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# Host immuno-inflammatory response and intravascular volume replacement therapy in critically ill septic patients – are fluids a double-edged sword?

## Imunsko-inflamacijski odgovor domaćina i terapija nadoknadom intravaskularnog volumena kod kritično obolelih sa sepsom – da li su tečnosti mač sa dve oštrice?

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**Abstract**

Intravascular volume replacement fluid therapy plays a pivotal role in the treatment of patients in circulatory shock. The interaction between various lines of therapy and immune response in critically ill septic patients remains a significant clinical challenge with no simple solution. Plasma expanders, crystalloids (such as physiological saline, balanced Ringer's lactate, and Plasma-Lyte solution), and human albumin solution–the only acceptable colloid for critically ill patients–should be considered as necessary potent drugs with significant adverse effects. Sepsis is a very heterogeneous syndrome, with various magnitudes and persistence of inflammatory responses. Bearing in mind that the natural course of sepsis is highly complex, with phases of hyperinflammation and immunosuppression often occurring simultaneously in different locations, it is almost impossible to avoid the adverse effects of crystalloids, which are first-line intravascular volume-replacement solutions. Large-volume replacement therapy or rapid intravenous fluid infusion may induce shedding or partial denudation of the endothelial glycocalyx, thereby propagating tissue injury, leukocyte and platelet adhesion and activation. A compromised glycocalyx leads to detrimental capillary leak syndrome in sepsis. In clinical practice, serum albumin levels may indicate the timing and need to administer intravenous human albumin solution during fluid resuscitation when substantial volumes of crystalloids are required. This is an example of a "glycoprotective" fluid approach, with lower volumes and slower crystalloid infusion rates. The complex interaction among fluid therapy, the endothelium, the glycocalyx, and immune mediators is pathophysiologically relevant and very important for clinicians in therapeutic approaches.

**Keywords:**
**cell membrane; critical illness; drug-related side effects and adverse reactions; infusions, intravenous; isotonic solutions; sepsis.**

**Apstrakt**

Terapija nadoknade intravaskularnog volumena tečnostima igra ključnu ulogu u lečenju bolesnika u cirkulatornom šoku. Interakcija između različitih vidova terapije i imunskog odgovora kod kritično obolelih sa sepsom i dalje predstavlja značajan klinički izazov bez jednostavnog rešenja. Plazma ekspandere, kristaloide (kao što su fiziološki rastvor, balansirani Ringer laktat i Plazma-Lyte rastvor) i rastvore humanog albumina–jedinog prihvatljivog koloida za kritično obolele–treba smatrati neophodnim potentnim lekovima sa značajnim neželjenim efektima. Sepsa je veoma heterogen sindrom, sa različitom jačinom i trajanjem inflamacijskog odgovora. Imajući na umu da je prirodni tok sepse vrlo složen, sa fazama hiperinflamacije i imunosupresije koje se često javljaju istovremeno u različitim delovima organizma, skoro je nemoguće izbeći neželjene efekte kristaloida, koji su terapija prve linije za nadoknadu intravaskularnog volumena. Primena velikog volumena tečnosti ili brza intravenska infuzija rastvora mogu izazvati oštećenje ili parcijalni gubitak endotelnog glikokaliksa, čime se podstiče oštećenje tkiva, adhezija i aktivacija leukocita i trombocita. Oštećeni glikokaliks dovodi do štetnog sindroma kapilarnog curenja kod sepse. U kliničkoj praksi, nivoi serumskog albumina mogu ukazati na vreme i potrebu uključivanja intravenskog rastvora humanog albumina tokom

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reanimacije tečnočšću kada su potrebni veći volumeni kristaloida. Ovo je primer „glikoprotektivnog“ pristupa nadoknadi tečnostima, uz primenu manjih volumena i sporije brzine infuzije kristaloidnih rastvora. Složena interakcija između primene tečnosti, endotela, glikokaliksa i imunskih medijatora je patofiziološki relevantan problem, veoma važan za kliničare u terapijskim pristupima.

**Ključne reči:**
**ćelija, membrana; kritična stanja; lekovi, neželjeni efekti i neželjene reakcije; infuzije, intravenske; rastvori, izotonični; sepsa.**

## Introduction

Over the past two decades, there have been significant advancements in our understanding of the complex pathogenic underpinnings of sepsis. This idiosyncratic medical condition, characterized as a dysregulated immune response (Ir) to infection, has led to continuous revisions of diagnostic criteria and management protocols, as well as heightened awareness among clinicians. The global burden of sepsis underscores the significance of the disease as a crucial health issue and a predominant factor in mortality and critical illness worldwide [1, 2].

Immune cells and mediators are the most important components of the Ir, but remain insufficiently elucidated to date [3, 4]. The combination of conflicting pro-inflammatory and anti-inflammatory signaling pathways heavily contributes to increased mortality risk as a result of multiple organ failure (MOF). Patients with sepsis typically exhibit a transient pro-inflammatory phase, followed by varying degrees of immunosuppression. The Ir in individual sepsis patients with different types of bacteria in the abdominal sepsis have different cytokine profiles [5, 6]. Moreover, due to the complexity of the Ir, it is rather challenging to determine independent predictors of lethal outcomes early enough to optimize individual therapeutic approaches [7, 8]. Interaction between various modalities of therapy and Ir in patients with sepsis remains a significant challenge with no simple solution [9].

Fluid administration is a very important intervention in the treatment of critically ill sepsis patients. The main goal of this therapy is to restore circulatory blood volume, expand venous return (VR), and ultimately support cardiac function and maintain mean arterial pressure. The resuscitation fluids are broadly divided into two main categories: crystalloid and colloid solutions. Crystalloids are categorized into unbalanced solutions, such as normal (isotonic) saline (0.9% sodium chloride – NaCl), and balanced (buffered) solutions, including Ringer's lactate, i.e., Hartmann's solution, and Plasma-Lyte. Colloid solutions are classified as either natural (albumin) or synthetic (hydroxyethyl starch – HES). The only allowed colloid solution in a critical care setting is human albumin [10].

### *Pivotal role of intravascular volume in sepsis and septic shock*

Simplification of the pathophysiology of circulatory shock leads to four basic types of this detrimental condition: hypovolemic, distributive, cardiogenic, and obstructive. Septic shock is distributive in nature. Intravascular volume is functionally divided into unstressed and stressed components. Approximately two-thirds of the entire intravascular volume is unstressed volume, which does not exert any pressure on the vascular walls. The remaining one-third is stressed volume, which stretches the vessel walls and generates the mean systemic filling pressure (Pmsf). Theoretically, Pmsf is the pressure in the entire circulatory system when the heart stops (the total blood volume is about 5.5 L, but only 1.3–1.4 L is stressed volume) [11]. Unstressed volume serves as a reservoir that can be mobilized through adrenergic stimulation.

At equilibrium, VR is equivalent to cardiac output (CO). The rate of blood flow is determined by the pressure difference between the veins and the right atrium, while the cardiac pump function maintains the right atrial pressure (RAP) at low levels. Thus, the heart maintains the pressure gradient between the upstream Pmsf and the downstream RAP. The VR directly depends on the pressure gradient between the downstream pressure (RAP) and the upstream pressure (Pmsf), divided by the resistance to VR (RVr) [9]. Therefore, VR is defined by the following equation: $VR = (Pmsf – RAP)/RVr$.

The normal value of Pmsf is approximately 7–8 mmHg and directly depends on circulatory volume and venous capacitance. In normal conditions in humans, RAP is an equilibrium between the return function and cardiac function, with a value of 0–2 mmHg. The RAP value is affected by pleural pressure changes during spontaneous breathing and especially during mechanical ventilation. RVr depends on the vein diameter, and it is under direct control of the adrenergic system [10]. Two main factors can modify Pmsf. Fluid administration increases the first factor, i.e., the volume of blood in large veins. The second is the distensible venous reservoir, which can be altered by regulating adrenergic tone (the administration of vasoactive drugs) [12].

Central venous pressure (CVP) reflects RAP as well as right ventricular filling pressure. Importantly, CVP reflects the backpressure on VR and, therefore, on organ perfusion. It is clinically important because high CVP reduces mean organ perfusion pressure, which can be detrimental to critically ill patients [13].

A large venous reservoir might be recruited during acute circulatory failure, as explained before [14]. The main goal of venous expansion is to augment VR and CO in these patients. However, only half of the patients respond to fluid administration. New research indicates that it is also a time-dependent process. In the case of "fluid responders", where the Frank-Starling curve is steep, fluid expansion increases Pmsf more than RAP does, and the pressure

gradient also increases. The test is positive if the increase in stroke volume or CO is 10–15%. CO is clinically expressed as cardiac index, with normal values being 2.5–3.5 L/min/m$^2$. In the early phase of sepsis, there may be hyperdynamic circulation with a cardiac index > 4 L/min/m$^2$. In the case of "fluid non-responders", where the Frank-Starling curve is flat, volume expansion increases Pmsf, but venous preload does not increase stroke volume. The increase in end-diastolic ventricular pressure leads to a rise in RAP. Thus, RAP and Pmsf values increase together while their pressure gradient decreases. In this scenario, despite fluid administration, CO will remain unchanged [15].

Fluid resuscitation and de-resuscitation are fundamental postulates in critical care medicine. Resuscitation strives to restore sufficient tissue perfusion and oxygenation, whereas de-resuscitation seeks to eliminate excess fluid to avert consequences such as pulmonary edema, abdominal compartment syndrome, and MOF [16].

*Composition of frequently utilized crystalloids*

Normal saline, considered a "normal and isotonic" or "physiological" solution, is the most commonly used intravenous (i.v.) solution globally, as opposed to the 0.45% NaCl, which is considered a hypotonic fluid. Normal saline solution contains 154 mmol of both sodium and chloride ions, but in an editorial published in 1970, it was neither described as normal nor physiological [17]. Moreover, it is considered "unbalanced" due to a high concentration of chloride ions [18, 19].

The administration of chloride-rich solutions can lead to hyperchloremic metabolic acidosis with a normal anion gap. Animal studies have shown that high chloride content causes constriction of the afferent arterioles and reduced glomerular filtration rate through the tubulo-glomerular feedback mechanism [20]. A randomized controlled trial comparing the use of "unbalanced" vs. "balanced" solutions did not show worsening of renal function. However, patients who received a larger volume of 0.9% saline had a higher probability of developing acute kidney injury [21].

Moreover, high salt intake can lead to low urinary output, peripheral and organ edema, including pulmonary edema. Today, there is clear evidence that fluid overload is an independent and poor prognostic factor in the treatment of critically ill patients with sepsis. Hyperchloremic metabolic acidosis may adversely affect the immune system through the large production of pro-inflammatory cytokines and oversynthesis of nitric oxide (NO) [22]. It is considered that the use of "balanced" or "buffered" solutions has minimal effect on the immune system and acid-base balance. Furthermore, these solutions contain a low concentration of chloride ions. Examples of these solutions include Ringer's lactate and Plasma-Lyte (which contains acetate and gluconate). Ringer's lactate solution is slightly hypotonic compared to plasma due to partial ionization of solutes in balanced solutions [23]. Individual fluid effects are difficult to delineate because i.v. fluid mixtures are commonly utilized in clinical practice.

*Human albumin solutions – the only acceptable colloids for critically ill patients*

The main measure of treatment of hypovolemia in critically ill patients is i.v. administration of crystalloid or colloid solutions. In sepsis, increased vascular permeability leads to the leakage of serum albumin into the interstitial space. This process contributes to the onset of hypoalbuminemia and edema formation [24]. Extensive evidence indicates that administration of human albumin reduces net fluid balance compared to crystalloids, with a smaller volume of the administered solution required for hemodynamic stabilization. The effectiveness of albumin solution is better when the serum albumin level is lower. In clinical practice, serum albumin levels may indicate the timing and necessity of incorporating human albumin into fluid resuscitation. There are different albumin solutions in clinical use: hyper-oncotic (20% or 25%, for the treatment of hypoalbuminemia) and iso-oncotic (4% or 5%, for the treatment of hypovolemia). Human albumin is the sole colloid solution that leads to an expansion of intravascular volume and the elevation of plasma oncotic pressure [25].

Crystalloid and colloid solutions are often used together in the treatment of hypovolemia. The duration of effect of i.v. solutions on plasma volume expansion is essential for the sustained enhancement of tissue perfusion. The duration depends on the hydrostatic pressure value, the oncotic pressure value, and the permeability of the vascular wall [26]. Both insufficient and excessive fluid administration can be detrimental; hence, all i.v. solutions are classified as medications. Recent advancements have led to the development of "low-volume resuscitation techniques" and the use of colloid solutions for patients at risk of hypervolemia [27].

Colloid solutions (including synthetic HES, gelatin-based colloids, and dextran) are contraindicated due to safety concerns and insufficient efficacy. In 2022, the European Medicines Agency – EMA, resolved to revoke the marketing license for i.v. solutions containing HES [28]. Human albumin possesses an adequate safety profile, making it the sole recommended colloid solution for volume resuscitation. Balanced crystalloids are the first-line option, with albumin advised as a secure adjunct when crystalloids are inadequate [29].

*General adverse effects of fluids*

The essential question is then, where does the fluid go? The patient received a bolus of i.v. fluid, but it was completely ineffective because there was no rise in CO. In this scenario of fluid overload, systemic inflammatory responses can be exacerbated, indicated by increased leukocyte adhesion, capillary leakage, and interstitial edema formation, which, in turn, can worsen the overall tissue oxygenation. Sympathetic reaction is decreased, which is induced by low CO. In addition, flow-dependent vasodilatation is reduced due to arteriolar NO production [30].

Sepsis is a very heterogeneous syndrome, with various magnitudes and persistence of inflammatory responses, both pro-inflammatory and anti-inflammatory. The complex in-

terplay among fluids, the endothelium, the glycocalyx, and immune mediators represents a clinically relevant challenge for therapeutic approaches, because what might save one patient could harm another [31].

Components of the sepsis host response include the immune system, endothelial dysfunction, and coagulopathy. Endothelium should be viewed as an organ system for several reasons. It covers virtually all blood vessels (one cell thick); there are $10^{13}$ cells in total, and the weight is circa 1 kg. The endothelial surface is enormous, spanning around 4,000–7,000 m², with substantial heterogeneity and diverse biological functions, most notably immune recruitment and barrier function. In critical illness, the endothelial phenotype tends to be pro-coagulant. In general, pro-inflammatory cytokines activate endothelial cells, which impair anticoagulant mechanisms. On the other hand, activated monocytes overexpress tissue factor, which combines with tissue factor present on microparticles. The formation of microvascular thrombi is often detrimental [28]. Adhesion molecules play a critical role in mediating firm adhesion of leukocytes to endothelial cells, followed by diapedesis and extravasation. Therefore, there is a pro-adhesive endothelial phenotype in critical illness [32].

For critically ill septic patients, another problem is altered vasomotor tone with elevated levels of endothelial vasodilators (e.g., NO, prostacyclin) and depletion of endothelial vasoconstrictors (e.g., endothelin, thromboxane $A_2$). This is the basis of vasoplegic septic shock. Disassembly of endothelial cell junctions leads to interstitial edema through increased vascular permeability and capillary leak [33].

Loss of vascular integrity worsens the negative effects of crystalloids used for fluid resuscitation. The natural course of sepsis is very complex, with phases of hyperinflammation and immunosuppression often occurring simultaneously in different locations [34]. It is almost impossible to avoid the adverse effects of crystalloids, which are the first-line solution in intravascular volume replacement therapy.

Volume expansion is one of the most important measures in the treatment of severe acute pancreatitis. In this condition, there is premature activation of digestive enzymes in the pancreas itself and inflammation of peripancreatic fat tissue. In addition, the pancreas secretes a large amount of pro-inflammatory cytokines, resulting in overactive Ir and systemic inflammatory response syndrome. Significant intravascular fluid depletion results in a combination of hypovolemic and distributive circulatory shock, ultimately leading to multiple organ dysfunction syndrome. Although aggressive i.v. fluid therapy offers distinct advantages, excessive fluid administration in the context of severe acute pancreatitis can lead to the development of abdominal hypertension and abdominal compartment syndrome [35].

A syndrome of globally increased permeability can arise from the interplay between severe inflammation (leading to elevated capillary leak) and a positive fluid balance (resulting in tissue edema), ultimately contributing to the development of MOF. Consequently, it is essential to meticulously tailor fluid therapy, as 1 in 5 patients has inadequate i.v. fluid administration, according to the International Fluid Academy. Moreover, i.v. fluids are administered to about 80% of hospitalized patients. As much as 33% of i.v. fluids are classified as “creep fluids”. This term is used for the application of fluids for other purposes (dissolving medications, flushing the system, etc.), which can lead to additional fluid overload. Misuse of i.v. fluids contribute to acute kidney injury, abdominal hypertension, and unnecessary intensive care unit admissions. It is time to treat fluids like the drugs they are, with the same care, stewardship, and precision [36].

*The endothelial surface layer and glycocalyx in sepsis*

Microvascular dysfunction in infection includes vasodilation, increased procoagulant activity, elevated permeability, and enhanced interactions between circulating cells and endothelium. All these pathological processes can lead to disease progression [37]. New findings indicate that changes in microcirculation begin with damage to the endothelial glycocalyx (EG) [38], and that protecting this structure is important for preserving organ function [39]. The existing guidelines for the treatment of sepsis in adult patients do not specifically address glycocalyx damage [40]; however, several guidelines align with efforts to protect the glycocalyx [41].

The endothelial surface layer (ESL) consists of the EG, together with related chemical particles suspended in a plasma layer. Aggressive administration of “clear” fluids (crystalloids) was previously considered essential to stabilize macrohemodynamic parameters. Nonetheless, microcirculation may not inherently derive advantages from this therapy. Growing evidence suggests that large-volume fluid resuscitation may adversely affect the endothelium by altering, detaching, or discarding the ESL. This structure acts as a protective barrier over the endothelium, and the loss or reduction of the ESL can induce tissue edema and inflammation [42].

The extracellular glycocalyx is a protective, gel-like layer of carbohydrates, up to 3 μm thick, located on the luminal surface of the blood vessel, and serves as a crucial component of cellular signaling and transvascular permeability. It is composed of proteoglycans (proteins anchored to endothelial cell membranes), glycosaminoglycans, and the polysaccharide hyaluronan. High-molecular-weight polysaccharides bind a large amount of water and associate with adsorbed plasma proteins such as albumin and antithrombin [43].

The glycocalyx regulates blood flow, vascular tone, permeability, coagulability, and inflammation. Furthermore, it minimizes endothelial contact with leukocytes and platelets. Glycoproteins contain adhesion molecules such as integrins and selectins [44]. In addition, they are crucial for leukocyte trafficking during inflammation [45]; quite a few of their activities are triggered only after the shedding or thinning of the ESL. The integral part of the ESL consists of proteins, including albumin and anticoagulants, and these proteins are important for preserving the normal structure and permeability of the ESL [46]. EG significantly influences alterations in pressure and blood flow in blood vessels. Proteoglycans are crucial in responding to alterations in vascular wall shear stress or pressure [47]. The identification of these mechanical

stresses results in morphological alterations in endothelial cells and the release of NO [48]. Shear stress may induce a relocation of proteoglycans or an increase in their expression on the cell surface [49]. The shedding (loss of glycocalyx constituents) or disruption of the ESL is a crucial process following tissue injury to promote leukocyte and platelet adhesion [50]. The shedding of ESL is linked to intensified inflammation and augmented vascular permeability.

A compromised glycocalyx leads to capillary leak syndrome in infection and sepsis, characterized by abnormal fluid transfer from the blood vessels to the interstitial space, causing relative hypovolemia, tissue edema, and hypoperfusion. The development of capillary leak syndrome is associated with longer stay in the intensive care unit and prolonged use of vasoactive drugs [51].

The heterogeneity of capillary blood flow may continue in sepsis even when macrohemodynamic indicators, including blood pressure and CO, are normalized [52]. The release of EG components into blood vessels may have downstream implications. Shed components can act as damage-associated molecular patterns or "alarmins", which can further aggravate inflammation. Soluble heparan sulfate molecules are crucial in regulating inflammation, encompassing leukocyte activation, amplifying cytokine production, and promoting endothelial activation. The shedding of the ESL can be identified by many biomarkers, including syndecan-1, heparan sulfate, and hyaluronan. The revealed temporal variations in the release of these biomarkers in individuals with sepsis indicate that hyaluronan levels rise early in therapy, while syndecan-1 levels increase subsequently [53, 54].

*Specific effects of fluid therapy on endothelial glycocalyx*

In patients requiring volume expansion therapy, partial or total damage to ESL has likely occurred already due to the influence of inflammatory mediators [55]. Considering that modifications to the ESL may already be present in patients with sepsis, there is increasing evidence that the application of "clear" fluids may exacerbate ESL shedding. Numerous clinical trials have established a correlation between the volume of the given fluid and concentrations of EG biomarkers such as hyaluronan [53], syndecan [56], and heparan sulfate [57].

The bolus fluid treatment may directly influence the ESL through hemodilution and the synthesis of natriuretic peptides. Consequently, there has been considerable interest in the development of "glycoprotective" fluid approaches or secondary treatments during the resuscitation phase. Fluid administration is fundamental in the management of acute circulatory failure, with certain exceptions, including cardiogenic shock. This is typically accomplished by providing substantial amounts (exceeding 20 mL/kg) of crystalloid fluid i.v. at a quick rate or as a bolus. That intervention is particularly useful in cases of hypovolemic shock; yet certain types of shock exhibit vasodilation and changes in microcirculation. This encompasses shock states resulting from uncontrolled inflammation, including sepsis and severe trauma. In the above-mentioned shock scenarios, enhancements in macrohemodynamic parameters (CO) may not correlate linearly with changes in microcirculation. This is especially important in the treatment of septic shock, where early vasopressor administration and fluid bolus therapy are recommended simultaneously [58]. In light of the absence of enhancement in microcirculation, it has been proposed that fluid expansion may exacerbate vasodilation. This may lead to the failure of applied vasopressor therapy. A preliminary clinical trial was conducted to assess the feasibility of early restriction of crystalloid fluid therapy in sepsis, addressing concerns that bolus fluids may be detrimental in such cases [59]. The degradation of the glycocalyx in sepsis is significant due to thromboinflammation, and therapies for sepsis and septic shock may worsen endotheliopathy by further damaging the glycocalyx.

Glycocalyx damage, indicated by increased syndecan-1 levels, correlates with the fluid volume required for resuscitation [60]. Hypotensive resuscitation, alongside reduced fluid administration, correlates with a decreased mortality risk in trauma patients [61]. A recent comprehensive review and meta-analysis determined that reduced fluid amounts yield minimal to no variation in all-cause mortality when compared with standard therapy in adult patients with sepsis [62]. Likewise, the research corroborates that reduced i.v. fluid amounts yield minimal to no variation in severe adverse outcomes. While consensus has yet to be reached on the optimal volume, restricted i.v. fluid amounts demonstrate non-inferiority.This is particularly applicable to critically ill septic patients with sufficient hemodynamic monitoring of fluid responsiveness.

Another method to safeguard EG is by reducing the rate of fluid infusion. The rapid fluid-delivery therapeutic regimen aims to rapidly improve macrocirculatory parameters. Nonetheless, hemodynamic incoherence, characterized by a detachment between macrocirculatory variables such as blood pressure and CO and microcirculation, is a perilous complication of circulatory shock [63, 64]. Considering the evidence suggesting that rapid fluid administration (within 10 min) offers no advantage over slower fluid administration (within 20–60 min) [65, 66], larger clinical trials are warranted to investigate the impact of fluid rate on microcirculation and clinical outcomes. EG protection also involves selecting a "clear" fluid type. The use of albumin solution offers advantages for the ESL compared to the exclusive use of "clear" fluids. A recent prospective trial showed an advantage of using human albumin compared to normal saline in sepsis patients with sustained peripheral hypoperfusion [67]. The endothelial coating by EG and its accompanying constituents performs various activities in the body, both when intact and when denuded. The infusion of substantial volumes of fluid disrupts this barrier, potentially leading to tissue edema and inflammation. Evidence suggests that slower administration of fluids or limiting the volume of crystalloid fluids may be advantageous for sepsis patients [68].

ESL is the main element that affects the hydrostatic and oncotic pressure difference between the capillaries and the interstitial space [69]. Volume expansion therapy does not generate the volume distribution anticipated by Starling's origi-

nal concept. Adsorbed plasma proteins and the high-molecular-weight polysaccharides of the glycocalyx enhance its stability, while albumin is the main factor of osmotic pressure. The initial Starling principle asserts that intravascular volume comprises plasma and cellular components. The amended Starling equation further includes glycocalyx volume. The primary Starling forces are the transcapillary pressure gradient and the difference in the plasma-interstitial colloid osmotic pressure (COP). In the changed version, the difference is between the plasma and subglycocalyx COP, rather than between the plasma and interstitial COP. A modification of Starling that includes the glycocalyx model seems to more accurately elucidate the clinical responses observed [70].

Vasoplegia, resulting in a refractory shock state, is characterized by the extensive synthesis of NO and prostaglandin [71]. In addition to fluid administration, early administration of vasoactive drugs is the primary strategy to resolve this condition. Martin et al. [72] showed augmented glycocalyx damage associated with the use of catecholamines in an *in vitro* model. Exogenously applied glycocalyx components, such as hyaluronan, might theoretically repair the glycocalyx structure; however, there is currently no evidence from animal models or clinical studies to support the efficacy of this approach [73].

Sulodexide is a heparan sulfate analog that is impervious to heparanase breakdown. Researchers have documented the safeguarding benefits of sulodexide in a murine sepsis model [74] and in pediatric patients with septic shock. At present, the current guidelines for the treatment of sepsis lack a description of glycocalyx restoration [75, 76].

## Conclusion

The optimal amount and speed of fluid administration in critically ill sepsis patients is still a matter of debate. Balanced crystalloids are the first-line option, with human albumin recommended as a safe adjunct when the administration of crystalloid solutions is insufficient. Current studies indicate simultaneous early vasopressor administration and fluid bolus therapy.

## REFERENCES


1. *Djordjević D, Surbatović M, Ugrinović D, Radaković S, Jevdjić J, Filipović N,* et al. New aspects of sepsis pathophysiology in critically ill. Vojnosanit Pregl 2012; 69(1): 58–68. (Serbian) DOI: 10.2298/vsp1201058d.
2. *Cidade JP, Guerreiro G, Póvoa P.* A clinical guide to assess the immune response to sepsis: from bench to bedside. Crit Care Sci 2024; 36: e20240179en. DOI: 10.62675/2965-2774.20240179-en.
3. *Surbatovic M, Veljovic M, Jevdjic J, Popovic N, Djordjevic D, Radakovic S.* Immunoinflammatory response in critically ill patients: severe sepsis and/or trauma. Mediators Inflamm 2013; 2013: 362793. DOI: 10.1155/2013/362793.
4. *Udovicic I, Stanojevic I, Djordjevic D, Zeba S, Rondovic G, Abazovic T,* et al. Immunomonitoring of Monocyte and Neutrophil Function in Critically Ill Patients: From Sepsis and/or Trauma to COVID-19. J Clin Med 2021; 10(24): 5815. DOI: 10.3390/jcm10245815.
5. *Rondovic G, Djordjevic D, Udovicic I, Stanojevic I, Zeba S, Abazovic T,* et al. From Cytokine Storm to Cytokine Breeze: Did Lessons Learned from Immunopathogenesis Improve Immunomodulatory Treatment of Moderate-to-Severe COVID-19? Biomedicines 2022; 10(10): 2620. DOI: 10.3390/biomedicines10102620.
6. *Surbatovic M, Popovic N, Vojvodic D, Milosevic I, Acimovic G, Stojicic M,* et al. Cytokine profile in severe Gram-positive and Gram-negative abdominal sepsis. Sci Rep 2015; 5: 11355. DOI: 10.1038/srep11355.
7. *Djordjevic D, Rondovic G, Surbatovic M, Stanojevic I, Udovicic I, Andjelic T,* et al. Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Mean Platelet Volume-to-Platelet Count Ratio as Biomarkers in Critically Ill and Injured Patients: Which Ratio to Choose to Predict Outcome and Nature of Bacteremia? Mediators Inflamm 2018; 2018: 3758068. DOI: 10.1155/2018/3758068.
8. *Zeba S, Surbatovic M, Udovicic I, Stanojevic I, Vojvodic D, Rondovic G,* et al. Immune Cell-Based versus Albumin-Based Ratios as Outcome Predictors in Critically Ill COVID-19 Patients. J Inflamm Res 2025; 18: 73–90. DOI: 10.2147/JIR.S488972.
9. *Surbatovic M, Jevdjic J, Veljovic M, Popovic N, Djordjevic D, Radakovic S.* Immune response in severe infection: could life-saving drugs be potentially harmful? Scientific World Journal 2013; 2013: 961852. DOI: 10.1155/2013/961852.
10. *Arabi YM, Belley-Cote E, Carsetti A, De Backer D, Donadello K, Juffermans NP,* et al. European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids. Intensive Care Med 2024; 50(6): 813–31. DOI: 10.1007/s00134-024-07369-9.
11. *Persichini R, Lai C, Teboul JL, Adda I, Guérin L, Monnet X.* Venous return and mean systemic filling pressure: physiology and clinical applications. Crit Care 2022; 26(1): 150. DOI: 10.1186/s13054-022-04024-x.
12. *Hamzaoui O, Teboul JL.* Central venous pressure (CVP). Intensive Care Med 2022; 48(10): 1498–500. DOI: 10.1007/s00134-022-06835-6. Erratum in: Intensive Care Med 2022; 48(10): 1512. DOI: 10.1007/s00134-022-06874-z.
13. *Caplan M, Chew MS, Hamzaoui O.* Central venous pressure: current uses and prospects for an old parameter. Intensive Care Med 2025; 51(7): 1363–66. DOI: 10.1007/s00134-025-07975-1.
14. *Monnet X, Lai C, Teboul JL.* How I personalize fluid therapy in septic shock. Crit Care 2023; 27(1): 123. DOI: 10.1186/s13054-023-04363-3.
15. *Pantet O, Ageron FX, Zingg T.* Advances in resuscitation and deresuscitation. Curr Opin Crit Care 2025; 31(3): 277–84. DOI: 10.1097/MCC.0000000000001267.
16. *Messmer AS, Dill T, Müller M, Pfortmueller CA.* Active fluid deresuscitation in critically ill patients with septic shock: A systematic review and meta-analysis. Eur J Intern Med 2023; 109: 89–96. DOI: 10.1016/j.ejim.2023.01.009.
17. *Wakim KG.* "Normal" 0.9 per cent salt solution is neither "normal" nor physiological. JAMA 1970; 214(9): 1710. DOI: 10.1001/jama.214.9.1710b.
18. *Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR,* et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012; 255(5): 821–9. DOI: 10.1097/SLA.0b013e31825074f5.
19. *Yau YW, Kuan WS.* Choice of crystalloids in sepsis: a conundrum waiting to be solved. Ann Transl Med 2016; 4(6): 121. DOI: 10.21037/atm.2016.02.09.
20. *Blumberg N, Cholette JM, Pietropaoli A, Phippis R, Spinelli SL, Eaton MP,* et al. 0.9% NaCl (Normal Saline) - perhaps not

so normal after all? Transfus Apher Sci 2018; 57(1): 127–31. DOI: 10.1016/j.transci.2018.02.021.
21. *Chowdhury AH, Cox EF, Francis ST, Lobo DN.* A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256(1): 18–24. DOI: 10.1097/SLA.0b013e318256be72. Erratum in: Ann Surg 2013; 258(6): 1118.
22. *Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED,* et al. Balanced crystalloids versus saline in the intensive care unit. The SALT randomized trial. Am J Respir Crit Care Med 2017; 195(10): 1362–72. DOI: 10.1164/rccm.201607-1345OC.
23. *Guidet B, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D,* et al. A balanced view of balanced solutions. Crit Care 2010; 14(5): 325. DOI: 10.1186/cc9230.
24. *Joannidis M, Wiedermann CJ, Ostermann M.* On myths about albumin and misconceptions that cause confusion: authors' reply to "What's wrong with the ten myths about albumin: three layers for an indisputable dispute". Intensive Care Med 2022; 48(9): 1255–7. DOI: 10.1007/s00134-022-06791-1.
25. *Wiedermann CJ.* Moderator Effect of Hypoalbuminemia in Volume Resuscitation and Plasma Expansion with Intravenous Albumin Solution. Int J Mol Sci 2022; 23(22): 14175. DOI: 10.3390/ijms232214175.
26. *Woodcock TE, Woodcock TM.* Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012; 108(3): 384–94. DOI: 10.1093/bja/aer515.
27. *Mårtensson J, Bihari S, Bannard-Smith J, Glassford NJ, Lloyd-Donald P, Cioccari L,* et al. Small volume resuscitation with 20% albumin in intensive care: physiological effects: The SWIPE randomised clinical trial. Intensive Care Med 2018; 44(11): 1797–806. DOI: 10.1007/s00134-018-5253-2.
28. *Song B, FU K, Zheng X, Liu C.* Fluid resuscitation in adults with severe infection and sepsis: a systematic review and network meta-analysis. Front Med 2025; 12: 1543586. DOI: 10.3389/fmed.2025.1543586.
29. *Wiedermann CJ.* Phases of fluid management and the roles of human albumin solution in perioperative and critically ill patients. Curr Med Res Opin 2020; 36(12): 1961–73. DOI: 10.1080/03007995.2020.1840970.
30. *Miranda M, Balarini M, Caixeta D, Bouskela E.* Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring and potential therapies. Am J Physiol Heart Circ Physiol 2016; 311(1): H24–35. DOI: 10.1152/ajpheart.00034.2016.
31. *Angus DC, van der Poll T.* Severe sepsis and septic shock. N Engl J Med 2013; 369(9): 840–51. DOI: 10.1056/NEJMra1208623. Erratum in: N Engl J Med 2013; 369(21): 2069.
32. *Hunt BJ.* Bleeding and coagulopathies in critical care. N Engl J Med 2014; 370(9): 847–59. DOI: 10.1056/NEJMra1208626.
33. *Dolmatova EV, Wang K, Mandavilli R, Griendling KK.* The effects of sepsis on endothelium and clinical implications. Cardiovasc Res 2021; 117(1): 60-73. DOI: 10.1093/cvr/cvaa070.
34. *Payen D, Velho TR, Moita LF.* Beyond inflammation: the role of metabolic dysregulation in sepsis diagnosis and treatment. Intensive Care Med 2025; 51(7): 1359–62. DOI: 10.1007/s00134-025-07948-4.
35. *Crosignani A, Spina S, Marrazzo F, Cimbanassi S, Malbrain MLNG, Van Regenmortel N,* et al. Intravenous fluid therapy in patients with severe acute pancreatitis admitted to the intensive care unit: a narrative review. Ann Intensive Care 2022; 12(1): 98. DOI: 10.1186/s13613-022-01072-y. Erratum in: Ann Intensive Care 2023; 13(1): 51. DOI: 10.1186/s13613-023-01149-2.
36. *Waskowski J, Salvato SM, Müller M, Hofer D, van Regenmortel N, Pfortmueller CA.* Choice of creep or maintenance fluid type and their impact on total daily ICU sodium burden in critically ill patients: A systematic review and meta-analysis. J Crit Care 2023; 78: 154403. DOI: 10.1016/j.jcrc.2023.154403.
37. *Helms J, Iba T, Connors JM, Gando S, Levi M, Meziani F,* et al. How to manage coagulopathies in critically ill patients. Intensive Care Med 2023; 49(3): 273–90. DOI: 10.1007/s00134-023-06980-6.
38. *Patterson EK, Cepinskas G, Fraser DD.* Endothelial glycocalyx degradation in critical illness and injury. Front Med 2022; 9: 898592. DOI: 10.3389/fmed.2022.898592.
39. *Drost CC, Rovas A, Kümpers P.* Protection and rebuilding of the endothelial glycocalyx in sepsis-science or fiction? Matrix Biol Plus 2021; 12: 100091. DOI: 10.1016/j.mbplus.2021.100091.
40. *Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C,* et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021; 47(11): 1181–247. DOI: 10.1007/s00134-021-06506-y.
41. *Levy JH, Iba T.* Endothelial Glycocalyx Protection in Sepsis. Juntendo Iji Zasshi 2024; 70(1): 23–5. DOI: 10.14789/jmj.JMJ23-0041-P.
42. *Smart L, Hughes D.* The Effects of Resuscitative Fluid Therapy on the Endothelial Surface Layer. Front Vet Sci 2021; 8: 661660. DOI: 10.3389/fvets.2021.661660.
43. *Iba T, Levy JH.* Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost 2019; 17(2): 283–94. DOI: 10.1111/jth.14371.
44. *Kolářová H, Ambrůzová B, Svihálková Šindlerová L, Klinke A, Kubala L.* Modulation of endothelial glycocalyx structure under inflammatory conditions. Mediators Inflamm 2014; 2014: 694312. DOI: 10.1155/2014/694312.
45. *Paulus P, Jennewein C, Zacharowski K.* Biomarkers of endothelial dysfunction: can they help us deciphering systemic inflammation and sepsis? Biomarker 2011; 16 Suppl 1: S11–21. DOI: 10.3109/1354750X.2011.587893.
46. *Bashandy GM.* Implications of recent accumulating knowledge about endothelial glycocalyx on anesthetic management. J Anesth 2015; 29(2): 269–78. DOI: 10.1007/s00540-014-1887-6.
47. *Cruz-Chu ER, Malafeev A, Pajarskas T, Pivkin IV, Koumoutsakos P.* Structure and response to flow of the glycocalyx layer. Biophys J 2014; 106(1): 232–43. DOI: 10.1016/j.bpj.2013.09.060.
48. *McDonald KK, Cooper S, Danielzak L, Leask RL.* Glycocalyx degradation induces a proinflammatory phenotype and increased leukocyte adhesion in cultured endothelial cells under flow. PLoS One 2016; 11(12): e0167576. DOI: 10.1371/journal.pone.0167576.
49. *Liu JX, Yan ZP, Zhang YY, Wu J, Liu XH, Zeng Y.* Hemodynamic shear stress regulates the transcriptional expression of heparan sulfate proteoglycans in human umbilical vein endothelial cell. Cell Mol Biol (Noisy-le-grand) 2016; 62(8): 28–34. DOI: 10.14715/cmb/ 2016.62.8.5.
50. *Lipowsky HH.* The endothelial glycocalyx as a barrier to leukocyte adhesion and its mediation by extracellular proteases. Ann Biomed Eng 2012; 40(4): 840–8. DOI: 10.1007/s10439-011-0427-x.
51. *Saravi B, Goebel U, Hassenzahl LO, Jung C, David S, Feldheiser A,* et al. Capillary leak and endothelial permeability in critically ill patients: a current overview. Intensive Care Med Exp 2023; 11(1): 96. DOI: 10.1186/s40635-023-00582-8.
52. *Pouska J, Tegl V, Astapenko D, Cerny V, Lehmann C, Benes J.* Impact of intravenous fluid challenge infusion time on macrocirculation and endothelial glycocalyx in surgical and critically ill patients. Biomed Res Int 2018; 2018: 8925345. DOI: 10.1155/2018/8925345.

53. *Smart L, Macdonald SPJ, Burrows S, Bosio E, Arendts G, Fatovich DM.* Endothelial glcyocalyx biomarkers increase in patients with infection during Emergency Department treatment. J Crit Care 2017; 42: 304–9. DOI: 10.1016/j.jcrc.2017.07.001.
54. *Smart L, Bosio E, Macdonald SPJ, Dull R, Fatovich DM, Neil C,* et al. Glycocalyx biomarker syndecan-1 is a stronger predictor of respiratory failure in patients with sepsis due to pneumonia, compared to endocan. J Crit Care 2018; 47: 93–8. DOI: 10.1016/j.jcrc.2018.06.015.
55. *Naumann DN, Hazeldine J, Davies DJ, Bishop J, Midwinter MJ, Belli A,* et al. Endotheliopathy of trauma is an on-scene phenomenon, and is associated with multiple organ dysfunction syndrome: a prospective observational study. Shock 2018; 49(4): 420–8. DOI: 10.1097/SHK.0000000000000999.
56. *Tapking C, Hernekamp JF, Horter J, Kneser U, Haug V, Vogelpohl J,* et al. Influence of burn severity on endothelial glycocalyx shedding following thermal trauma: A prospective observational study. Burns 2021; 47(3): 621–7. DOI: 10.1016/j.burns.2020.07.021.
57. *Hippensteel JA, Uchimido R, Tyler PD, Burke RC, Han X, Zhang F,* et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care 2019; 23(1): 259. DOI: 10.1186/s13054-019-2534-2.
58. *Marik PE, Byrne L, van Haren F.* Fluid resuscitation in sepsis: the great 30 mL per kg hoax. J Thor Dis 2020; 12(Suppl 1): S37–47. DOI: 10.21037/jtd.2019.12.84.
59. *Macdonald SPJ, Keijzers G, Taylor DM, Kinnear F, Arendts G, Fatovich DM,* et al. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive Care Med 2018; 44(12): 2070–8. DOI: 10.1007/s00134-018-5433-0.
60. *Saoraya J, Wongsamita L, Srisawat N, Musikatavorn K.* Plasma syndecan-1 is associated with fluid requirements and clinical outcomes in emergency department patients with sepsis. Am J Emerg Med 2021; 42: 83–9. DOI: 10.1016/j.ajem.2021.01.019.
61. *Safiejko K, Smereka J, Filipiak KJ, Szarpak A, Dabrowski M, Ladny JR,* et al. Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock: A systematic review and meta-analysis of randomized controlled trials. Cardiol J 2022; 29(3): 463–71. DOI: 10.5603/CJ.a2020.0096.
62. *Sivapalan P, Ellekjaer KL, Jessen MK, Meyhoff TS, Cronhjort M, Hjortrup PB,* et al. Lower vs higher fluid volumes in adult patients with sepsis: an updated systematic review with meta-analysis and trial sequential analysis. Chest 2023; 164(4): 892–912. DOI: 10.1016/j.chest.2023.04.036.
63. *Dilken O, Ergin B, Ince C.* Assessment of sublingual microcirculation in critically ill patients: consensus and debate. Ann Transl Med 2020; 8(12): 793. DOI: 10.21037/atm.2020.03.222.
64. *Huang L, Huang Q, Ma W, Yang H.* Understanding hemodynamic incoherence: mechanisms, phenotypes, and implications for treatment. Shock 2025; 63(3): 342–50. DOI: 10.1097/SHK.0000000000002507.
65. *Ho L, Lau L, Churilov L, Riedel B, McNicol L, Hahn RG,* et al. Comparative evaluation of crystalloid resuscitation rate in a human model of compensated haemorrhagic shock. Shock 2016; 46(2): 149–57. DOI: 10.1097/SHK.0000000000000610.
66. *Iro MA, Sell T, Brown N, Maitland K.* Rapid intravenous rehydration of children with acute gastroenteritis and dehydration: a systematic review and meta-analysis. BMC Pediatr 2018; 18(1): 44. DOI: 10.1186/s12887-018-1006-1.
67. *Gabarre P, Desnos C, Morin A, Missri L, Urbina T, Bonny V,* et al. Albumin versus saline infusion for sepsis-related peripheral tissue hypoperfusion: a proof-of-concept prospective study. Crit Care 2024; 28(1): 43. DOI: 10.1186/s13054-024-04827-0.
68. *Taniguchi TM, Taniguchi LU.* Fluid management in sepsis: 5 reasons why less fluid might be more rational. Crit Care Sci 2024; 36: e20240111en. DOI: 10.62675/2965-2774.20240111-en.
69. *Pillinger NL, Kam P.* Endothelial glycocalyx: basic science and clinical implications. Anaesth Intensive Care 2017; 45(3): 295–307. DOI: 10.1177/0310057X1704500305.
70. *Dargent A, Dumargne H, Labruyère M, Brezllion S, Brassart-Pasco S, Blot M,* et al. Role of the interstitium during septic shock: a key to the understanding of fluid dynamics? J Intensive Care 2023; 11(1): 44. DOI: 10.1186/s40560-023-00694-z.
71. *Knuefermann P, Boehm O, Baumgarten G, Zacharowski K.* Sepsis-induced vasoplegia–is vasopressin V1A-receptor a new target? Crit Care Med 2008; 36(8): 2468–9. DOI: 10.1097/CCM.0b013e31818104b7.
72. *Martin JV, Liberati DM, Diebel LN.* Disparate effects of catecholamines under stress conditions on endothelial glycocalyx injury: an in vitro model. Am J Surg. 2017; 214(6):1166–72. DOI: 10.1016/j.amjsurg.2017.09.018.
73. *Song JW, Zullo JA, Liveris D, Dragovich M, Zhang XF, Goligorsky MS.* Therapeutic restoration of endothelial glycocalyx in sepsis. J Pharmacol Exp Ther 2017; 361(1): 115–21. DOI: 10.1124/jpet.116.239509.
74. *Ying J, Zhang C, Wang Y, Liu T, Yu Z, Wang K,* et al. Sulodexide improves vascular permeability via glycocalyx remodelling in endothelial cells during sepsis. Front Immunol 2023; 14: 1172892. DOI: 10.3389/fimmu.2023.1172892.
75. *Schulman S, Sholzberg M, Spyropoulos AC, Zarychanski R, Resnick HE, Bradbury CA,* et al. International society on thrombosis and haemostasis ISTH guidelines for antithrombotic treatment in COVID-19. J Thromb Haemost 2022; 20(10): 2214–25. DOI: 10.1111/jth.15808.
76. *Iba T, Maier CL, Helms J, Ferrer R, Thachil J, Levy JH.* Managing sepsis and septic shock in an endothelial glycocalyx-friendly way: from the viewpoint of surviving sepsis campaign guidelines. Ann Intensive Care 2024; 14(1): 64. DOI: 10.1186/s13613-024-01301-6.-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012; 256(1): 18–24.


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