Renal Replacement Therapy for Septic Shock Patients in ICU: A Systematic Review

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ABSTRACT

Introduction: Septic shock is a life-threatening condition frequently complicated by acute kidney injury (AKI), often necessitating renal replacement therapy (RRT) in the intensive care unit. This systematic review aims to critically appraise renal replacement therapy modalities in adult patients with septic shock in the ICU.

Methods: This comprehensive systematic review synthesizes evidence from 80 sources, including meta-analyses, randomized controlled trials, and observational studies from 2004 to 2025. A structured screening process focused on adult ICU patients with septic shock receiving RRT, excluding chronic dialysis patients. Data were extracted on RRT modalities, patient characteristics, comparators, clinical outcomes, safety profiles, and study context.

Results: High-volume hemofiltration (HVHF) showed no consistent mortality benefit over standard-volume therapy. Early RRT initiation may reduce mortality in specific subgroups. Blood purification techniques like Polymyxin-B hemoperfusion (PMX-HP) and the oXiris filter showed mortality benefits, particularly in intermediate-to-high-risk patients, though with notable regional variance. Vasopressin use was consistently associated with reduced RRT requirements compared to catecholamines. Fluid choice significantly impacted renal outcomes, with hydroxyethyl starch (HES) solutions consistently increasing the risk of RRT compared to balanced crystalloids.

Conclusion: RRT strategies in septic shock should be individualized. For moderate AKI, early RRT may be beneficial. Vasopressin is recommended to reduce RRT dependency, and balanced crystalloids are preferred over HES for fluid resuscitation. Future research should focus on personalized medicine approaches and well-designed RCTs for emerging blood purification technologies.

Keywords: Intensive care unit, renal replacement therapy, septic shock

Terapi Pengganti Ginjal untuk Pasien Syok Sepsis di ICU: Sebuah Tinjauan Sistematis

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ABSTRAk

Pendahuluan: *Syok sepsis adalah kondisi yang mengancam jiwa dan sering disertai dengan cedera ginjal akut (AKI), yang seringkali memerlukan terapi penggantian ginjal (RRT) di unit perawatan intensif (ICU). Ulasan sistematis ini bertujuan untuk mengevaluasi secara kritis berbagai metode terapi penggantian ginjal pada pasien dewasa dengan syok sepsis di ICU.*

Metode: *Ulasan sistematis ini mensintesis bukti dari 80 sumber, termasuk meta-analisis, uji klinis terkontrol acak, dan studi observasional dari tahun 2004 - 2025. Proses penyaringan terstruktur difokuskan pada pasien dewasa di ICU dengan syok sepsis yang menerima RRT dengan mengesampingkan pasien dialisis kronis. Data diekstraksi mengenai modalitas RRT, karakteristik pasien, perbandingan, hasil klinis, profil keamanan, dan konteks studi.*

Hasil: *Hemofiltrasi volume tinggi (HVHF) tidak menunjukkan manfaat dalam menurunkan mortalitas yang konsisten dibandingkan terapi volume standar. Inisiasi RRT dini mungkin mengurangi mortalitas pada subkelompok tertentu. Teknik pemurnian darah seperti hemoperfusi Polymyxin-B (PMX-HP) dan filter oXiris menunjukkan manfaat menurunkan mortalitas, terutama pada pasien berisiko sedang hingga tinggi. Penggunaan vasopresin secara konsisten terkait dengan penurunan kebutuhan RRT dibandingkan dengan katekolamin. Pilihan cairan secara signifikan mempengaruhi hasil ginjal, dengan larutan hidroksietil pati (HES) secara konsisten meningkatkan risiko RRT dibandingkan dengan kristaloid seimbang.*

Simpulan: *Strategi RRT pada syok sepsis harus disesuaikan secara individual. Pada AKI sedang, RRT dini mungkin bermanfaat. Vasopresin direkomendasikan untuk mengurangi ketergantungan pada RRT, dan kristaloid seimbang lebih diutamakan daripada HES untuk resusitasi cairan. Penelitian di masa depan harus berfokus pada pendekatan pengobatan individual dan uji klinis terkontrol acak yang dirancang dengan baik untuk teknologi pemurnian darah yang sedang berkembang*

Kata Kunci: *Intensive care unit, terapi pengganti ginjal, syok sepsis*

INTRODUCTION

Septic shock, a subset of sepsis with profound circulatory and cellular abnormalities, carries a high mortality rate and represents a major global health burden.[1] A frequent and devastating complication is sepsis-associated acute kidney injury (SA-AKI), which occurs in over half of septic shock patients and significantly worsens prognosis.[2] Renal replacement therapy becomes a cornerstone of supportive management for these patients in the intensive care unit, aiming to correct metabolic derangements, manage fluid balance, and potentially modulate the dysregulated inflammatory response.[3] However, the landscape of RRT in septic shock is complex, encompassing debates on optimal modality (e.g., continuous vs. intermittent), dosing intensity, timing of initiation, and the role of adjunctive blood purification techniques.[4] Furthermore, decisions on RRT do not occur in isolation but intersect with other critical aspects of septic shock management, including vasopressor selection, fluid resuscitation strategy, and corticosteroid use, all of which can independently influence renal outcomes.[5]

Despite extensive research, significant knowledge gaps and clinical equipoise persist. Evidence on the mortality benefit of high-intensity RRT regimens like HVHF is conflicting.[6] The optimal timing for initiating RRT, whether an “early” or “late” strategy is preferable, remains controversial, with meta-analyses yielding disparate conclusions.[7] The efficacy of novel blood purification devices (e.g., oXiris, CytoSorb) appears promising but is based largely on observational data.[8] Moreover, there is a paucity of synthesized evidence that holistically examines how choices in vasopressor therapy, fluid composition, and adjunctive treatments interact with and influence the need for and outcomes of RRT in septic shock.

This comprehensive systematic review offers novelty by synthesizing a vast and contemporary body of evidence (80 sources up to 2025) that spans not only traditional RRT parameters but also their intricate interplay with other pillars of septic shock resuscitation. It moves beyond analyzing RRT in isolation to provide an integrated analysis of how vasopressor choice (e.g., vasopressin vs. norepinephrine), fluid selection (e.g., crystalloids vs. starches), and adjuvant therapies (e.g., corticosteroids, HAT therapy) directly impact renal outcomes and RRT requirements. This integrative approach is crucial for developing nuanced, patient-centered management protocols. Therefore, this systematic review aims to critically appraise and synthesize the existing evidence on the effectiveness, safety, and optimal application of various renal replacement therapy modalities and related management strategies in adult patients with septic shock in the ICU.

METHODS

Research Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Eligibility Criteria

The inclusion criteria in this study are: 1) adult patients (≥18 years) with septic shock requiring intensive care, 2) patients receiving any form of renal replacement therapy (continuous renal replacement therapy, intermittent hemodialysis, sustained low-efficiency dialysis, peritoneal dialysis, or hybrid therapies), 3) the study report relevant clinical outcomes (mortality, organ function recovery, ICU length of stay, hemodynamic parameters, or renal recovery), and 4) randomized controlled trial, quasi-randomized trial, cohort study, case-control study, systematic review, or meta-analysis. Meanwhile, the exclusion criteria in this study are: 1) patients with chronic kidney disease on maintenance dialysis prior to septic shock, 2) the study that did not focus on septic shock, 3) a case report, case series with <10 patients, editorial, or conference abstract. We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research-based PICO (Table 1):

Tabel 1. PICO frameworks

Elements	P (Population)	I (Intervention/ Exposure)	C (Comparison/ Context)	O (Outcome)
Keyword 1	Septic Shock Patients	Renal Replacement Therapy	Standard Intensive Care	Mortality
Keyword 2	Adults with Septic Shock	Continuous Renal Replacement Therapy (CRRT)	Intermittent Hemodialysis (IHD)	Renal Recovery
Keyword 3	ICU Patients with Sepsis-associated AKI	High-Volume Hemofiltration	Low-Volume Hemofiltration	Organ Function Recovery
Keyword 4	Critically Ill Patients with Septic AKI	Blood Purification Techniques	Conventional Therapy	ICU Length of Stay

The Boolean MeSH keywords inputted on databases for this research are: *("Septic Shock Patients" OR "Adults with Septic Shock" OR "ICU Patients with Sepsis-associated AKI" OR "Critically Ill Patients with Septic AKI") AND ("Renal Replacement Therapy" OR "Continuous Renal Replacement Therapy (CRRT)" OR "High-Volume Hemofiltration" OR "Blood Purification Techniques") AND ("Standard Intensive Care" OR "Intermittent Hemodialysis (IHD)" OR "Low-Volume Hemofiltration" OR "Conventional Therapy") AND ("Mortality" OR "Renal Recovery" OR "Organ Function Recovery" OR "ICU Length of Stay")*.

Data extraction

During data extraction, we collected granular information on the RRT intervention to enable meaningful comparability across studies. This included the exact modality (e.g., CVVH, HVHF, plasma exchange, hemoperfusion), dose/ intensity parameters (such as effluent and blood flow rates), initiation timing (early vs late and the explicit start criteria), treatment duration, and key technical specifications (membrane type and replacement fluid composition), as well as any protocol modifications or adjunctive therapies delivered alongside RRT. High-volume hemofiltration (HVHF) is defined as hemofiltration administered at an effluent dose exceeding 50 mL/kg/h, whereas standard-volume hemofiltration (SVHF) refers to conventional doses below this threshold, typically ranging from 20–35 mL/kg/h in accordance with contemporary CRRT practice. In this review, early RRT initiation refers to the commencement of renal replacement therapy before the development of conventional emergency indications for dialysis, typically within 24–48 hours after AKI diagnosis or during KDIGO stage 2 AKI. In contrast, late RRT initiation refers to delaying RRT until the occurrence of severe metabolic disturbances, refractory fluid overload, persistent oliguria/anuria, or progression to advanced AKI stages. Because definitions varied across studies, the timing reported by each original study was accepted and categorized according to the authors' criteria. In parallel, we extracted detailed population descriptors relevant to septic shock and renal dysfunction, sepsis severity (e.g., SOFA score, vasopressor exposure), AKI classification (KDIGO/RIFLE or equivalent), baseline demographics and comorbidities, ICU setting, sample size, and baseline imbalances, to support clinical stratification and sensitivity analyses.

We also captured comparator details (standard care or alternative RRT strategies, including modality, dosing, timing, and co-interventions such as antibiotics, vasopressors, and fluid resuscitation) to minimize confounding from non-RRT components of care. Outcomes extraction covered mortality endpoints (ICU, hospital, 28-day, 90-day), organ dysfunction metrics (SOFA/organ failure scores), renal recovery (dialysis independence and creatinine recovery), resource-related endpoints (ICU/hospital length

of stay, vasopressor duration), and reported effect estimates with confidence intervals when available. Safety data included adverse events (hemodynamic instability, electrolyte disturbances, bleeding), discontinuations, technical complications (circuit clotting, vascular access issues), and resource utilization signals (staffing burden, cost considerations), alongside study-level context (design, eligibility criteria, setting/country/year, analysis type, risk-of-bias indicators, and author-noted limitations affecting generalizability).

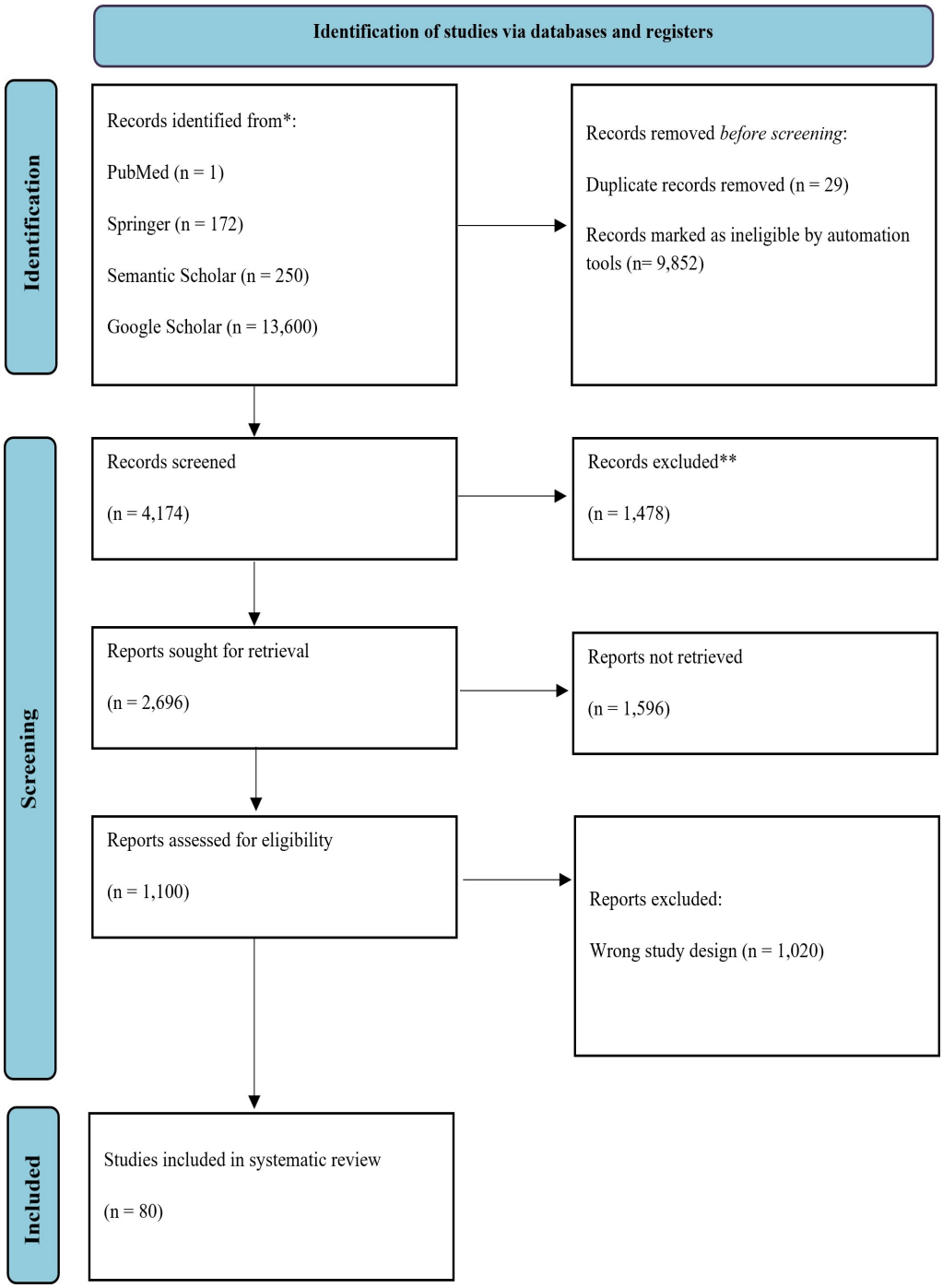

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This systematic review synthesizes evidence from 80 studies examining renal replacement therapy modalities and factors influencing renal outcomes in septic shock patients treated in the intensive care unit. The included literature demonstrates substantial heterogeneity in patient populations, definitions of AKI, criteria for RRT initiation, and outcome measures.

Most studies consisted of systematic reviews, meta-analyses, RCTs, and large observational cohorts, with sample sizes ranging from single-center ICU populations to large multicenter studies. The investigated interventions broadly encompassed RRT modality and timing, blood purification techniques, anticoagulation strategies, vasopressor use, corticosteroid therapy, and fluid resuscitation approaches.

The studies were conducted across diverse healthcare settings, including the United States, Europe, China, and Australia, reflecting variability in clinical practice patterns and resource availability. This heterogeneity underscores the need for cautious interpretation of pooled outcomes and contextualization of findings within specific clinical settings.

Effects of RRT Modalities and Intensity

High-volume hemofiltration, defined as effluent rates greater than 50 mL/kg/hour, has been extensively studied as a potential adjunctive therapy for septic acute kidney injury. The theoretical rationale involves enhanced removal of inflammatory cytokines and bacterial toxins. However, the pooled evidence does not support routine use of HVHF over standard-volume approaches.

A systematic review of four trials including 470 participants found no meaningful difference in 28-day mortality between HVHF and standard-volume hemofiltration. The Cochrane review of high-volume hemofiltration similarly found no mortality benefit with a pooled risk ratio of 0.89 (95% CI 0.60-1.32) for 28-day mortality across two trials with 146 participants. One meta-analysis of five RCTs with 241 participants confirmed these findings with a pooled risk ratio of 0.96 (0.67-1.38).

A contrasting finding from an earlier Chinese meta-analysis suggested HVHF may reduce mortality compared to low-volume hemofiltration with an odds ratio of 0.33 (0.17-0.64).[6] However, this analysis included lower-quality studies and exhibited significant heterogeneity. Adverse events were more commonly observed in HVHF-treated patients, including hypophosphatemia and hypokalemia. HVHF is also more resource-intensive, adding considerable nursing requirements and replacement fluid costs.

Tabel 2. High-volume hemofiltration versus standard-volume hemofiltration

Outcome	HVHF Effect	Effect Size (95% CI)	Evidence Quality
28-day mortality	No significant difference	OR 0.76 (0.45-1.29)	Low
28-day mortality (pooled)	No significant difference	RR 0.89 (0.60-1.32)	Low
28-day mortality (alternative pooling)	No significant difference	RR 0.96 (0.67-1.38)	Low
Overall mortality	Reduced with HVHF	OR 0.33 (0.17-0.64)	Very low
Recovery of kidney function	No significant difference	Not quantified	Low
ICU/hospital length of stay	No significant difference	Not quantified	Low
Vasopressor dose reduction	Mixed results	RR 2.22 (1.01-4.51) in one study	Very low

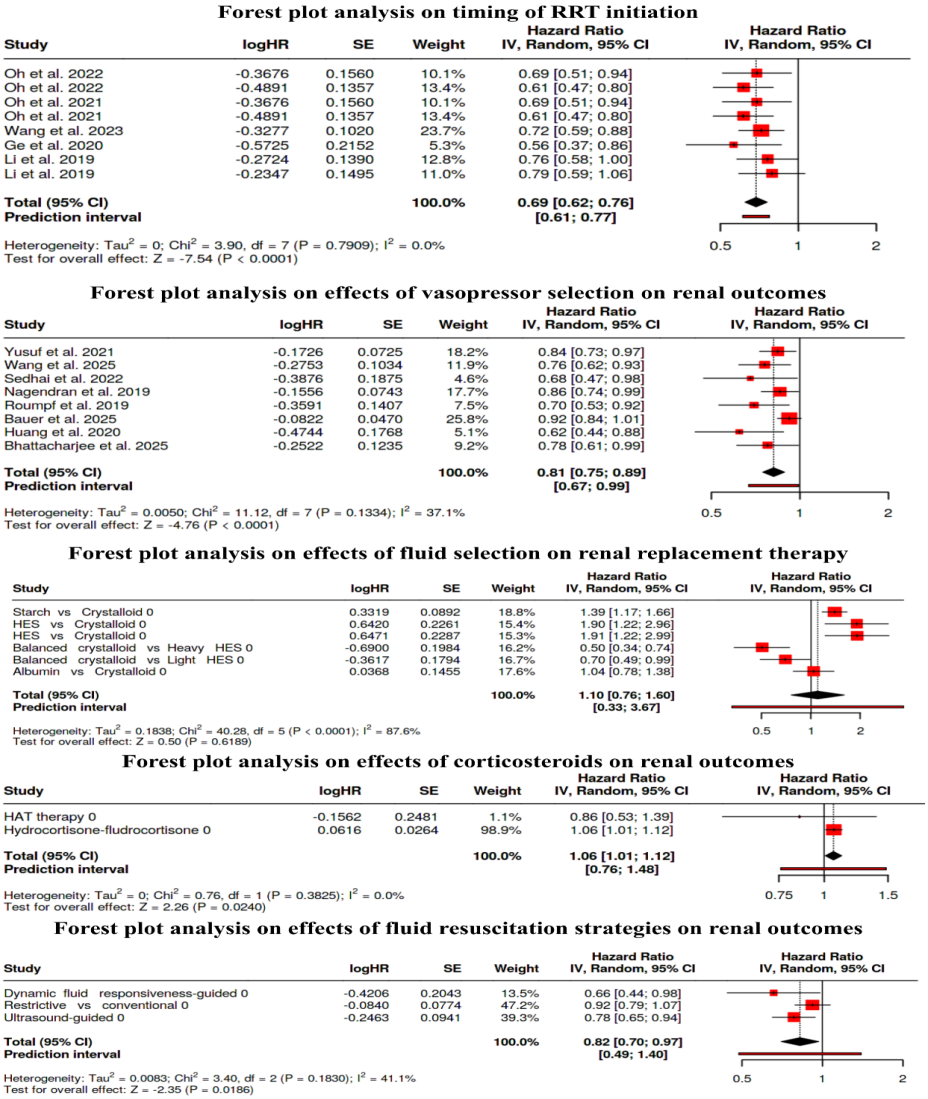

Figure 2. Forest plot analysis on effects of RRT-related strategies on renal

Timing of RRT Initiation

The optimal timing of RRT initiation in septic acute kidney injury remains a subject of substantial investigation. Multiple meta-analyses have examined early versus late initiation strategies with somewhat conflicting results. Two overlapping meta-analyses by Oh and colleagues found that early RRT initiation was associated with significantly lower 28-day mortality (RR 0.69; 95% CI 0.51-0.94) and 90-day mortality (RR 0.61; 95% CI 0.47-0.80).[11,14] Subgroup analysis for continuous RRT specifically also demonstrated significantly lower mortality rates in the early treatment group.

Wang et al.[12] reported similar findings with early RRT showing lower 28-day mortality (RR 0.72; 95% CI 0.59-0.88), particularly in patients with KDIGO stage 2 AKI and SOFA scores less than or equal to 12. Ge et al.[15] found that early RRT initiation within 48 hours reduced 28-day mortality with an odds ratio of 0.56 (95% CI 0.37-0.86). However, other analyses have not confirmed these benefits. Li et al.[26] found no significant difference in 28-day mortality (OR 0.76; 95% CI 0.58-1.00) or 90-day mortality (OR 0.79; 95% CI 0.59-1.06) between early and late CRRT initiation. Similarly, Somaili et al.[7] concluded that early initiation probably results in little or no difference regarding death. ICU and hospital length of stay did not differ significantly between early and late RRT groups across multiple analyses.[7] The early strategy may result

in a slight increase in adverse events, though it may slightly reduce hospital length of stay.

Figure 2 presents a random-effects forest plot evaluating the association between the timing of RRT initiation and clinical outcomes. Individual studies report hazard ratios (HRs) with 95% confidence intervals, and most point estimates lie below 1.0, indicating a consistent trend favoring earlier RRT initiation. The pooled effect estimate shows a statistically significant reduction in hazard with early initiation (HR 0.69, 95% CI 0.62–0.76), with a narrow prediction interval (0.61–0.77) suggesting that the direction of effect is likely consistent across comparable settings. Between-study heterogeneity is negligible ($I^2 = 0.0\%$, $\chi^2 = 3.90$, $p = 0.79$; $\tau^2 = 0$), and the overall effect is significant ($Z = -7.54$, $p < 0.00001$).

Blood Purification Techniques

Blood purification techniques beyond conventional renal replacement therapy have been investigated for their potential to modulate the inflammatory response in sepsis. Polymyxin-B Hemoperfusion showed that network meta-analysis found polymyxin-B hemoperfusion associated with reduced mortality (RR 0.70; 95% CI 0.57-0.86) compared to standard care. A comprehensive meta-analysis of 30 trials with 25,680 patients reported reduced 28-day mortality with PMX-HP (OR 0.75; 95% CI 0.65-0.88). PMX hemoperfusion uses polymyxin B covalently bound to polystyrene fiber to inactivate endotoxin, with blood flow rates of 80-100 mL/min and treatment durations of 2-24 hours.

Importantly, disease severity subgroup analysis revealed that mortality reduction was significant in intermediate and high-risk groups (RR 0.84; 95% CI 0.77-0.92 and RR 0.64; 95% CI 0.52-0.78, respectively) but not in the low-risk group. Differences were also observed across geographic regions, with positive treatment effects reported predominantly in Asian studies but not consistently replicated in studies from North America or Europe.

These regional differences may reflect variations in patient populations, including the prevalence of gram-negative infections, baseline disease severity, timing of intervention, and standards of sepsis management, rather than a true geographic effect. In addition, differences in study design, inclusion criteria, and healthcare system practices may have contributed to the heterogeneity of outcomes observed across regions.

Plasma exchange study showed that therapeutic plasma exchange demonstrated potential mortality benefits with a relative risk of 0.61 (95% CI 0.42-0.91). A focused meta-analysis found that mortality significantly reduced in septic shock patients receiving plasma exchange compared to standard care (OR 0.43; 95% CI 0.26-0.72). Adverse events included hypocalcemia, hypotension (0.4-15%), and citrate toxicity, particularly in patients with underlying renal or liver issues.

CRRT with the oXiris filter, which features an adsorption coating for endotoxins and inflammatory mediators, was associated with significant reductions in 28-day mortality (OR 0.53; 95% CI 0.36-0.77) and shorter ICU stay (WMD -1.91; 95% CI -2.56 to -1.26). SOFA scores and norepinephrine requirements were also lower in the oXiris group. However, evidence certainly was rated low to very low due to predominantly observational study designs.

The CytoSorb hemoadsorption device showed associations with reduced in-hospital mortality (OR 0.64; 95% CI 0.42-0.97) and 28–30-day mortality (OR 0.49; 95% CI 0.28-0.83). Significant reductions in vasopressor requirements were also observed. No major adverse events were directly attributed to the device.

In contrast to other blood purification techniques, Coupled Plasma Filtration Adsorption (CPFA) did not demonstrate mortality benefits. A meta-analysis of six studies with 537 patients found no statistically significant difference in all-cause mortality (OR 0.75; 95% CI 0.53-1.06). Concerns were raised about potential removal of beneficial substances including antibiotics.

A comprehensive network meta-analysis of 31 RCTs found that PMX and HA330 filters were the only devices that notably decreased mortality compared to standard treatment. Notably, all patients who received convection at any prescribed convective dose exhibited greater mortality compared to those receiving standard therapy.

Anticoagulation Strategies for CRRT

Anticoagulation strategies during CRRT were evaluated as a secondary outcome. A meta-analysis comparing citrate and heparin anticoagulation in patients with septic acute kidney injury demonstrated that citrate anticoagulation was associated with improved renal function, significantly longer filter lifespan (WMD 6.93; 95% CI 6.30–7.55), and a markedly lower risk of bleeding complications compared with heparin (RR 0.14; 95% CI 0.06–0.32).

Effects of Vasopressor Selection on Renal Outcomes

The choice of vasopressor in septic shock has consistent implications for renal replacement therapy requirements. Multiple meta-analyses demonstrate that vasopressin and its analogues are associated with reduced need for RRT compared to catecholamines.

A meta-analysis of 18 trials with 4,024 patients found vasopressin or its analogues associated with reduced need for renal replacement therapy (RR 0.84; 95% CI 0.73-0.97) and lower AKI incidence (RR 0.93; 95% CI 0.86-1.00). Wang et al. confirmed reduced RRT utilization with vasopressin compared to norepinephrine (RR 0.76; 95% CI 0.62-0.93) along with significantly lower serum creatinine levels (MD -0.15 mg/dL; 95% CI -0.29 to -0.02).[10]

An individual patient data meta-analysis of 1,453 patients found vasopressin reduced RRT requirement (RR 0.86; 95% CI 0.74-0.99), though this finding was not robust to sensitivity analyses. The renal benefit appeared consistent when limiting analysis to low risk of bias studies, with reduced RRT rates (RR 0.70; 95% CI 0.53-0.92).

Timing of vasopressin initiation may also be relevant. Early initiation within 6 hours of septic shock onset was associated with reduced RRT use (OR 0.63; 95% CI 0.44-0.88) and decreased RRT incidence (RR 0.78; 95% CI 0.61-0.99). Despite consistent renal benefits, mortality effects of vasopressin remain uncertain. Multiple analyses found no significant difference in 28-day mortality between vasopressin and norepinephrine groups. Vasopressin was associated with increased digital ischemia (ARD 1.7%; 95% CI 0.3-3.2%) but fewer arrhythmias (ARD -2.8%; 95% CI -0.2% to -5.3%). Terlipressin, a synthetic vasopressin analogue, showed improved renal function with decreased creatinine levels (SMD -0.65; 95% CI -1.09 to -0.22) but also increased peripheral ischemia (OR 8.65; 95% CI 1.48-50.59).

Figure 2 shows a random-effects forest plot assessing how vasopressor selection influences renal outcomes. Most individual studies report hazard ratios (HRs) below 1.0, suggesting that the vasopressor strategy of interest is generally associated with a lower hazard of adverse renal outcomes compared with the comparator strategy. The pooled analysis demonstrates a statistically significant benefit (HR 0.81, 95% CI 0.75–0.89), while the prediction interval (0.67–0.99) indicates that the effect is likely to remain favorable across similar clinical settings, although the magnitude may vary. Between-study heterogeneity is moderate (I^2 = 37.1%, χ^2 = 11.12, p = 0.13; τ^2 = 0.005), implying some variability in effects across studies but not enough to negate the overall direction of benefit. The overall pooled effect is statistically significant (Z = −4.76, p < 0.00001).

Effects of Fluid Selection on Renal Replacement Therapy

The choice of resuscitation fluid significantly impacts renal replacement therapy requirements in septic shock. Network meta-analyses have consistently demonstrated increased RRT use with hydroxyethyl starch solutions.

Starch compared with crystalloid was associated with increased risk of receiving RRT (OR 1.39; 95% CI 1.17-1.66; high certainty). Multiple meta-analyses confirmed this finding, with HES associated with odds ratios for RRT of 1.90 (95% CI 1.22-2.96) and 1.91 (95% CI 1.22-2.99).

Balanced crystalloids demonstrated advantages over hydroxyethyl starch preparations. The risk of receiving RRT was lower with balanced crystalloid compared to heavy HES (OR 0.50; 95% CI 0.34-0.74; moderate certainty) and light HES (OR 0.70; 95% CI 0.49-0.99; high certainty). Network meta-analysis ranked balanced crystalloids highest for reducing all-cause mortality (SUCRA 83.1%).

Albumin did not significantly differ from crystalloids for RRT risk (OR 1.04; 95% CI

0.78-1.38; moderate certainty). Hyperoncotic albumin showed the lowest occurrence of RRT events (SUCRA 94.1%) but demonstrated no significant reduction in sepsis overall, though a significant reduction was observed in septic shock subgroups (OR 0.82; 95% CI 0.68-0.98).

High molecular weight HES was consistently associated with worse outcomes including increased risk of AKI and RRT compared to gelatin, balanced solutions, and low molecular weight HES. Both high and low molecular weight HES should be avoided in septic shock due to increased AKI and RRT risks.

Intensive insulin therapy combined with HES versus Ringer's lactate demonstrated that HES led to more acute renal failure (35% vs 23%) and RRT (31% vs 19%) compared to Ringer's lactate.

Figure 2 presents a random-effects forest plot examining the impact of resuscitation fluid selection on the risk of requiring renal replacement therapy (RRT). Across comparisons, effect estimates vary substantially: several analyses show an increased hazard associated with starch solutions (notably hydroxyethyl starch, HES) relative to crystalloids, while balanced crystalloids tend to favor lower hazard compared with heavier HES exposure. The pooled effect indicates an overall increased risk of RRT with the fluid strategies summarized (HR 1.10, 95% CI 0.76–1.60), although this estimate is not statistically significant because the confidence interval crosses 1.0. Importantly, heterogeneity is very high ($I^2 = 87.6\%$, $\chi^2 = 40.28$, $p < 0.0001$; $\tau^2 = 0.1883$), and the prediction interval is extremely wide (0.33–3.67), suggesting that the true effect may differ markedly across settings and is highly dependent on the specific fluid comparator, dosing/exposure, and patient context. The overall pooled test is not significant ($Z = 0.50$, $p = 0.62$).

Effects of Corticosteroids on Renal Outcomes

Corticosteroid therapy in septic shock has been extensively studied, with mixed implications for renal outcomes. Prolonged low-dose corticosteroid treatment increased 28-day shock reversal (RR 1.12; 95% CI 1.02-1.23) and reduced ICU length of stay by 4.49 days (95% CI -7.04 to -1.94) without increasing adverse renal events.

The combination of hydrocortisone and fludrocortisone demonstrated reduced 28-day mortality (RR 0.88; 95% CI 0.78-0.99) and improved shock reversal at 28 days (OR 1.06; 95% CI 1.01-1.12). This combination was associated with lower in-hospital mortality (OR 0.86; 95% CI 0.80-0.92) and increased vasopressor-free days.

HAT therapy (hydrocortisone, ascorbic acid, and thiamine) showed no significant difference in new-onset AKI requiring renal replacement therapy (OR 0.856; 95% CI 0.526-1.391). SOFA score improvement was noted (SMD -0.429; 95% CI -0.737 to 0.120) along with reduced vasopressor duration (SMD -0.373; 95% CI -0.619 to -0.128).

Figure 2 illustrates a random-effects forest plot evaluating the effect of corticosteroid therapy on renal outcomes. Only two comparisons contribute to the analysis, with one estimate suggesting no clear benefit (HAT therapy) and the other indicating a small but statistically significant increase in hazard (hydrocortisone–fludrocortisone). The pooled effect shows a modest increase in risk associated with corticosteroids (HR 1.06, 95% CI 1.01–1.12), and the overall effect is statistically significant ($Z = 2.26$, $p = 0.024$). Between-study heterogeneity

Tabel 3. Anticoagulation strategies for CRRT

Anticoagulation	Outcome	Effect	Effect Size (95% CI)
Citrate vs Heparin	Renal function improvement	Better with citrate	Not quantified
Citrate vs Heparin	Filter lifespan	Longer with citrate	WMD 6.93 (6.30-7.55)
Citrate vs Heparin	Bleeding adverse events	Less with citrate	RR 0.14 (0.06-0.32)

is negligible ($I^2 = 0.0\%$, $\chi^2 = 0.76$, $p = 0.38$; $\tau^2 = 0$), but the prediction interval is wide (0.76–1.48), reflecting uncertainty due to the small number of included studies and suggesting that effects may vary in other clinical contexts.

Effects of fluid resuscitation strategies on renal outcomes

Dynamic measures of fluid responsiveness to guide resuscitation demonstrated renal protective effects. A meta-analysis of nine RCTs found that using dynamic measures may reduce the risk of AKI (RR 0.66; 95% CI 0.44-0.98; low certainty) and cumulative fluid balance on day 3 (MD -1.57L; 95% CI -2.44L to -0.69L). A randomized trial found fewer patients required renal replacement therapy in the intervention arm using passive leg raise-guided resuscitation (5.1% vs 17.5%; P = 0.04).

Ultrasound-guided fluid resuscitation was associated with reduced mortality (RR 0.78; 95% CI 0.65-0.94) and 24-hour fluid volume (MD -1.02; 95% CI -1.28 to -0.75), though with increased vasopressor requirements. Inferior vena cava-related measures reduced hospital length of stay (MD -2.91; 95% CI -5.2 to -0.62) and ICU length of stay (MD -2.77; 95% CI -4.51 to -1.02).

Restrictive fluid resuscitation compared to conventional approaches showed no difference in AKI incidence (RR 0.92; 95% CI 0.79-1.07) or ICU mortality (RR 1.00; 95% CI 0.9-1.12). This suggests restrictive strategies may be a safe alternative without increasing renal harm.

Figure 2 presents a random-effects forest plot assessing the impact of fluid resuscitation strategies on renal outcomes. Across studies, strategies emphasizing dynamic, fluid-responsiveness–guided resuscitation and ultrasound-guided approaches generally show hazard ratios below 1.0 compared with conventional care, indicating a trend toward improved renal outcomes. The pooled analysis demonstrates a statistically significant overall benefit (HR 0.82, 95% CI 0.70–0.97). However, between-study heterogeneity is moderate ($I^2 = 41.1\%$, $\chi^2 = 3.40$, $p = 0.18$; $\tau^2 = 0.0083$), suggesting some variability in effect magnitude across protocols and patient contexts. The prediction interval is wide (0.49–1.40), indicating that while the average effect favors these strategies, the true effect in a new setting could range from substantial benefit to no clear advantage. The overall pooled effect remains statistically significant ($Z = -2.35$, $p = 0.019$).

DISCUSSION

This comprehensive synthesis of 80 studies reveals a complex and sometimes contradictory evidence landscape regarding RRT in septic shock. The discussion will interpret these findings, reconcile discrepancies, and explore their clinical implications.

The conflicting results on high-volume hemofiltration (HVHF) are paradigmatic of the challenges in this field. While an early meta-analysis suggested a significant mortality reduction, more recent and methodologically rigorous systematic reviews of RCTs found no benefit of HVHF over standard-volume therapy.[9] This discrepancy may be explained by the inclusion of older studies with methodological limitations and heterogeneous comparators in earlier analyses. Although HVHF was developed based on the premise that enhanced convective clearance could remove circulating inflammatory mediators and attenuate the dysregulated immune response characteristic of septic shock, current evidence suggests that cytokine removal alone is insufficient to alter the complex pathophysiology of sepsis. Septic shock involves multiple interconnected mechanisms, including immune dysregulation, endothelial dysfunction, microcirculatory impairment, mitochondrial injury, and organ cross-talk, many of which are not adequately addressed by increasing filtration intensity alone. Furthermore, higher filtration volumes may lead to unintended consequences such as excessive losses of electrolytes, nutrients, and therapeutic agents, including antibiotics, potentially offsetting any theoretical immunomodulatory benefit. The increased risks of hypophosphatemia, hypokalaemia, and greater resource utilization further limit its routine applicability.[28] Notably, a network meta-analysis by Chen et al. found that any convective therapy was associated with higher mortality compared to standard care, casting doubt on the aggressive use of convection. Therefore, routine

use of HVHF is not supported by current less rigorous studies.[13]

In contrast, certain blood purification techniques targeting specific inflammatory mediators show more promise, albeit with caveats. Polymyxin-B hemoperfusion (PMX-HP) demonstrates a striking regional variation, with significant mortality benefits shown in Asian trials but not in North American or European studies. This suggests that patient factors (e.g., prevalence of gram-negative infections), timing of intervention, and standard care practices significantly modulate its effect. Crucially, its benefit appears confined to patients with intermediate-to-high baseline mortality risk, indicating it is a therapy for selected, sicker populations rather than all-comers.[30] Similarly, CRRT using the adsorptive oXiris filter and CytoSorb hemoadsorption have been associated with reduced mortality and vasopressor needs in meta-analyses.[8] The reported reductions in vasopressor requirements and mortality suggest that these devices may help restore hemodynamic stability in selected patients experiencing hyperinflammatory states. Nevertheless, the current evidence remains limited by the predominance of observational studies and small-scale trials, making it difficult to determine whether the observed benefits are attributable to the devices themselves or to differences in patient selection and concurrent management strategies. Consequently, these therapies should currently be viewed as promising adjunctive interventions rather than standard treatments until validated by adequately powered multicenter randomized controlled trials. In contrast, coupled plasma filtration adsorption (CPFA) has not demonstrated a consistent mortality benefit, suggesting that broader and less targeted removal of inflammatory mediators may be insufficient to improve clinically meaningful outcomes in septic shock.[29]

The debate on early versus late RRT initiation mirrors the intensity debate, with meta-analyses reaching different conclusions. Several studies report significant mortality reductions with early RRT, while others find no significant difference.[7,11,26] This heterogeneity can be largely explained by differences in the included patient populations. Wang et al. identified that that benefits were greatest among patients with KDIGO stage 2 AKI and SOFA scores ≤12 suggests that there may be a therapeutic window during which renal support can alter the course of organ dysfunction. In contrast, initiating RRT too early in patients with mild AKI may expose them to unnecessary complications such as catheter-related infections, bleeding, electrolyte disturbances, and hemodynamic instability, while delaying therapy in patients with advanced multiorgan failure may be insufficient to reverse established injury. These findings indicate that the optimal timing of RRT should not be determined solely by predefined time thresholds but should instead be guided by an individualized assessment of disease severity, organ dysfunction trajectory, fluid balance, and metabolic needs. From a clinical perspective, a personalized approach to RRT initiation is likely more appropriate than a universal early- or late-initiation strategy for all patients with septic shock.[12]

A key strength of this review is its integration of RRT evidence with other critical care decisions. The most consistent finding across high-quality meta-analyses is that vasopressin (or its analogues) reduces the need for RRT compared to norepinephrine alone.[9,21] This renal-protective effect, attributed to vasopressin's preferential vasoconstriction of efferent glomerular arterioles, which helps maintain glomerular filtration pressure, is notable because it occurs without a consistent corresponding reduction in overall mortality.[17,19] This dissociation underscores that mitigating AKI is a valuable goal in itself, improving morbidity and resource use, even if it does not singularly alter the multifaceted pathophysiology of fatal septic shock. The trade-off is an increased risk of digital ischemia, necessitating careful patient selection and monitoring.[19]

Similarly, the choice of resuscitation fluid has a profound impact on renal outcomes. Network meta-analyses provide high-certainty evidence that hydroxyethyl starch (HES) solutions, both heavy and light molecular weight, significantly increase the risk of AKI and the need for RRT compared to balanced crystalloids.[5] HES molecules can accumulate within renal tubular cells, leading to osmotic

nephrosis-like lesions, tubular dysfunction, and impaired renal recovery. HES may exacerbate microcirculatory disturbances and inflammatory responses that are already prominent in septic shock. The consistency of these findings across high-quality meta-analyses suggests that the detrimental renal effects of HES are not merely statistical associations but likely reflect a true pathophysiological effect. From a clinical perspective, this evidence supports the avoidance of HES in septic shock resuscitation, particularly in patients at high risk for AKI. In contrast, balanced crystalloids appear to better preserve renal function by minimizing hyperchloremia and maintaining a more physiological acid–base balance, which may contribute to improved renal perfusion. Although albumin has theoretical advantages related to oncotic support and endothelial stabilization, current evidence does not demonstrate a clear reduction in RRT requirements compared with crystalloids in the general sepsis population. Therefore, balanced crystalloids should remain the preferred first-line resuscitation fluid, while albumin may be reserved for selected clinical situations rather than routine use.[25]

Evidence on corticosteroids presents a more mixed picture for direct renal outcomes. While prolonged low-dose corticosteroids improve shock reversal and may reduce ICU length of stay, they do not appear to significantly increase the risk of AKI requiring RRT. The benefits of prolonged low-dose corticosteroids in accelerating shock reversal are likely mediated through restoration of vascular responsiveness to catecholamines, attenuation of excessive inflammation, and stabilization of endothelial function. However, the absence of a consistent reduction in AKI requiring RRT suggests that improvement in systemic hemodynamics does not necessarily translate into prevention of septic kidney injury, which is driven by multifactorial mechanisms including microcirculatory dysfunction, inflammatory injury, and metabolic disturbances.[27] The hydrocortisone-fludrocortisone combination has shown mortality benefit.[22] However, the HAT therapy bundle (Hydrocortisone, Ascorbic acid, Thiamine) did not significantly affect the incidence of new AKI requiring RRT, though interestingly, thiamine supplementation alone was associated with reduced RRT use and mortality.[17] Thiamine's role in mitochondrial energy metabolism and cellular oxygen utilization, both of which are frequently impaired during septic shock. These findings suggest that future therapeutic strategies should focus on targeting specific pathophysiological pathways rather than broadly combining adjunctive treatments. Furthermore, fluid management strategy matters; using dynamic measures of fluid responsiveness to guide resuscitation may reduce the risk of AKI and fluid overload compared to fixed-volume strategies.[16]

This review is limited by the inherent heterogeneity and varying quality of the included primary studies. Many promising interventions, like novel hemoadsorption devices, lack large, pragmatic RCTs. Future research must prioritize such trials. Furthermore, the field should move towards more personalized medicine approaches, potentially using biomarkers or real-time clinical data to identify which patients are most likely to benefit from specific RRT modalities or timing, and which adjunctive therapies synergize best with renal support to improve overall survival and recovery.

CONCLUSION

This systematic review concludes that renal replacement therapy (RRT) in septic shock should be individualized rather than protocolized: high-volume hemofiltration does not improve mortality and increases complications, while selected blood purification strategies (PMX-B hemoperfusion and adsorptive membranes such as oXiris and CytoSorb) may benefit carefully chosen high-risk patients, although the certainty of evidence remains low. The advantage of "early" RRT is not consistent across all populations but appears most relevant in patients with moderate AKI (KDIGO stage 2) and moderate overall illness severity (SOFA ≤12). Among adjunctive measures, vasopressin is associated with reduced RRT requirements versus norepinephrine alone, balanced crystalloids are preferred, and hydroxyethyl starch should be avoided due to increased AKI and RRT risk; additionally, dynamic fluid responsiveness

assessment may be kidney protective. Accordingly, clinicians should integrate AKI stage and global severity when deciding RRT timing and modality, avoid routine HVHF and HES, and consider early vasopressin where appropriate, while researchers and guideline developers should prioritize high-quality multicenter RCTs and validated biomarkers/algorithms to enable more precise, patient-specific RRT strategies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: A systematic review and meta-analysis. Crit Care. 2019 May 31;23(1):196. doi: 10.1186/s13054-019-2478-6
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock. JAMA. 2016 Feb 23;315(8):775-87. doi: 10.1001/jama.2016.0289
3. Zha J, Li C, Cheng G, Huang L, Bai Z, Fang C. The efficacy of renal replacement therapy strategies for septic-acute kidney injury A PRISMA-compliant network meta-analysis. Medicine (Baltimore). 2019;98(16):e15257. doi: 10.1097/MD.0000000000015257
4. Putzu A, Schorer R, Lopez-Delgado JC, Cassina T, Landoni G. Blood Purification and Mortality in Sepsis and Septic Shock: A Systematic Review and Meta-analysis of Randomized Trials. Anesthesiology. 2019;131(3):580-93. doi: 10.1097/ALN.0000000000002820
5. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. Ann Intern Med. 2014 Sep 2;161(5):347-55. doi: 10.7326/M14-0178
6. Luo Y, Sun G, Zheng C, Wang M, Li J, Liu J, et al. Effect of high-volume hemofiltration on mortality in critically ill patients: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2018 Sep;97(38):e12406. doi: 10.1097/MD.0000000000012406
7. Somaili M. Early versus Delayed Strategies for Renal Replacement Therapy Initiation in Adult Patients with Severe Acute Kidney Injury Complicating Septic Shock: A Systematic Review and Meta-analysis. Saudi J Kidney Dis Transpl. 2022 May-Jun;33(3):449-86. doi: 10.4103/1319-2442.385969
8. Steindl D, Schroeder T, Krannich A, Nee J. Hemoadsorption in the Management of Septic Shock: A Systematic Review and Meta-Analysis. J Clin Med. 2025 Mar 27;14(7):2285. doi: 10.3390/jcm14072285
9. Yusuf AE, He W, YU R, Sun L. Effect of Vasopressin and its Analogs versus Catecholamines on the Renal Outcomes in Septic Shock:A Systematic Review and Meta-Analysis of Randomized Trials. Res Sq. 2021. doi:10.21203/rs.3.rs-779297/v1
10. Wang H, Liu X, Zhang H. Comparison of short-term and long-term renal function effects of vasopressin and norepinephrine in patients with septic shock: a systematic review and meta-analysis. Front Pharmacol. 2025 Nov 18;16:1669636. doi: 10.3389/fphar.2025.1669636
11. Jung Oh H, Su Ku N, Eun Chung Y. MO346: Timing of Renal Replacement Therapy Initiation in Patients With Septic Acute Kidney Injury: A Systematic Review and Meta-Analysis. Nephrology Dialysis Transplantation. 2022;37(Supplement_3). doi:10.1093/ndt/gfac135.001
12. Wang Q, Liu F, Tao W, Qian K. Timing of renal replacement therapy in patients with sepsis-associated acute kidney injury: A systematic review and meta-analysis. Aust Crit Care. 2024 Mar;37(2):369-79. doi: 10.1016/j.aucc.2023.06.011
13. Chen J-J, Lai P-C, Lee T-H, Huang Y-T. Blood Purification for Adult Patients With Severe Infection or Sepsis/Septic Shock: A Network Meta-Analysis of Randomized Controlled Trials. Crit Care Med. 2023 Dec 1;51(12):1777-89. doi: 10.1097/CCM.0000000000005991
14. Oh HJ, Min IK, Roh YH, Kim J ho, Ahn JY, Jeong SJ, et al. Timing of Renal Replacement Therapy Initiation in Patients with Septic Acute Kidney Injury; A Systematic Review and

Meta-Analysis. Res Sq. 2021. doi: 10.21203/rs.3.rs-966692/v1
15. Ge C, Jiang Y, Peng Q, Ai Y. Early versus late initiation of renal replacement therapy impacts mortality in septic patients with acute kidney injury: a meta-analysis. Res Sq. 2020. doi: 10.21203/rs.3.rs-16023/v1
16. Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, et al. Fluid Response Evaluation in Sepsis Hypotension and Shock. Chest. 2020 Oct;158(4):1431-45. doi: 10.1016/j.chest.2020.04.025
17. Sedhai YR, Shrestha D, Budhathoki P, Memon W, Acharya R, Asija A, et al. Vasopressin Versus Norepinephrine as the First-Line Vasopressor in Septic Shock: A Systematic Review and Meta-Analysis. Crit Care Med. 2021;50(1):p762. doi:10.1097/01.ccm.0000812392.83483.a3
18. Bannard-Smith J, Elrakhawy M, Norman G, Owen R, Felton T, Dark P. The efficacy, safety and effectiveness of hyperoncotic albumin solutions in patients with sepsis: A systematic review and meta-analysis. J Intensive Care Soc. 2024 Jun 19;25(3):308-18. doi: 10.1177/17511437241259437
19. Bauer SR, Wieruszewski PM, Bissell Turpin BD, Dugar S, Sacha GL, Sato R, et al. Adjunctive vasopressors and short-term mortality in adults with septic shock: a systematic review and meta-analysis. Shock. 2025 May 1;63(5):668-76. doi: 10.1097/SHK.0000000000002558
20. Huang L, Zhang S, Chang W, Xia F, Liu S, Yang Y, et al. Terlipressin for the treatment of septic shock in adults: a systematic review and meta-analysis. BMC Anesthesiol. 2020 Mar 5;20(1):58. doi: 10.1186/s12871-020-00965-4
21. Nagendran M, Russell JA, Walley KR, Brett SJ, Perkins GD, Hajjar L, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. 2019 Jun;45(6):844-55. doi: 10.1007/s00134-019-05620-2
22. Yamamoto R, Nahara I, Toyosaki M, Fukuda T, Masuda Y, Fujishima S. Hydrocortisone with fludrocortisone for septic shock: a systematic review and meta-analysis. Acute Med Surg. 2020 Sep 1;7(1):e563. doi: 10.1002/ams2.563
23. Roumpf SK, Hunter BR. Does the addition of vasopressin to catecholamine vasopressors affect outcomes in patients with distributive shock? Ann Emerg Med. 2019;74(1):153–5. doi: 10.1016/j.annemergmed.2018.10.001
24. Bhattacharjee A, Datta PK, Kumar V, Ravikumar RH, Sathe P, Kundu R. Timing of Vasopressin Initiation in Patients with Septic Shock: An Updated Systematic Review and Meta-analysis with Trial Sequential Analysis. J Crit Care Med. 2025 Oct;29(10):839-50. doi: 10.5005/jp-journals-10071-25054
25. Thompson BT. In patients with severe sepsis, adding albumin to crystalloid solution did not reduce 28- or 90-day mortality. Ann Intern Med. 2014;161(2):JC6. doi: 10.7326/0003-4819-161-2-201407150-02006
26. Li Y, Li H, Zhang D. Timing of continuous renal replacement therapy in patients with septic AKI. Medicine (Baltimore). 2019;98(33):e16800. doi: 10.1097/MD.0000000000016800
27. Rygård SL, Butler E, Granholm A, Møller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2018;44(7):1003-16. doi: 10.1007/s00134-018-5197-6
28. Oudemans-van Straaten HM, Elbers PW. How to explain and exploit the beneficial effects of high-volume hemofiltration on hemodynamics and strong ion gap. Intensive Care Med. 2013;39(6):1140–2. doi:10.1007/s00134-013-2820-4
29. Li Y, Li H, Guo J, Wang Y, Zhang D. Coupled plasma filtration adsorption for the treatment of sepsis or septic shock: a systematic review and meta-analysis. BMC Infect Dis. 2022;22(1):714. doi: 10.1186/s12879-022-07689-5
30. Chang T, Tu Y-K, Lee C-T, Chao A, Huang C-H, Wang M-J, et al. Effects of Polymyxin B Hemoperfusion on Mortality in Patients With Severe Sepsis and Septic Shock: A Systemic Review, Meta-Analysis Update, and Disease Severity Subgroup Meta-Analysis. Crit Care Med. 2017 Aug;45(8):e858-e864. doi: 10.1097/CCM.0000000000002362