Fluid Resuscitation in Sepsis and Septic Shock; What to Give and How Much to Give: A Systematic Review of Randomized Controlled Trials

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Introduction. The optimal composition and volume of intravenous fluids for sepsis resuscitation remain uncertain. We conducted a systematic review focused on two core questions: what fluid to administer and how much to give in adult sepsis and septic shock.
Methods. We searched PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for randomized controlled trials published from January 2020 to September 2025. Eligible trials enrolled adults with sepsis or septic shock and compared either fluid composition (e.g., balanced crystalloids, saline, albumin, plasma) or resuscitation volume/strategy (restrictive versus liberal or protocolized versus usual care). Two reviewers screened and extracted data; risk of bias was assessed using RoB 2. Owing to clinical heterogeneity and overlapping parent datasets, findings were synthesized qualitatively.
Results. We identified contemporary multicenter RCTs and prespecified or post hoc analyses spanning ED and ICU settings. Balanced crystalloids consistently reduced hyperchloremic acidosis and showed context-dependent signals for improved short-term outcomes versus saline; absolute mortality effects were modest. Albumin and plasma-based strategies produced transient physiologic gains without durable outcome benefits. Large trials comparing volume strategies (CLASSIC, CLOVERS) showed no overall mortality difference despite approximately two liters less fluid and earlier vasopressors in restrictive arms. Subgroup data suggested advantage for restrictive, vasopressor-prioritized care in advanced chronic kidney disease, while mechanistic sub-studies demonstrated no adverse effects on cardiac strain or endothelial glycocalyx. Feasibility trials targeting non-resuscitation fluids reduced administered volumes without safety concerns.
Conclusions. Current randomized evidence supports balanced crystalloids as default resuscitation fluids and indicates that clinically guided restrictive strategies are generally as safe as liberal ones, with potential benefit in fluid-intolerant phenotypes. Effectiveness depends less on a fixed fluid or volume and more on timing, patient context, and physiologic tolerance, reinforcing the paradigm of precision fluid therapy.

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INTRODUCTION

In the era of precision medicine, fluid resuscitation in sepsis and septic shock remains a paradoxical challenge. Despite decades of research, uncertainty persists regarding the optimal type, volume, and timing of fluid administration. Sepsis continues to impose a substantial global health burden, with approximately 48.9 million cases and 11 million deaths reported in 2017.[1] The age-standardized incidence has been estimated at 677 cases per 100,000 people, and mortality remains significantly higher in low- and middle-income countries compared with high-income regions.[1] These figures highlight that, despite scientific progress, sepsis remains one of the deadliest syndromes worldwide, underscoring the urgent need for more effective fluid resuscitation strategies.

At the dawn of the 21st century, Rivers *et al.* introduced the concept of Early Goal-Directed Therapy (EGDT). In this landmark trial, aggressive fluid administration during the first six hours of management significantly reduced mortality (from 46.5 to 30.5%) among patients with severe sepsis and septic shock.[2] This success led to the incorporation of high-volume fluid administration as a standard of care in international guidelines. However, subsequent multicenter studies yielded conflicting results and demonstrated that excessive fluid loading may cause volume overload and secondary complications. Consequently, the debate over the type, volume, and timing of resuscitation fluids remains ongoing.

The international Surviving Sepsis Campaign (SSC) continues to recommend an initial bolus of 30 mL/kg of crystalloids for patients with hypotension or elevated lactate levels. Nevertheless, this recommendation is supported by low-to-moderate quality evidence, and many experts now advocate for a more tailored approach. Intravenous fluids should be prescribed with the same rigor as pharmacologic agents (guided by the four principles of drug, dose, duration, and de-escalation) and adapted to the four dynamic phases of the ROSE model (Resuscitation, Optimization, Stabilization, and Evacuation). According to this model, fluid therapy should be adjusted to the phase of shock and patient-specific characteristics, replacing the outdated "one-volume-fits-all" paradigm with a phase-based, individualized strategy.[3]

Over the past five years, a new wave of large-scale randomized controlled trials—including ANDROMEDA-SHOCK,[4] BaSICS,[5] PLUS,[6] CLASSIC,[7] and CLOVERS;[8] has redefined the landscape of fluid resuscitation research in sepsis. These landmark studies have stimulated a gradual shift toward more individualized and physiology-informed approaches, challenging the traditional concept of uniform fluid administration. Yet, beyond these high-profile trials, numerous other RCTs have been conducted within the same period, each exploring different aspects of fluid type, timing, and hemodynamic endpoints. A comprehensive and comparative analysis of these studies is now essential to integrate their findings into a coherent framework and to achieve a clearer, evidence-based perspective on optimal fluid resuscitation strategies in septic patients. This growing body of evidence has not only reshaped trial-based understanding but has also deepened the physiologic perspective of fluid resuscitation.

Emerging physiologic concepts such as fluid responsiveness and fluid tolerance have further advanced this field. Clinicians are now encouraged to not only evaluate whether a patient will augment cardiac output following a fluid bolus but also to assess venous congestion as an indicator of intolerance. A 2024 multicenter proof-of-concept study demonstrated that venous congestion can coexist with fluid responsiveness, highlighting the need to balance perfusion optimization against the risk of interstitial edema and organ dysfunction. This integrative perspective reflects a nuanced evolution: fluid resuscitation should no longer be guided by static targets or rigid protocols but rather by individualized hemodynamic assessments and context-specific thresholds.[9]

Despite decades of research, the optimal composition and volume of intravenous fluids for sepsis resuscitation remain uncertain. This systematic review aimed to synthesize evidence from randomized controlled trials published between 2020 and 2025 investigating intravenous fluid resuscitation in adult patients with sepsis and septic shock. The review focused on two principal questions, what type of fluid to administer and how much fluid to give; to clarify how recent

evidence has shaped current understanding and practice of fluid therapy in sepsis.

MATERIALS AND METHODS

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[10]

Search Strategy

A comprehensive literature search was performed in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov to identify randomized controlled trials (RCTs) investigating fluid resuscitation in adult patients with sepsis or septic shock. The search covered publications from January 2020 to September 2025. Keywords and MeSH terms included combinations of: "sepsis", "septic shock", "fluid resuscitation", "intravenous fluids", "crystalloids", "colloids", "fluid restriction", "fluid balance", and "randomized controlled trial"; using Boolean operators (AND, OR, NOT) to optimize retrieval. Reference lists of included trials and relevant reviews were also screened to identify additional studies.

Eligibility Criteria

Eligible studies were randomized controlled trials enrolling adult patients aged 18 years or older with sepsis or septic shock who received intravenous fluid resuscitation. Trials were included if they investigated either the composition of fluids, such as crystalloids, colloids, or albumin, or the resuscitation volume and strategy, including restrictive versus liberal or protocolized versus usual care approaches. Comparators included standard care or alternative fluid regimens, and eligible outcomes encompassed mortality, hemodynamic parameters, organ dysfunction, renal outcomes, and other clinically relevant endpoints. Studies were excluded if they were non-randomized, conducted in pediatric populations, or designed as observational studies, case series, editorials, conference abstracts, or narrative reviews, or if they lacked primary data or did not specifically evaluate intravenous fluid resuscitation in sepsis.

Data Extraction

Two independent reviewers screened the titles and abstracts, followed by full-text assessment for eligibility. Data were extracted using a standardized template, capturing: first author, year, country, setting, sample size, intervention and comparator details, primary outcome, and key findings. Discrepancies were resolved by consensus with a third reviewer.

Quality Assessment

The methodological quality and risk of bias of included RCTs were appraised using the Cochrane Risk of Bias 2 (RoB 2) tool.[11] Each study was evaluated across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Disagreements were resolved by discussion among the authors.

Data Synthesis

Given the heterogeneity in interventions and outcome measures, a qualitative (narrative) synthesis was performed. The included studies were organized around two core domains of fluid therapy: fluid type ("What to give") and fluid volume or strategy ("How much to give"), with comparative analysis of clinical outcomes.

RESULTS

Our search identified contemporary randomized evidence on fluid resuscitation in adult sepsis and septic shock across ED and ICU settings from 2020 to 2025. We included pivotal multicenter RCTs comparing restrictive versus liberal or standard volume strategies (CLASSIC and CLOVERS) and feasibility trials targeting non-resuscitation or early ED restriction, alongside prespecified and post hoc analyses that interrogated phenotype-specific effects, endothelial and cardiac physiology, lactate kinetics, and site-level practice intensity. In parallel, we included RCTs and secondary analyses evaluating fluid composition, chiefly balanced crystalloids versus saline, albumin strategies, and plasma-based products. Across studies, primary outcomes were predominantly 90-day mortality and patient-centered days alive outcomes, with physiologic endpoints such as acid–base status,

microcirculation, glycocalyx biomarkers, and echocardiographic strain used in mechanistic sub-studies. Risk of bias by RoB-2 was generally low or raised some concerns mainly due to open-label designs and treatment cross-over; randomization and outcome measurement were usually low risk. Given heterogeneity in interventions, endpoints, and overlapping parent datasets (e.g., multiple CLOVERS and CLASSIC sub-studies), we performed a qualitative synthesis without meta-analysis.

DISCUSSION

The contemporary era of sepsis resuscitation was ushered in at the turn of the millennium, when Rivers and colleagues introduced EGDT.[2] This protocolised approach emphasised aggressive fluid resuscitation within the first six hours and dramatically reduced mortality. The success of EGDT led to widespread adoption of high-volume fluid administration, yet subsequent trials revealed that unchecked fluid loading causes volume overload and secondary complications. As evidence grew, clinicians began to treat intravenous fluids as potent therapeutics requiring stewardship; Malbrain *et al.* formalised this view by introducing the "four D's" (drug, dose, duration and de-escalation) and four phases (resuscitation, optimization, stabilization and evacuation) of fluid therapy.[12]

This framework evolved as newer reviews highlighted that each phase of ROSE requires distinct tactics: after an initial bolus (e.g., 30 mL/kg over three hours), further resuscitation should be guided by dynamic assessments, and later phases focus on fluid minimization and active de-resuscitation with diuretics or ultrafiltration.[13] Chen *et al.*'s 2025 narrative review underscored that the evacuation phase (first proposed in 2013) must be integrated throughout shock management to reverse fluid accumulation.[14] Positive fluid balance is consistently associated with organ dysfunction and mortality, reinforcing the need for judicious fluid removal.[15]

Physiologic understanding has also expanded from mere fluid responsiveness to include fluid tolerance and venous congestion. Traditionally, any rise in cardiac output after a preload challenge justified further fluids; however, Kattan *et al.* defined "fluid tolerance" as the volume a patient can receive without organ injury.[16] This concept bridges the gap between responsiveness and fluid overload and balances arterial flow gains against venous congestion. A 2024 multicenter study found that markers of venous congestion often coexist with fluid responsiveness in mechanically ventilated septic patients, implying that clinicians must assess both responsiveness and tolerance (using tools like passive leg raise tests and venous ultrasound) to avoid worsening organ congestion.[9,17]

This paradigm shifts from liberal, protocol-driven resuscitation to deliberately constrained, physiology-guided therapy challenges long-held assumptions and compels us to rethink our practice. Integrating the ROSE phases, the four-D stewardship principles and emerging ideas such as fluid tolerance and venous congestion marks only the beginning of this evolution. The real questions now lie ahead: which fluids truly matter, how much volume is enough, how should we titrate therapy and what endpoints should guide us, and when must we initiate or stop fluid administration? The following sections dissect these critical issues through the lens of recent clinical trials, tracing a roadmap toward precision fluid therapy in sepsis.

Fluid Composition: What to Give?

Fluid choice in sepsis resuscitation remains one of the most debated and clinically consequential questions in critical care. Early goal-directed therapy and the Surviving Sepsis Campaign guidelines positioned crystalloids as the first-line fluid for initial resuscitation, yet the fundamental question persists: does the type of fluid meaningfully alter patient outcomes, or are these differences largely physiologic rather than survival-defining? The answer requires integrating data from modern randomized controlled trials and meta-analyses, as summarized in Table 1, which compares recent trials published between 2021 and 2025.

Balanced Crystalloids Versus Saline

Over the past decade, multiple landmark trials have compared balanced solutions (such as lactated Ringer's and Plasma-Lyte) with 0.9% saline. Collectively, evidence trends in favour of balanced crystalloids, although absolute survival benefit remains modest and context-dependent.

Table 1. Comparative Evidence from Randomized Controlled Trials on Fluid Type and Composition in Sepsis Resuscitation

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Cusack et al.	2025	Ireland	ICU	103	20% Albumin (100 mL boluses to clinical effect)	Crystalloid	Change in microvascular density and flow at 15 min and 60 min (SDF imaging)	Albumin significantly improved microvascular density and flow at 15 and 60 min (P < 0.005) compared with crystalloids, without differences in fluid balance, vasopressor use, ICU stay, or mortality—suggesting selective benefit for microcirculatory optimization.	(18)
Gelbenegger et al.	2025	USA	ICU and ED	1563	Lactated Ringer's solution (≥95% of pre-randomization fluid)	0.9% Normal Saline	90-day mortality	In this secondary analysis of the CLOVERS trial, initial resuscitation with lactated Ringer's reduced 90-day mortality compared with saline (12.2% vs 15.9%; adjusted HR = 0.71, 95% CI 0.51–0.99; P = 0.043) and increased hospital-free days (adjusted mean difference = 1.6 days; P = 0.009). Patients receiving saline had higher chloride and lower bicarbonate levels, suggesting a possible role of balanced crystalloids in mitigating hyperchloremic acidosis.	(19)
Williams et al.	2025	Australia	ED	464	400 mL 20% Albumin + standard crystalloids	Standard crystalloids only	SBP at 24 hours	Early administration of concentrated albumin did not improve SBP at 24 h (mean 110.5 vs 110 mmHg), but increased SBP at 6 h, reduced total fluid volume and vasopressor use, and improved organ function scores without affecting mortality—suggesting feasibility and potential physiologic benefit warranting larger trials.	(20)
Zhang et al.	2024	China	ICU	143	Ringer's acetate solution (RAS)	Normal saline solution (NSS)	MAKE28 (Major Adverse Kidney Events within 28 days)	No significant difference in MAKE28 (23.3% vs 20.0%, OR 1.2, P = 0.69). Patients in the NSS group had longer mechanical ventilation duration (P = 0.04) and higher incidence of hyperchloremia (P = 0.03). No differences were found in mortality, AKI, or RRT—suggesting physiologic but not outcome-level advantages of balanced solutions over saline.	(21)
Gray et al.	2024	UK	ED	300	5% Human Albumin Solution (HAS)	Balanced crystalloids (Plasma-Lyte)	Recruitment rate and 30-day mortality	In this multicenter feasibility RCT, 5% HAS showed no clinical advantage over balanced crystalloids. Thirty-day mortality was numerically higher with HAS (21.1% vs 14.8%; adjusted OR 1.50, 95% CI 0.84–2.83). No differences were seen in ICU or hospital LOS, while critical care interventions and complications were less frequent in the crystalloid group. Findings suggest feasibility but no outcome benefit for albumin as a primary resuscitation fluid.	(22)
Clausen et al.	2024	Denmark	ICU	44	OctaplasLG® (pathogen-inactivated pooled plasma)	Ringer's acetate	Change in endothelial biomarkers and microvascular perfusion (baseline–24 h)	No significant improvement in microvascular perfusion or most endothelial biomarkers. VEGFR1 increased with OctaplasLG while it decreased with Ringer's acetate (mean diff = 0.36; P = 0.003). Patients receiving OctaplasLG had fewer CRRT-free days (P = 0.015). Fluid resuscitation with plasma was feasible but did not improve endothelial integrity or clinical outcomes.	(23)

Table 1. Continued

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Maiwall et al.	2022	India	Liver ICU and ED	100	20% Albumin (0.5–1.0 g/kg over 3 h)	Plasma-Lyte (30 mL/kg over 3 h)	Reversal of hypotension (MAP >65 mmHg at 3 h)	20% albumin achieved target MAP more frequently (62% vs 22%; P < 0.001) and showed faster lactate decline (P = 0.03), with modest renal benefits but no difference in 28-day mortality (58% against 62%). Pulmonary complications were more frequent, requiring discontinuation in 22% of albumin-treated patients. Albumin improved hemodynamics but at the cost of increased adverse effects.	(24)
Zampieri et al.	2022	Brazil	ICU	10520	Balanced crystalloid (Plasma-Lyte 148)	0.9% saline (saline-only, mixed, or none pre-enrollment)	90-day mortality	In this post hoc analysis of the BaSICS trial, balanced crystalloids showed a low overall probability of mortality benefit (OR = 0.95; 89% CrI 0.66–1.51; probability = 0.58). However, patients who had received only balanced fluids before enrollment demonstrated a higher probability of survival benefit (OR = 0.78; CrI 0.56–1.03; probability = 0.92), particularly among unplanned septic admissions (OR = 0.70; CrI 0.50–0.97; probability = 0.96). These findings suggest pre-randomization fluid type may modulate treatment effect.	(25)
Cortegiani et al.	2021	Italy	ICU	304	20% Albumin (target ≥30 g/L) + crystalloid	Crystalloid alone	90-day mortality	In this ALBIOS secondary analysis of immunocompromised septic patients, albumin replacement (HR 0.94; 95% CI 0.69–1.29) did not reduce 90-day or 28-day mortality, nor improve SOFA scores, renal outcomes, or length of stay. Albumin showed no independent association with survival, supporting neutral effects in this subgroup.	(26)
Jackson et al.	2021	USA	ICU and ED	1641	Balanced crystalloids (Lactated Ringer's or Plasma-Lyte A)	0.9% Normal Saline	30-day in-hospital mortality	In this secondary analysis of the SMART trial, balanced crystalloids reduced 30-day mortality when fluid choice was controlled from both the ED and ICU (24.9% vs 30.6%; OR 0.68, 95% CI 0.52–0.89). No mortality difference was seen when fluids were controlled only in the ICU. Balanced fluids also increased ICU-, ventilator-, and vasopressor-free days, emphasizing the benefit of early initiation of balanced crystalloids in sepsis resuscitation.	(27)

Secondary analyses from large pragmatic trials, including SMART and BaSICS, demonstrated that balanced crystalloids may reduce mortality when administered consistently from the emergency department through the ICU phase.[25,27] The CLOVERS secondary analysis confirmed this finding, showing that initial resuscitation with lactated Ringer's reduced 90-day mortality compared with saline (12.2 vs. 15.9%; adjusted HR = 0.71, 95% CI: 0.51 to 0.99; P = .043) and increased hospital-free days.[19] Similarly, the SMART analysis by Jackson *et al.* reported lower 30-day mortality when balanced crystalloids were initiated early, emphasizing that timing of administration is as crucial as fluid composition.[27] By contrast, the post-hoc BaSICS analysis found no overall mortality difference but identified a higher probability of benefit among patients who had received only balanced fluids before enrollment (OR = 0.78, CrI: 0.56 to 1.03), especially in unplanned septic admissions.[25] This observation highlights that pre-randomization fluid exposure can modulate treatment effect, a pattern mirrored across several studies in Table 1. Smaller RCTs further clarified physiologic effects; Zhang *et al.* (2024) showed that patients resuscitated with saline developed more hyperchloremia and required longer mechanical ventilation without mortality differences.[21] Collectively, these findings suggest that balanced crystalloids may not dramatically alter survival but consistently confer acid–base and renal advantages.

Meta-analytic data reinforce these trends. A 2025 network meta-analysis including 28 888 patients ranked balanced crystalloids highest for reducing all-cause mortality (SUCRA = 83%), outperforming saline (SUCRA ≈ 43%) and starch-based colloids.[28] Another 2022 systematic review and meta-analysis of 15 RCTs (20329 patients) likewise found reduced overall and 28/30-day mortality (RR = 0.88, 95% CI: 0.81 to 0.96) and lower acute kidney injury (RR = 0.85, 95% CI: 0.77 to 0.93) with balanced crystalloids.[29] However, neither analysis demonstrated a consistent benefit for 90-day mortality or renal replacement therapy, indicating that improvements are predominantly physiologic and short-term. Meanwhile, the FLUID cluster-randomized trial (> 43000 hospitalized patients) found no significant difference in mortality or dialysis between hospitals primarily using lactated Ringer's and those using saline.[30] Yet, because only ≈ 15% of participants were ICU patients and adherence to the lactated Ringer's protocol was incomplete, the trial likely diluted any treatment effect.

Despite near-equipoise in these large pragmatic studies, balanced crystalloids consistently reduce hyperchloremic metabolic acidosis, a mechanism associated with renal vasoconstriction and dysfunction. Consequently, current sepsis guidelines continue to favour balanced crystalloids as first-line resuscitation fluids.

Albumin and Other Colloids

The rationale for albumin administration derives from its oncotic properties and theoretical ability to restore the endothelial glycocalyx. Recent evidence, however, paints a nuanced picture.

As summarized in Table 1, Cusack *et al.* (2025) demonstrated that 20% albumin improved sublingual microvascular density and flow at 15 and 60 min versus crystalloids, but had no impact on vasopressor requirement, ICU stay, or mortality.[18] Similarly, Williams *et al.* (2025) reported improved short-term hemodynamics and reduced vasopressor use, yet no sustained blood-pressure or survival benefit.[20] In cirrhotic septic patients, Maiwall *et al.* (2022) showed that 20% albumin achieved faster lactate clearance and earlier reversal of hypotension than Plasma-Lyte but increased pulmonary complications and did not improve 28-day survival.[24] The Cortegiani *et al.* (2021) sub-analysis of ALBIOS similarly found albumin to be outcome-neutral in immunocompromised patients.[26]

Synthesizing these data, albumin appears to produce transient physiologic gains without durable survival benefit. The 2025 network meta-analysis ranked iso-oncotic albumin second to balanced crystalloids for mortality (SUCRA ≈ 71%), but credible intervals overlapped.[28] High cost, monitoring burden, and risk of pulmonary edema continue to restrict albumin use to select phenotypes (e.g., cirrhosis, severe hypoalbuminemia).

Plasma-based and Novel Fluids

Attempts to repair endothelial injury through

Table 2. Comparative Evidence from Randomized Controlled Trials on Fluid Volume and Resuscitation Strategies in Sepsis and Septic Shock

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Sivapalan et al.	2025	Denmark	ICU	1366	Restrictive IV fluid therapy	Standard IV fluid therapy	90-day mortality	Secondary analysis of the CLASSIC trial using machine-learning–derived site intensity subgroups. Across five subgroups with varying standard-fluid volumes, restrictive and standard strategies yielded comparable 90-day mortality, SAEs, DAWOLS, and DAOH. No dose-response relationship was observed, suggesting that baseline variation in standard fluid intensity did not modify the treatment effect of fluid restriction.	(38)
Oshima et al.	2025	USA	ED, ICU, mixed hospital settings	574	Liberal crystalloid resuscitation strategy	Restrictive crystalloid resuscitation strategy	90-day mortality	Secondary biomarker analysis of the CLOVERS trial evaluating endothelial glycocalyx degradation (plasma heparan sulfate, syndecan-1). Higher baseline heparan sulfate strongly predicted mortality (adjusted HR 3.12, 95% CI 2.18–4.46), but assigned fluid strategy did not affect glycocalyx degradation or modify mortality across tertiles. Findings indicate that endothelial injury predicts outcome but is not altered by resuscitation volume.	(33)
Ahlstedt et al.	2024	Multinational (19 ICU sites)	ICU	777	Restrictive IV fluid strategy	Standard IV fluid therapy	Time to resolution of hyperlactatemia (within 72 h)	Post hoc analysis of CLASSIC participants with serial lactate data. Restrictive strategy did not significantly affect time to lactate normalization compared with standard care (HR 0.94 at day 1; 1.21 at days 2–3; both NS). Findings suggest that fluid restriction does not delay metabolic recovery in septic shock.	(39)
Lanspa et al.	2024	USA	ICU and ED	131	Restrictive fluid + vasopressor-priority strategy	Liberal fluid strategy	Left ventricular global longitudinal strain (LV GLS)	Prospective echocardiographic substudy of the CLOVERS trial. No significant differences between groups in LV GLS (coef. 1.22, P = 0.23), ΔLV GLS (–1.97, P = 0.27), or right ventricular free-wall longitudinal strain (P = 0.19). Restrictive fluid resuscitation did not impair short-term cardiac function.	(32)
Lindén A et al.	2024	Sweden	ICU	92	Protocolized restriction of non-resuscitation fluids	Usual care	Total IV fluid volume within 3 days of randomization	Median total fluid at 72 h was 6008 mL (IQR 3960–8123) vs 9765 mL (IQR 6804–12,401) in controls (P < 0.001), a reduction of ~3.6 L. No differences in 90-day mortality, ventilator-free days, or AKI events. Demonstrated feasibility of targeting non-resuscitation fluid reduction in septic shock.	(35)
Jorda et al.	2024	USA	ICU and ED	196	Restrictive fluid strategy with early vasopressor prioritization	Liberal fluid strategy	90-day all-cause mortality before discharge home	Restrictive fluid group had significantly lower mortality (21.7% vs 39.4%; HR 0.50, 95% CI 0.29–0.85; P = 0.009), more vasopressor-free days (mean diff +4.3; P = 0.01), and more ventilator-free days (mean diff +4.5; P = 0.015). Findings suggest benefit of conservative resuscitation in advanced CKD patients.	(31)
Shapiro et al.	2023	USA	ICU and ED	1563	Restrictive fluid strategy with early vasopressor prioritization	Liberal fluid strategy	90-day all-cause mortality before discharge home	No significant difference in 90-day mortality (14.0% vs 14.9%; P = 0.61). Restrictive group received 2.1 L less fluid and had earlier, longer vasopressor use. No significant differences in ventilator-, vasopressor-, or RRT-free days, nor in serious adverse events.	(8)

Table 2. Continued

First author	Year	Country	Setting	N	Intervention	Comparator	Primary outcome	Key results	R
Boulet et al.	2023	France	ICU	48	Restrictive fluid strategy targeting reduced maintenance and drug-dilution fluids	Standard fluid strategy	Cumulative fluid balance over first 5 days	Optimized restrictive protocol reduced total fluid intake modestly (mean diff −35.9 mL/kg; P = 0.05) but did not significantly change fluid balance, organ failure, LOS, or 28-day survival. Demonstrated safety and feasibility of stricter fluid limitation early in septic shock.	(34)
Jessen et al.	2022	Denmark	ED	123	Restrictive IV crystalloid strategy (boluses only if hypoperfusion criteria met)	Standard care (discretionary fluids)	Total IV crystalloid volume at 24 h post-randomization	Restrictive group received significantly less IV fluid (562 ± 1076 mL vs 1370 ± 1438 mL; mean diff −801 mL, 95% CI −1257 to −345; P = 0.001). No differences in adverse events, AKI, ventilation, vasopressor use, or mortality. Demonstrated feasibility and safety of restrictive fluid administration in non-shock sepsis.	(36)
Meyhoff et al.	2022	Multinational study (across Europe)	ICU	1544	Restrictive IV fluid therapy	Standard IV fluid therapy	90-day mortality	No significant difference in 90-day mortality (42.3% vs 42.1%; adj. diff 0.1%, 95% CI −4.7–4.9; P = 0.96). Serious adverse events and days alive without life support or out of hospital were similar. Restrictive strategy reduced cumulative fluid volumes (median 1.8 L vs 3.8 L) without increasing harm.	(7)
Semler et al.	2020	USA	ICU	30	Conservative fluid management protocol (restricted fluids + loop diuretic to maintain neutral balance)	Usual care	Mean daily fluid balance (Phase II) and ICU-free days (Phase III)	Conservative strategy did not achieve ≥ 500 mL/day reduction in mean fluid balance (−398 mL vs target −500 mL); cumulative input/output similar between groups. Hemodynamic, renal, and respiratory outcomes were comparable, confirming feasibility but limited efficacy.	(37)

plasma-derived or glycocalyx-restoring solutions have been largely unsuccessful. In the Clausen *et al.* (2024) phase IIa trial, pathogen-inactivated pooled plasma (OctaplasLG) did not improve endothelial biomarkers or sublingual microcirculation; VEGFR1 levels rose, and patients had fewer CRRT-free days.[23] Likewise, Gray *et al.* (2024) found that 5% human albumin offered no clinical advantage over balanced crystalloids and was associated with numerically higher 30-day mortality.[22] Together, these findings show that plasma-based fluids remain feasible but not superior, echoing the prior withdrawal of starch and gelatin colloids due to renal injury and coagulopathy.

Volume and Strategy: How Much to Give?

Determining the optimal volume of intravenous fluids in sepsis remains one of the most contentious questions in critical care. For decades, aggressive fluid loading was equated with effective resuscitation, yet evidence now underscores that excess volume may induce venous congestion, organ edema, and delayed recovery.

Modern randomized trials have shifted this paradigm toward physiologic restraint. Both the CLASSIC and CLOVERS trials showed no significant mortality difference between restrictive and liberal fluid strategies despite a two-liter gap in cumulative volumes.[7,8] This neutrality implies that within a clinically reasonable range, how much fluid is given may matter less than when, to whom, and under what physiologic guidance it is administered. Recent analyses have refined these findings by identifying subgroups in whom fluid intensity may have distinct consequences. Restrictive approaches appear beneficial in patients with impaired renal clearance,[31] while no adverse cardiac[32] or endothelial[33] effects have been linked to early vasopressor prioritization. Conversely, smaller feasibility trials focusing on post-resuscitation or non-resuscitation fluids reveal that much of avoidable overload occurs beyond the initial shock phase.[34,35]

Collectively, these insights mark a conceptual evolution from fixed-volume resuscitation to individualized fluid stewardship. The future of sepsis management lies in tailoring volume therapy to dynamic hemodynamics, tolerance thresholds, and recovery phases. Liberal and restrictive strategies can both be safe when applied judiciously, yet precision remains the true determinant of efficacy.[36,37]

CONCLUSIONS

Over the past five years, the landscape of sepsis fluid resuscitation has transitioned from uniform, protocol-driven practice to a nuanced, evidence-informed science. Across randomized controlled trials, balanced crystalloids have consistently emerged as the most physiologically favorable resuscitation fluid, mitigating hyperchloremic acidosis and preserving renal function without incurring additional risk. Nonetheless, their superiority over saline in terms of mortality remains modest. Albumin and plasma-derived solutions may offer transient hemodynamic or endothelial benefits but have not demonstrated sustained outcome advantages, confining their role to selected clinical phenotypes rather than routine use.

Regarding fluid volume and strategy, recent multicenter trials such as CLASSIC and CLOVERS confirm that restrictive and liberal regimens achieve comparable survival, provided they are guided by continuous hemodynamic assessment. Restrictive approaches appear especially advantageous in patients with impaired renal clearance, while early vasopressor prioritization has not been associated with adverse cardiac or endothelial effects.

Taken together, current evidence underscores that the efficacy of fluid therapy in sepsis depends less on the specific fluid or absolute volume administered than on timing, patient context, and physiologic tolerance. The future of sepsis resuscitation lies in precision fluid therapy—a dynamic, patient-centered approach integrating advanced hemodynamic monitoring, endothelial biomarkers, and real-time decision support. In this evolving paradigm, the goal is no longer to give more or less, but to give appropriately—the right fluid, in the right amount, at the right time, for the right patient.

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Ethical Considerations

As this study is a secondary analysis of previously published data, no ethical approval or patient consent was required.

Conflicts of Interest

Ilad Alavi Darazam and Amir Ahmad Nassiri are a member of the editorial team of RJCCN. The authors have no involvement in the peer-review or editorial decision-making process for this manuscript.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the study and approved the final version of the manuscript.

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