endotoxin and other PAMPs), as well as molecules released due to cytolysis/necrosis (DAMPs), indicate the specific cause and severity of the development of systemic inflammation; their concentration/activity is quantifiable; and, already at the present moment, they can be subject to targeted (and non-selective) effective removal, especially after sanitization of the source of infection and antibiotic therapy.

It has been proven that infectious and non-infectious causes provoke the development of several endotypes of the systemic inflammatory response of the body with different characteristics and, accordingly, distinguishable clinical conditions [2]. This allows you to target the search for specific biomarkers (including using omics and genetic technologies), and make them surrogate research endpoints. The choice of targeted methods of EH and assessment of its effectiveness should be carried out taking into account the effect on a specific biological process. It is planned that well-designed randomized clinical trials will evaluate whether sequential application of different EH methods (acting in stages on different biological processes) can achieve an effect on biological endpoints and "treatable" clinical signs. The next step will require studies assessing the achievement of specific goals by specific methods at specific stages of treatment in specific subgroups of patients, rather than mortality within specified time frames. Of course, after obtaining positive results from the applied technologies in certain patient phenotypes, it is necessary to evaluate the impact of a set of EH methods on the final result of the combined treatment of multiple organ dysfunction [6]. All these efforts are meaningless without a complex of effective extracorporeal life support not only for saving lives (preventing the onset of multiple organ failure, or preparing for organ transplantation), but also for restoring the body and rehabilitation.

The laws of philosophy and biology explain the processes of interaction between the external environment and the microcosm with the human body, maintaining a balance between microbial/toxic load and inflammation, the unity and diversity of signaling mechanisms and the disruption of feedback, the evolution of the processes of adaptive reactions of the body. Apparently, the time has come to re-analyze the logic and harmony of biological processes, and not just invent technologies for influencing them.

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