



ORIGINAL ARTICLE

Extracorporeal Blood Purification Techniques in Sepsis and ARDS: Evaluation of ECCO₂R and CytoSorb® Hemoadsorption – A Narrative Review

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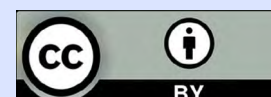
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ABSTRAKT

Background: Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection. It is associated with an imbalance between pro-inflammatory and anti-inflammatory pathways, leading to multiple organ injury, including acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS). Despite advances in critical care medicine, sepsis remains one of the leading causes of mortality in intensive care units (ICUs). Increasing interest has focused on extracorporeal blood purification techniques aimed at modulating cytokine levels and facilitating carbon dioxide removal.

Aim: The aim of this study was to provide an overview and critical evaluation of two extracorporeal blood purification modalities—extracorporeal carbon dioxide removal (ECCO₂R) and CytoSorb therapy.

Materials and Methods: A narrative literature review was conducted using the PubMed database. Publications available up to April 2026 were identified using keywords related to CytoSorb, hemoadsorption, ECCO₂R, sepsis, ARDS, and critical care. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, and observational studies. The retrieved evidence was synthesized narratively.

Results: Both ECCO₂R, which facilitates carbon dioxide clearance, and CytoSorb hemoadsorption therapy, which removes circulating cytokines and inflammatory mediators, demonstrate high efficacy. However, current clinical trials have not shown significant improvements in mortality. This discrepancy may be related to patient heterogeneity and the lack of phenotype-based selection. ECCO₂R may be beneficial in ARDS phenotypes characterized by predominant hypercapnia, whereas CytoSorb therapy may be most effective in patients with the hyperinflammatory delta sepsis phenotype.

KEYWORDS

Extracorporeal carbon dioxide removal (ECCO₂R),
CytoSorb, Hemoadsorption, Sepsis, Septic

1. Introduction

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection. Septic shock represents its most severe manifestation and is characterized by profound circulatory and metabolic abnormalities, leading to tissue hypoperfusion and substantially increased mortality. Despite considerable advances in critical care medicine, sepsis and septic shock remain among the leading causes of death in intensive care units worldwide. Since the introduction of the first international consensus definition of sepsis in 1991, the reported incidence of the syndrome has steadily increased (Srzić, 2022). Current estimates indicate that sepsis affects approximately 49 million individuals annually and is responsible for nearly 13 million deaths worldwide (Prescott et al., 2026). Despite extensive research efforts and successive updates of the Surviving Sepsis Campaign guidelines, clinical outcomes remain unsatisfactory. In response to the complex and multifactorial nature of sepsis-associated organ dysfunction, increasing attention has been directed toward Multi-Organ Support Therapy (MOST). This concept is based on the integrated application of extracorporeal support techniques aimed at the simultaneous or sequential support of multiple failing organ systems in critically ill patients (Ronco et al., 2019).

The pathophysiology of sepsis provides the rationale for the use of extracorporeal blood purification techniques. Under physiological conditions, the host response to infection is regulated by a dynamic balance between pro-inflammatory mediators, such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), and anti-inflammatory pathways, primarily mediated by interleukin-10 (IL-10) and transforming growth factor- β (TGF- β). The progression from a localized inflammatory response to systemic inflammation is accompanied by the release of cytokines and acute-phase proteins, which contribute to the development of organ dysfunction and septic shock (Suchomska et al., 2019). In sepsis and septic shock, this delicate equilibrium becomes dysregulated, resulting in an uncontrolled and maladaptive immune response. This immune dysregulation plays a central role in the development of organ dysfunction, both at the site of infection and in distant organs. The clinical course of sepsis remains highly unpredictable, as severe organ dysfunction may develop even in young patients without significant comorbidities, emphasizing the importance of early recognition and treatment (Brzozowska et al., 2024). Excessive activation of inflammatory pathways contributes to tissue injury and may lead to acute kidney injury (AKI), acute

liver injury, and acute lung injury manifesting as acute respiratory distress syndrome (ARDS). As the severity of organ dysfunction progresses, the host's compensatory mechanisms become overwhelmed, ultimately resulting in multiple organ failure (Daniel et al., 2022).

Continuous renal replacement therapy (CRRT) represents a cornerstone of extracorporeal organ support in the management of critically ill patients with sepsis. By facilitating the removal of excess fluid, uremic toxins, and metabolic waste products, CRRT enables effective control of fluid balance and metabolic homeostasis. The correction of fluid overload contributes to improved tissue perfusion, reduction of interstitial edema, and subsequent enhancement of pulmonary and cardiovascular function (Xu, 2023). Given its well-established role as a standard therapeutic modality in intensive care medicine, a detailed discussion of CRRT is beyond the scope of the present review. Nevertheless, CRRT frequently serves as a platform for the integration of other extracorporeal blood purification techniques, including extracorporeal carbon dioxide removal (ECCO₂R) and CytoSorb hemoadsorption therapy, which are discussed in the following sections.

2. Methodology

A narrative review of the literature regarding the use of CytoSorb hemoadsorption and extracorporeal carbon dioxide removal (ECCO₂R) in critically ill patients was conducted. A systematic search of the PubMed database was performed to identify relevant studies published in English. Priority was given to recent publications, randomized controlled trials, prospective observational studies, systematic reviews, and meta-analyses. Additional landmark studies were included when considered essential for understanding the physiological rationale, technical aspects, and clinical applications of both therapies. The retrieved literature was critically analyzed with particular emphasis on treatment efficacy, safety, patient selection, and current areas of controversy.

3. Extracorporeal carbon dioxide removal system (ECCO₂R)

The pathophysiology of ARDS and hypercapnia in sepsis

During sepsis, there is a marked activation of the immune response, accompanied by a substantial release

of pro-inflammatory cytokines. One of the key mechanisms amplifying this response is activation of the NLRP3 inflammasome. This process contributes to increased permeability of the alveolar-capillary barrier, resulting in interstitial and alveolar edema, as well as disturbances in the ventilation-perfusion ratio (Slobod et al., 2022). Consequently, surfactant depletion and an increase in physiological dead space occur (Ferluşa et al., 2018), creating a pathophysiological substrate for the development of sepsis-induced acute respiratory distress syndrome (ARDS) (Thompson et al., 2017). In parallel, sepsis is associated with increased tissue metabolic demand, leading to elevated carbon dioxide (CO₂) production, while effective alveolar ventilation is reduced. In the early stages of sepsis, hypercapnia is uncommon due to compensatory hyperventilation. CO₂ retention typically develops in advanced respiratory failure, particularly in the context of lung-protective ventilation strategies. It should also be emphasized that, although ARDS may be triggered by a variety of etiologies, sepsis remains the most common underlying cause. This applies both to pulmonary sepsis, most commonly secondary to pneumonia, and to extrapulmonary sources of infection (Bos & Ware, 2022).

Protective ventilation and the problem of permissive hypercapnia

In acute respiratory distress syndrome (ARDS), mechanical ventilation is typically guided by a lung-protective strategy based on low tidal volumes, limitation of plateau pressure, and reduction of driving pressure (Malhotra, 2007). This approach reduces the risk of ventilator-induced lung injury (VILI) (Slutsky & Ranieri, 2013). However, a consequence of this strategy is the development of permissive hypercapnia. Hypercapnia exerts systemic effects across multiple organ systems. It may indirectly reduce myocardial contractility and increase pulmonary vascular resistance (PVR), thereby contributing to hemodynamic instability and increasing right ventricular afterload. In addition, it has been hypothesized to adversely affect the microcirculation by inducing heterogeneous systemic vasodilation, which may result in impaired and uneven tissue perfusion (De Backer et al., 2011). In the central nervous system, hypercapnia increases cerebral blood flow and may elevate intracranial pressure (ICP), potentially exacerbating disturbances in consciousness (Duffin et al., 2021). Although permissive hypercapnia is often accepted as a necessary trade-off to minimize VILI in patients with sepsis and ARDS, its clinical tolerance is limited by

the aforementioned systemic and organ-specific effects.

The design and operating principle of the ECCO₂R system

The extracorporeal carbon dioxide removal (ECCO₂R) system is an extracorporeal technique that enables the selective elimination of carbon dioxide from venous or arteriovenous blood without the need to increase minute ventilation (Karagiannidis et al., 2019), which has prompted growing interest in its potential application in sepsis-induced acute respiratory distress syndrome (ARDS). ECCO₂R systems may function as standalone veno-venous (VV) extracorporeal circuits, however, in clinical practice they are most frequently integrated with continuous renal replacement therapy (CRRT). The fundamental principles of operation are similar across configurations. Via vascular access, most commonly through a central venous catheter, venous blood is drawn through a 13–18 Fr cannula and propelled by a pump through a membrane oxygenator composed of hollow fibers made of polypropylene or polymethylpentene (PMP). On the opposite side of the semipermeable membrane, a sweep gas system functions as the driving force for carbon dioxide removal. This gas—typically air or oxygen—flows through the circuit at rates of approximately 2–10 L/min (Romy & Ferrer, 2016), although newer-generation systems allow for a substantially broader range of flow rates, extending up to 30 L/min.

Carbon dioxide removal mechanisms

Only the fraction of carbon dioxide dissolved in plasma (approximately 5–10% of total blood CO₂ content) is capable of diffusing across the semipermeable membrane. However, continuous removal of CO₂ shifts the bicarbonate equilibrium to the left. Through the catalytic action of carbonic anhydrase, this process drives the ongoing conversion of bicarbonate (HCO₃[−]) into CO₂, thereby enabling the extracorporeal system to remove clinically relevant amounts of carbon dioxide from the blood (Lundskog, 1997). Typical blood flow rates through ECCO₂R circuits range from 300 mL/min to approximately 700–1000 mL/min. The system remains effective at relatively low flow rates due to the rapid enzymatic conversion of bicarbonate and the approximately 20-fold higher diffusivity of CO₂ compared with O₂. In addition, lower blood flow rates increase the residence time of blood within the membrane lung, thereby enhancing

CO₂ extraction efficiency per unit volume of blood. At blood flow rates exceeding approximately 1000 mL/min, CO₂ removal efficiency reaches a plateau. This phenomenon is attributable, first, to the finite catalytic capacity of carbonic anhydrase in regenerating dissolved CO₂; and, second, to the maximal gas transfer capacity of the membrane lung (Tiruvoipati et al., 2023).

Clinical efficacy of ECCO₂R

Despite a well-characterized biological rationale and the potential physiological benefits of carbon dioxide removal, available clinical trial data have not confirmed a corresponding improvement in clinically meaningful outcomes. Most recent studies indicate that ECCO₂R therapy effectively reduces arterial carbon dioxide tension (PaCO₂), as well as ventilator parameters such as driving pressure (Worku et al., 2023), tidal volume, and plateau pressure (Stommel et al., 2024). However, meta-analyses have not demonstrated a reduction in 90-day mortality (Derdak, 2022). Moreover, some analyses suggest an increased incidence of hemorrhagic complications in patients undergoing extracorporeal carbon dioxide removal (Miller et al., 2022).

Limitations of treatment and safety considerations

Several explanations have been proposed for the lack of a convincing impact of ECCO₂R on mortality and other hard clinical endpoints. First, acute respiratory distress syndrome (ARDS) is not a purely „CO₂-driven” condition, but rather a heterogeneous inflammatory-mechanical syndrome characterized by predominant parenchymal injury. While correction of hypercapnia enables the application of ultra-protective ventilation strategies, it does not directly address systemic inflammation, pulmonary microcirculatory dysfunction, or endothelial injury. Second, patient populations enrolled in clinical trials are highly heterogeneous, as ARDS may result from a wide range of underlying etiologies beyond sepsis. ECCO₂R appears to be most beneficial in patients in whom hypercapnia is primarily attributable to ventilation limitation imposed by lung-protective strategies. In contrast, in most study populations, CO₂ retention represents a secondary phenomenon related to severe parenchymal lung injury rather than a primary pathophysiological driver. Third, although ECCO₂R may facilitate reductions in tidal volume and, consequently, respiratory rate, overall ventilatory mechanical power often remains elevated

due to the need for high positive end-expiratory pressure (PEEP) and the presence of the „baby lung” phenomenon. These factors are key determinants of ventilator-induced lung injury (VILI). Finally, therapy-related complications must be considered. The most frequently reported adverse events are bleeding complications, including both cannulation-site bleeding and intracranial hemorrhage, largely related to the requirement for continuous systemic anticoagulation with heparin. Thrombotic complications represent the second major category of adverse events. Both peripheral thrombosis and intracircuit thrombus formation within the oxygenator have been reported. This issue appears to be particularly pronounced in systems operating at blood flow rates below 500 mL/min (Yu et al., 2022). Taken together, the available evidence suggests that, although ECCO₂R may facilitate optimization of ventilatory strategies in selected patients, its effect on clinically meaningful outcomes remains unproven. These limitations have led to increasing interest in adjunctive extracorporeal therapies targeting alternative pathophysiological mechanisms involved in critical illness, particularly systemic inflammation.

4. CytoSorb hemoadsorption system

The pathophysiology of the inflammatory response in sepsis

In sepsis, there is a profound dysregulation of the host immune response, characterized by excessive production of pro-inflammatory cytokines. One of the earliest mediators released is tumor necrosis factor alpha (TNF-α), which induces endothelial activation, upregulation of adhesion molecules, vasodilation, and increased vascular permeability. Clinically, these processes manifest as septic hypotension, capillary leakage, microcirculatory dysfunction, and disseminated intravascular coagulation (DIC) (Hotchkiss et al., 2016). Interleukin-1β (IL-1β) acts synergistically with TNF-α, contributing to fever induction, neutrophil activation, and amplification of the acute-phase response (Lopez-Castejon & Brough, 2011). Interleukin-6 (IL-6) is currently regarded as one of the most important prognostic cytokines in sepsis. Alterations in cytokine homeostasis have been demonstrated in patients with abdominal sepsis, where persistent disturbances in IL-6 and IL-4 concentrations reflected ongoing immune dysregulation and systemic inflammatory activation

(Polyvyonyy et al., 2021). Elevated IL-6 levels correlate with the severity of septic shock, mortality, and progression to multiple organ failure through effects on hepatocyte activation, endothelial dysfunction, and coagulation pathway activation. Moreover, increased IL-6 concentrations are associated with myocardial depression and the severity of vasoplegia in sepsis (Tanaka et al., 2014). High-mobility group box 1 (HMGB1) represents a late-phase mediator of sepsis. Released secondarily from damaged cells, it functions as a damage-associated molecular pattern (DAMP), sustaining macrophage activation, stimulating Toll-like receptor signaling, and perpetuating chronic inflammation. Elevated HMGB1 levels have been associated with late multiple organ failure, septic encephalopathy, and disruption of the intestinal barrier (Andersson & Tracey, 2003). These complex immunological mechanisms provide the rationale for therapeutic strategies aimed at modulating the circulating inflammatory response, including extracorporeal blood purification techniques such as CytoSorb.

The CytoSorb System – mechanism of action and technical specifications

Understanding the mechanisms of action and the biological role of cytokines is fundamental to the rationale for CytoSorb therapy in sepsis. CytoSorb is a hemoadsorption system designed for the non-selective removal of inflammatory mediators, particularly cytokines, from the patient's circulation (Kenda et al., 2026). From a technical perspective, the CytoSorb cartridge consists of biocompatible polystyrene-divinylbenzene copolymer beads coated with polyvinylpyrrolidone (PVP). The bead diameter ranges from 300 to 800 μm . This highly porous structure provides an adsorption surface area of approximately 40,000 m^2 per single 300 mL cartridge (Spatola et al., 2025). The system operates on the principle of size-dependent adsorption based on molecular weight. The highest adsorption efficiency is observed for molecules within the 5–60 kDa range, which includes most pro-inflammatory and anti-inflammatory cytokines, chemokines, complement fragments, and damage-associated molecular patterns (DAMPs). In contrast, albumin (~66 kDa) and immunoglobulins (>150 kDa) are generally not removed due to their larger molecular size. CytoSorb can be used as a standalone extracorporeal circuit; however, it is most commonly integrated with continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO). It is also employed in cardiac surgery during cardiopulmonary bypass procedures.

When combined with CRRT or ECMO, the adsorber is incorporated directly into the extracorporeal circuit, eliminating the need for additional vascular access. According to manufacturer specifications, optimal performance is achieved at blood flow rates of 100–700 mL/min. In most CRRT configurations, this does not require modification of standard flow settings, whereas in ECMO systems the adsorber is typically placed in parallel or in series to ensure adequate perfusion of the cartridge without compromising circuit stability. The described physicochemical properties of the system translate into measurable cytokine adsorption, which has been investigated in both experimental and clinical studies.

Biological efficacy, clinical outcomes, and limitations of the therapy

In vitro studies using human plasma stimulated with lipopolysaccharide (LPS) have demonstrated a high cytokine removal capacity of the adsorber, reaching up to 99.6% for interleukin-6 (IL-6) (Harm et al., 2015). In vivo, reductions in cytokine concentrations are less pronounced but remain statistically significant, with decreases of 58% for tumor necrosis factor- α (TNF- α), 71% for IL-6, and 48% for IL-8 (Jansen et al., 2023). Despite these biological effects, clinical data have not demonstrated a clear association between reductions in IL-6 levels and primary clinical endpoints, particularly overall mortality. A large systematic review published in 2023, which included patients with sepsis and septic shock, COVID-19 infection, and cardiac surgery populations, reported no reduction in overall mortality associated with CytoSorb therapy (RR 1.07; 95% CI 0.88–1.31). In addition, no significant effects were observed on long-term IL-6 concentrations, ICU length of stay, or lactate levels, while in the post-cardiac arrest subgroup, worse clinical outcomes were reported. More recent evidence from studies focusing exclusively on patients with sepsis and septic shock remains conflicting. A meta-analysis by Orban et al. demonstrated no effect on overall mortality, with a potential benefit observed only in patients receiving concomitant continuous renal replacement therapy (CRRT) (Orban et al., 2025). Notably, the analysis also suggested that earlier initiation of hemoadsorption may be associated with increased mortality. In contrast, a systematic review by Steindl et al. reported a reduction in both in-hospital mortality (OR 0.64) and 28-30-day mortality (OR 0.49), as well as improved hemodynamic stability reflected by reduced vasopressor requirements (Steindl et al., 2025). The discrepancy between pronounced biological effects

and inconclusive clinical outcomes has been largely attributed to methodological limitations and patient heterogeneity across studies.

Immunological consequences of non-selective adsorption

A key methodological limitation affecting the interpretation of studies on CytoSorb, and potentially explaining the discrepancies between meta-analyses, is the substantial heterogeneity of available evidence. In particular, differences in study design appear to play a crucial role. Steindl et al. included retrospective, often single-center studies, whereas Orban et al. focused exclusively on prospective and controlled trials. Notably, smaller single-center studies tend to report stronger beneficial effects of therapy; however, when these studies are excluded, the overall positive effect is no longer observed. This does not imply that the concept of extracorporeal removal of pro-inflammatory cytokines should be abandoned. Rather, it has led to a reassessment of the notion that hemoadsorption represents a universal therapy for all patients with septic shock. Increasing attention is now being directed toward the concept of precision extracorporeal immunomodulation, in which therapy is tailored to the right patient, administered at the right time, and delivered with appropriate intensity. Current research has focused primarily on patients with a hyperinflammatory phenotype, characterized by markedly elevated IL-6 levels, refractory vasoplegia, and hyperlactatemia; however, evidence in this subgroup remains limited (Lotz et al., 2026).

This perspective is aligned with a broader conceptual shift in sepsis research, which increasingly recognizes sepsis not as a homogeneous disease entity, but as a syndrome comprising multiple distinct biological states that share a similar clinical presentation. Within this framework, four clinical phenotypes have been proposed. The alpha phenotype, the most prevalent, is characterized by the lowest levels of inflammatory biomarkers, corresponding to a lower risk of organ dysfunction and the lowest mortality. In this group, cytokine adsorption is unlikely to yield measurable clinical benefit due to relatively low circulating cytokine concentrations. The beta phenotype typically includes older patients with multiple comorbidities and frequent renal dysfunction, in whom continuous renal replacement therapy (CRRT) is often required, while the degree of systemic inflammation remains moderate. The gamma phenotype is primarily defined by predominant respiratory failure, whereas the delta phenotype most closely resembles the classical „cytokine storm” profile, cha-

racterized by extremely elevated IL-6 levels, severe shock, multi-organ dysfunction, and high mortality (Seymour et al., 2019). It is within this subgroup that extracorporeal blood purification strategies may have the greatest therapeutic potential. However, this phenotype accounts for only approximately 10% of septic patients, and the lack of patient stratification in most clinical studies likely leads to dilution of any potential treatment effect in overall analyses.

A key feature of the CytoSorb system is its non-selective adsorption profile. This implies that the filter removes not only pro-inflammatory cytokines, but also anti-inflammatory mediators, as well as circulating drugs with a molecular weight not exceeding approximately 60 kDa. Interleukin-10 (IL-10) is one of the most important endogenous anti-inflammatory cytokines involved in limiting tissue injury during sepsis. Among its functions, it inhibits the production of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Owing to its relatively low molecular weight (approximately 18–20 kDa), IL-10 is also effectively removed by the system, with a degree of adsorption comparable to that of pro-inflammatory cytokines. Consequently, initiation of therapy during the immunosuppressive phase of sepsis may interfere with the physiological regulation of the host immune response. Similarly, other anti-inflammatory mediators are subject to removal, including interleukin-1 receptor antagonist (IL-1Ra), a key endogenous inhibitor of IL-1 signaling responsible for limiting fever, neutrophil activation, and adhesion molecule expression, as well as interleukin-4 (IL-4) and interleukin-13 (IL-13) (Graf, Gräfe, Bruegel, Häppich, et al., 2024). Beyond immunological modulation, CytoSorb therapy may also significantly influence pharmacokinetics of concurrently administered drugs.

Pharmacokinetic interactions and clinical relevance

Drug adsorption is an additional and clinically relevant aspect of CytoSorb therapy. The most comprehensive synthesis to date evaluating its impact on pharmacotherapy is a systematic review published in 2026, which analyzed 26 studies encompassing 36 different drugs (Kenda et al., 2026). The review provides compelling evidence of clinically significant adsorption of linezolid and vancomycin, as well as indications of effective removal of ticagrelor and apixaban in the context of cardiac surgery. Consequently, the authors strongly recommend therapeutic drug monitoring during CytoSorb therapy. Vancomycin, the most extensively studied antibiotic in the

context of extracorporeal therapies, demonstrates a marked increase in clearance following initiation of hemoadsorption, with reports of up to a nearly 300% rise. The most pronounced effect is observed immediately after cartridge replacement. Accordingly, an additional 500 mg dose has been shown to reduce the risk of subtherapeutic concentrations (Scharf et al., 2022). Experimental data also suggest potential adsorption of albumin and catecholamines by the semipermeable membrane; however, clinical studies have not confirmed a significant reduction in circulating albumin or catecholamine levels (Brozat et al., 2025), (Körtge et al., 2026). In the case of norepinephrine, some studies have even reported a reduction in vasopressor requirements within 24 hours of therapy initiation (Hawchar et al., 2021). Beyond potential limitations, the non-selective adsorption profile of CytoSorb also expands possible therapeutic applications. In rhabdomyolysis, for example, the system has demonstrated effective removal of myoglobin, although a marked decline in adsorption efficiency has been observed approximately 3 hours after cartridge exchange (Graf, Gräfe, Bruegel, Zoller, et al., 2024). Nevertheless, no studies to date have demonstrated a reduction in the incidence of acute kidney injury compared with control groups or a clear survival benefit, indicating that further investigation is required.

6. Summary

Sepsis remains one of the most significant challenges in modern intensive care medicine. Its pathophysiology is characterized by complex interactions between the host immune response, microcirculatory dysfunction, progressive organ failure, and disturbances in gas exchange. In this context, both hemoadsorption using the CytoSorb system and extracorporeal carbon dioxide removal (ECCO₂R) were developed as targeted strategies aimed at modifying selected components of this pathophysiological cascade. Both techniques demonstrate pronounced efficacy in terms of their direct biological effects. CytoSorb effectively reduces circulating concentrations of cytokines and other inflammatory mediators, whereas ECCO₂R enables extracorporeal removal of carbon dioxide, thereby facilitating the implementation of more protective mechanical ventilation strategies. However, despite these physiological benefits, clinical trials have not yet provided conclusive evidence of improved hard clinical endpoints, particularly overall survival. This limitation is most evident in large studies involving unselected populations of patients

with sepsis and acute respiratory distress syndrome (ARDS). Increasing evidence suggests that this discrepancy is not primarily attributable to insufficient technical performance, but rather to the failure to account for the marked heterogeneity of critically ill patients. Contemporary sepsis research increasingly rejects the concept of sepsis as a single uniform disease entity, instead emphasizing the identification of distinct clinical and biological phenotypes. Within this framework, both CytoSorb and ECCO₂R should not be regarded as universal therapies, but rather as adjunctive tools targeted at carefully selected patient subgroups in which the underlying pathophysiological processes are amenable to modulation by a given extracorporeal technique. Accordingly, the future of extracorporeal blood purification and gas exchange therapies in sepsis appears closely linked to the concept of precision extracorporeal support. This approach encompasses appropriate patient selection, optimal timing of intervention, and individualization of therapy based on disease phenotype. Only through such stratification is it likely to fully realize the physiological potential of these technologies and translate observed biological effects into meaningful clinical outcomes.

References

- Andersson, U., & Tracey, K. J. (2003). HMGB1 in Sepsis. *Scandinavian Journal of Infectious Diseases*, 35(9), 577-584. <https://doi.org/10.1080/00365540310016286>
- Bos, L. D. J., & Ware, L. B. (2022). Acute respiratory distress syndrome: Causes, pathophysiology, and phenotypes. *The Lancet*, 400(10358), 1145-1156. [https://doi.org/10.1016/S0140-6736\(22\)01485-4](https://doi.org/10.1016/S0140-6736(22)01485-4)
- Brozat, C. I., Zoller, M., Frank, S., Bruegel, M., Gräfe, C., Rebholz, D., Paal, M., Graf, H., Liebchen, U., & Scharf, C. (2025). Albumin and Platelet Loss during the Application of CytoSorb® in Critically Ill Patients: A post hoc Analysis of the Cyto-SOLVE Trial. *Blood Purification*, 54(2), 93-101. <https://doi.org/10.1159/000542009>
- Brzozowska, P., Nowińska, B., Lissak, K., Binczyk, W., Drózd, O., Siudek, B., & Wiśniewska, A. (2024). A case report: Acute sinusitis turned into shockingly rapid sepsis at young male adult. *Quality in Sport*, 16, 52676. <https://doi.org/10.12775/QS.2024.16.52676>

- Daniel, M., Bedoui, Y., Vagner, D., Raffray, L., Ah-Pine, F., Doray, B., & Gasque, P. (2022). Pathophysiology of Sepsis and Genesis of Septic Shock: The Critical Role of Mesenchymal Stem Cells (MSCs). *International Journal of Molecular Sciences*, 23(16), 9274. <https://doi.org/10.3390/ijms23169274>
- De Backer, D., Donadello, K., Taccone, F. S., Ospina-Tascon, G., Salgado, D., & Vincent, J.-L. (2011). Microcirculatory alterations: Potential mechanisms and implications for therapy. *Annals of Intensive Care*, 1(1), 27. <https://doi.org/10.1186/2110-5820-1-27>
- Derdak, S. (2022). Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation Effect on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure. *JAMA*, 327(1), 82. <https://doi.org/10.1001/jama.2021.21002>
- Duffin, J., Mikulis, D. J., & Fisher, J. A. (2021). Control of Cerebral Blood Flow by Blood Gases. *Frontiers in Physiology*, 12. <https://doi.org/10.3389/fphys.2021.640075>
- Ferluga, M., Lucangelo, U., & Blanch, L. (2018). Dead space in acute respiratory distress syndrome. *Annals of Translational Medicine*, 6(19), 388-388. <https://doi.org/10.21037/atm.2018.09.46>
- Graf, H., Grafe, C., Bruegel, M., Happich, F. L., Wustrow, V., Wegener, A., Wilfert, W., Zoller, M., Liebchen, U., Paal, M., & Scharf, C. (2024). Extracorporeal Elimination of Pro- and Anti-inflammatory Modulators by the Cytokine Adsorber CytoSorb® in Patients with Hyperinflammation: A Prospective Study. *Infectious Diseases and Therapy*, 13(9), 2089-2101. <https://doi.org/10.1007/s40121-024-01028-8>
- Graf, H., Grafe, C., Bruegel, M., Zoller, M., Maciuga, N., Frank, S., Weidhase, L., Paal, M., & Scharf, C. (2024). Myoglobin adsorption and saturation kinetics of the cytokine adsorber Cytosorb® in patients with severe rhabdomyolysis: A prospective trial. *Annals of Intensive Care*, 14(1), 96. <https://doi.org/10.1186/s13613-024-01334-x>
- Harm, S., Gabor, F., & Hartmann, J. (2015). Characterization of Adsorbents for Cytokine Removal from Blood in an In Vitro Model. *Journal of Immunology Research*, 2015, 1-11. <https://doi.org/10.1155/2015/484736>
- Hawchar, F., Rao, C., Akil, A., Mehta, Y., Rugg, C., Scheier, J., Adamson, H., Deliargyris, E., & Molnar, Z. (2021). The Potential Role of Extracorporeal Cytokine Removal in Hemodynamic Stabilization in Hyperinflammatory Shock. *Biomedicines*, 9(7). <https://doi.org/10.3390/biomedicines9070768>
- Hotchkiss, R. S., Moldawer, L. L., Opal, S. M., Reinhart, K., Turnbull, I. R., & Vincent, J.-L. (2016). Sepsis and septic shock. *Nature Reviews Disease Primers*, 2(1), 16045. <https://doi.org/10.1038/nrdp.2016.45>
- Jansen, A., Waalders, N. J. B., van Lier, D. P. T., Kox, M., & Pickkers, P. (2023). CytoSorb hemoperfusion markedly attenuates circulating cytokine concentrations during systemic inflammation in humans in vivo. *Critical Care*, 27(1), 117. <https://doi.org/10.1186/s13054-023-04391-z>
- Karagiannidis, C., Hesselmann, F., & Fan, E. (2019). Physiological and Technical Considerations of Extracorporeal CO₂ Removal. *Critical Care*, 23(1), 75. <https://doi.org/10.1186/s13054-019-2367-z>
- Kenda, S., Gubenšek, J., & Vovk, T. (2026). Antibiotics and Other Drugs Removal by the CytoSorb® Haemoadsorber: A Systematic Review of Available Evidence. *Antibiotics*, 15(4), 409. <https://doi.org/10.3390/antibiotics15040409>
- Kortge, A., Klinkmann, G., Kamper, C., Wasserkort, R., & Mitzner, S. (2026). Effects of hemoadsorption on plasma catecholamine levels: An in vitro study. *Scientific Reports*, 16(1). <https://doi.org/10.1038/s41598-026-49101-1>
- Lindskog, S. (1997). Structure and mechanism of carbonic anhydrase. *Pharmacology & Therapeutics*, 74(1), 1-20. [https://doi.org/10.1016/S0163-7258\(96\)00198-2](https://doi.org/10.1016/S0163-7258(96)00198-2)
- Lopez-Castejon, G., & Brough, D. (2011). Understanding the mechanism of IL-1 β secretion. *Cytokine & Growth Factor Reviews*, 22(4), 189-195. <https://doi.org/10.1016/j.cytog.2011.10.001>
- Lotz, C., Heckelmann, J., Lenzian, C., Herrmann, J., Haack, B., Gieselmann, M., Wedekink, F., Röder, D., Schlegel, N., Meybohm, P., Wischhusen, J., & Notz, Q. (2026). Clinical and Immunologic Effects of Extracorporeal Cytokine Removal in Patients with Septic Shock: A Randomized Con-

- trolled Trial. *Shock*, 65(4), 637-647. <https://doi.org/10.1097/SHK.0000000000002802>
- Malhotra, A. (2007). Low-Tidal-Volume Ventilation in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, 357(11), 1113-1120. <https://doi.org/10.1056/NEJMct074213>
- Millar, J. E., Boyle, A. J., Drake, T. M., Adams, C. E., Glass, A. W., Blackwood, B., McNamee, J. J., & McAuley, D. F. (2022). Extracorporeal carbon dioxide removal in acute hypoxaemic respiratory failure: A systematic review, Bayesian meta-analysis and trial sequential analysis. *European Respiratory Review*, 31(166), 220030. <https://doi.org/10.1183/16000617.0030-2022>
- Orban, C., Bratu, A., Agapie, M., Borjog, T., Jafal, M., Sima, R.-M., Dumitraşcu, O. C., & Popescu, M. (2025). To Hemoadsorb or Not to Hemoadsorb—Do We Have the Answer Yet? An Updated Meta-Analysis on the Use of CytoSorb in Sepsis and Septic Shock. *Biomedicines*, 13(1), 180. <https://doi.org/10.3390/biomedicines13010180>
- Polyvov, V., Dzyubanovsky, I., Kovalchuk, A., Dzyubanovsky, O., & Dzhvyak, V. (2021). Dynamics of cytokine profile in patients with abdominal sepsis caused by pancreonecrosis. *Journal of Education, Health and Sport*, 11(5), 207-212. <https://doi.org/10.12775/JEHS.2021.11.05.021>
- Prescott, H. C., Antonelli, M., Alhazzani, W., Moller, M. H., Alshamsi, F., Azevedo, L. C. P., Belley-Cote, E., De Waele, J., Derde, L., Dionne, J. C., Evans, L., Gershengorn, H. B., Hodgson, C. L., Honarmand, K., Kesecigolu, J., McIntyre, L., Mer, M., Nunnally, M. E., Oczkowski, S. J. W., ... Cooper-smith, C. M. (2026). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2026. *Critical Care Medicine*. <https://doi.org/10.1097/CCM.0000000000007075>
- Romay, E., & Ferrer, R. (2016). Extracorporeal CO2 removal: Technical and physiological fundamentals and principal indications. *Medicina Intensiva (English Edition)*, 40(1), 33-38. <https://doi.org/10.1016/j.medine.2015.12.002>
- Ronco, C., Ricci, Z., & Husain-Syed, F. (2019). From Multiple Organ Support Therapy to Extracorporeal Organ Support in Critically Ill Patients. *Blood Purification*, 48(2), 99-105. <https://doi.org/10.1159/000490694>
- Scharf, C., Weinelt, F., Schroeder, I., Paal, M., Weigand, M., Zoller, M., Irlbeck, M., Kloft, C., Briegel, J., & Liebchen, U. (2022). Does the cytokine adsorber CytoSorb® reduce vancomycin exposure in critically ill patients with sepsis or septic shock? A prospective observational study. *Annals of Intensive Care*, 12(1), 44. <https://doi.org/10.1186/s13613-022-01017-5>
- Seymour, C. W., Kennedy, J. N., Wang, S., Chang, C.-C. H., Elliott, C. F., Xu, Z., Berry, S., Clermont, G., Cooper, G., Gomez, H., Huang, D. T., Kellum, J. A., Mi, Q., Opal, S. M., Talisa, V., van der Poll, T., Visweswaran, S., Vodovotz, Y., Weiss, J. C., ... Angus, D. C. (2019). Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA*, 321(20), 2003. <https://doi.org/10.1001/jama.2019.5791>
- Slobod, D., Damia, A., Leali, M., Spinelli, E., & Mauri, T. (2022). Pathophysiology and Clinical Meaning of Ventilation-Perfusion Mismatch in the Acute Respiratory Distress Syndrome. *Biology*, 12(1), 67. <https://doi.org/10.3390/biology12010067>
- Slutsky, A. S., & Ranieri, V. M. (2013). Ventilator-Induced Lung Injury. *New England Journal of Medicine*, 369(22), 2126-2136. <https://doi.org/10.1056/NEJMr1208707>
- Spatola, L., Granata, A., D'Amico, M., Oddo, G., & Gambaro, A. (2025). Hemadsorption with CytoSorb®: Focus on the latest experiences in cardiac surgery patients. *Journal of Artificial Organs*, 28(3), 317-328. <https://doi.org/10.1007/s10047-024-01485-5>
- Srzic, I. (2022). Sepsis definition: What's new in the Treatment Guidelines. *Acta Clinica Croatica*. <https://doi.org/10.20471/acc.2022.61.s1.11>
- Steindl, D., Schroeder, T., Krannich, A., & Nee, J. (2025). Hemoadsorption in the Management of Septic Shock: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine*, 14(7), 2285. <https://doi.org/10.3390/jcm14072285>
- Stommel, A.-M., Herkner, H., Kienbacher, C. L., Wildner, B., Hermann, A., & Staudinger, T. (2024). Effects of extracorporeal CO2 removal on gas exchange and ventilator settings: A systematic review and meta-analysis. *Critical Care*, 28(1), 146. <https://doi.org/10.1186/s13054-024-04927-x>

- Suchomska, M., Halota, W., & Olczak, A. (2019). Systemic inflammatory response syndrome and sepsis - epidemiology, differentiation, diagnostics in clinical practice. <https://doi.org/10.5281/ZENODO.2579349>
- Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harbor Perspectives in Biology*, 6(10), a016295-a016295. <https://doi.org/10.1101/cshperspect.a016295>
- Thompson, B. T., Chambers, R. C., & Liu, K. D. (2017). Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, 377(6), 562-572. <https://doi.org/10.1056/NEJMra1608077>
- Tiruvoipati, R., Akkanti, B., Dinh, K., Barrett, N., May, A., Kimmel, J., & Conrad, S. A. (2023). Extracorporeal Carbon Dioxide Removal With the Hemolung in Patients With Acute Respiratory Failure: A Multicenter Retrospective Cohort Study*. *Critical Care Medicine*, 51(7), 892-902. <https://doi.org/10.1097/CCM.0000000000005845>
- Worku, E., Brodie, D., Ling, R. R., Ramanathan, K., Combes, A., & Shekar, K. (2023). Venovenous extracorporeal CO₂ removal to support ultraprotective ventilation in moderate-severe acute respiratory distress syndrome: A systematic review and meta-analysis of the literature. *Perfusion*, 38(5), 1062-1079. <https://doi.org/10.1177/02676591221096225>
- Xu, J. (2023). A review: Continuous renal replacement therapy for sepsis-associated acute kidney injury. *All Life*, 16(1). <https://doi.org/10.1080/26895293.2022.2163305>
- Yu, T. Z., Tatum, R. T., Saxena, A., Ahmad, D., Yost, C. C., Maynes, E. J., O'Malley, T. J., Massey, H. T., Swol, J., Whitson, B. A., & Tchantchaleishvili, V. (2022). Utilization and outcomes of extracorporeal CO₂ removal (ECCO₂R): Systematic review and meta-analysis of arterio-venous and veno-venous ECCO₂R approaches. *Artificial Organs*, 46(5), 763-774. <https://doi.org/10.1111/aor.14130>

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