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Goal-Directed Fluid Therapy in Sepsis and Septic Shock: A Review of Current Therapeutic Strategies and Outcomes

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Abstract

Introduction and purpose: Sepsis induces profound microvascular derangements, making prompt fluid resuscitation a management cornerstone. Historically guided by Early Goal-Directed Therapy (EGDT), landmark trials have refuted EGDT's rigidity, driving a shift toward individualized hemodynamics. The purpose of this review is to systematically evaluate goal-directed fluid therapy in septic shock, contrasting fluid composition, timing, and volume dosing to delineate clinical strategies that optimize survival.

Description of the state of knowledge: Guidelines recommend crystalloids as first-line therapy and restrict synthetic colloids due to severe acute kidney injury (AKI) risks. Balanced crystalloids demonstrate marginal or comparable efficacy in reducing mortality rates relative to normal saline, the administration of which is often associated with the development of hyperchloremic metabolic acidosis. Hyperoncotic albumin appears to mitigate the risk of renal injury. The 30 mL/kg fluid mandate faces scrutiny, as non-individualized dosing may increase the risk of severe fluid overload. Current management utilizes the ROSE framework, favoring restrictive strategies and de-escalation. Obese patients require Ideal Body Weight dosing to prevent miscalculations.

Summary: Meticulous fluid stewardship is essential to mitigate organ failure and maximize survival. Dynamic physiological indices outperform static parameters in predicting fluid responsiveness. Integrating personalized targets like capillary refill time normalization improves clinical outcomes. Individualized resuscitation appears to mitigate pathological venous congestion, which is often associated with improved long-term prognostic benefits.
Keywords: Fluid Therapy; Septic Shock; Sepsis; Resuscitation; Hemodynamics.

Introduction and purpose

Sepsis is defined by the Third International Consensus (Sepsis-3) as a life-threatening organ dysfunction resulting from a dysregulated host immune response to infection 33. A comprehensive analysis from the Global Burden of Disease Study estimated 48.9 million incident cases of sepsis and 11.0 million sepsis-related deaths globally in 2017, accounting for nearly 20% of all global deaths 21. Hospital-acquired (HA) and intensive care unit-acquired (ICU) sepsis contribute significantly to this burden, with the mortality of ICU patients experiencing HA sepsis with organ dysfunction exceeding 52% 15. At the microcirculatory level, sepsis induces profound vascular changes, including capillary leakage, venodilation, and degradation of the endothelial glycocalyx layer, leading to absolute and relative hypovolemia 28, 30. Consequent tissue hypoxia may persist despite macro-hemodynamic improvements due to underlying mitochondrial dysfunction and microvascular failure 27. Therefore, fluid resuscitation is a cornerstone of initial management, aimed at restoring intravascular volume, improving cardiac output, and optimizing cellular oxygen delivery 17, 28.

Over the past two decades, the scientific community has sought to optimize fluid resuscitation protocols through extensive clinical research 3, 10. Historically, fluid management in sepsis was guided by Early Goal-Directed Therapy (EGDT), which protocolized the aggressive targeting of central venous pressure, mean arterial pressure, and central venous oxygen saturation within the first six hours 22. While early studies demonstrated profound mortality reductions, the superiority of EGDT has been refuted 17, 22. Three landmark multicenter randomized controlled trials ProCESS, ARISE, and ProMISe confirmed that rigid EGDT protocols do not improve 90-day survival over modern standard care 3, 23. This paradigm shift underscores the necessity of moving toward individualized, dynamically guided hemodynamic resuscitation, such as targeting the normalization of capillary refill time (CRT) as explored in the ANDROMEDA-SHOCK trials 29.

Current Surviving Sepsis Campaign (SSC) guidelines, supported by recent evidence highlights, suggest administering an initial 30 mL/kg intravenous crystalloid fluid bolus within the first three hours of resuscitation 10, 24. However, the Infectious Diseases Society of America (IDSA) heavily criticizes the rigidity of the SEP-1 mandate, arguing that a non-individualized approach risks driving iatrogenic fluid overload and inappropriate antibiotic use in ambiguous, non-shock patients 25. Consequently, the 2021 SSC guidelines

downgraded the 30 mL/kg bolus to a weak recommendation based on low-quality evidence. Following initial resuscitation, fluid management must be carefully balanced to avoid the detrimental sequelae of fluid overload, conceptually guided by the ROSE framework (Resuscitation, Optimization, Stabilization, Evacuation) 30.

Selecting the optimal resuscitation fluid remains a highly debated topic. Current SSC guidelines strongly recommend crystalloids as the first-line fluid and explicitly recommend against synthetic starches 10. Extensive Cochrane reviews and network meta-analyses (NMAs) consistently associate synthetic colloids with an increased risk of severe acute kidney injury (AKI), the necessity for renal replacement therapy (RRT), and overall mortality 2, 13, 19.

Given the rapidly evolving landscape characterized by shifting guideline mandates, conflicting massive clinical trials, and emerging microcirculatory assessment tools, identifying the optimal fluid strategy is paramount to preventing iatrogenic harm. Therefore, the primary purpose of this comprehensive review is to systematically evaluate the current state of knowledge regarding goal-directed fluid therapy in septic shock. By rigorously contrasting fluid composition, precise administration timing, individualized volume dosing, and their collective impact on patient prognosis, this manuscript aims to delineate cohesive, evidence-based clinical strategies that optimize hemodynamic stabilization and maximize long-term survival in critically ill patients.

Description of the state of knowledge

Comparison of Fluid Types: Crystalloids versus Colloids and Formulation Nuances

Current Surviving Sepsis Campaign (SSC) guidelines strongly recommend the administration of crystalloids as the first-line therapy for the fluid resuscitation of patients with sepsis and septic shock, while issuing weak recommendations for specific crystalloid subtypes and restricting the use of synthetic colloids 10, 24. Within the category of crystalloids, a significant and ongoing clinical debate persists regarding the comparative efficacy of normal saline (0.9% sodium chloride) versus balanced crystalloid (BC) solutions. Normal saline administration has been frequently associated with the induction of hyperchloremic metabolic acidosis, a pathophysiological state that can provoke renal vasoconstriction, increase the secretion of circulating inflammatory cytokines, and subsequently precipitate acute kidney injury (AKI) 6. Foundational evidence from the SMART trial demonstrated that the use of balanced crystalloids such as lactated Ringer's or Plasma-Lyte resulted in a lower rate of the composite outcome of death from any cause when compared to normal saline. 9. However, subsequent trials failed to replicate this superiority 8.

Superiority of balanced crystalloids was subsequently challenged by two major randomized controlled trials (RCTs). The BaSICS trial, which enrolled over 10,000 intensive care unit (ICU) patients, reported no statistically significant difference in 90-day mortality between patients receiving a balanced solution (26.4%) and those receiving normal saline (27.2%) 5. Similarly, the PLUS trial failed to demonstrate a significant reduction in 90-day survival or renal complications when comparing Plasma-Lyte 148 to normal saline in critically ill adults - 21.8% BC group and 22.0% in the saline group 11. Notably, balanced crystalloids were calculated to rank highest in reducing both 28-day and 90-day mortality, achieving a surface under the cumulative ranking curve (SUCRA) score of 86.3% for 90-day mortality reduction 20. These findings were corroborated by a reported SUCRA value of 83.1% for BC in mortality reduction 18. It was highlighted that while BC is optimal for sepsis and surgical patients, saline may be more appropriate for patients with traumatic brain injury 31. Although the conflicting conclusions of the preceding studies make it difficult to unequivocally determine whether balanced crystalloids affect 90-day mortality compared to normal saline, current guidelines nevertheless support the use of balanced crystalloids as the first-line therapy for the fluid resuscitation of patients with sepsis.

Extensive Cochrane reviews suggest little or no overall difference in mortality between crystalloids and colloids broadly, but synthetic colloids specifically high and low molecular weight hydroxyethyl starches (HES) and gelatins exacerbate the risk of AKI, thereby increasing the necessity for RRT and elevating overall mortality rates 13, 18. Consequently, international guidelines strongly recommend against the use of HES and gelatins in septic patients 10, 18. Meta-analyses indicate that while crystalloids are less efficient than colloids at stabilizing macro-hemodynamic parameters (requiring larger infusion volumes), synthetic colloids remain unsafe 2. In contrast, human albumin displays a significantly safer and potentially more efficacious physiological profile. Foundational RCTs such as the SAFE and ALBIOS trials explored the role of albumin, leading the SSC to issue a weak recommendation for the administration of albumin specifically when patients require substantial volumes of crystalloids to maintain intravascular volume 10, 17. In comparing distinct formulations of albumin, contemporary NMAs indicate that hyperoncotic albumin (e.g., 20% or 25% solutions) is particularly advantageous. Hyperoncotic albumin was the single most effective fluid intervention for reducing the incidence of renal injury in septic shock, achieving a SUCRA score of 74.5%. 20.

Timing of Administration and the Evolution of Early Goal-Directed Therapy

The pathophysiology of sepsis constitutes a critical medical emergency wherein treatment delays are associated with a progressively increased risk of morbidity and mortality. Epidemiological data reveal a significant incidence of hospital-acquired (HA) sepsis and ICU-acquired sepsis, conditions fundamentally complicated by pre-existing organ dysfunction and highlighting the critical need for timely intervention 15. To standardize early intervention, the Centers for Medicare & Medicaid Services (CMS) introduced the mandate SEP-1, establishing a "30by3" clinical benchmark that dictates the intravenous administration of a 30 mL/kg crystalloid fluid bolus within three hours of severe sepsis or septic shock recognition 16, 25. The efficacy of this strict timing is supported by observational data; a comprehensive retrospective cohort study demonstrated that failure to meet this 30 mL/kg target within the three-hour window was independently associated with a significantly increased risk of in-hospital mortality, delayed hypotension, and an extended duration of ICU length of stay 16. Crucially, this mortality benefit was maintained even among patients perceived to be at high risk for volume overload, such as those with pre-existing end-stage renal disease, heart failure or obesity, suggesting that the initial, rapid expansion of intravascular volume provides a critical window of intervention before irreversible endothelial dysfunction ensues. However, the rigidity of "30by3" mandate remains a subject of intense controversy. Professional organizations argue that aggressive, non-individualized fluid mandates in clinically ambiguous, non-shock patients may inadvertently contribute to iatrogenic fluid overload, pulmonary edema, and worse outcomes, emphasizing that the "one-size-fits-all" metric fails to account for heterogeneous patient phenotypes and infectious mimickers 25.

The historical paradigm governing the timing and sequence of fluid administration was fundamentally shaped by Early Goal-Directed Therapy (EGDT), a highly protocolized resuscitation strategy. The original EGDT protocol demonstrated profound hospital mortality reductions by aggressively targeting central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation (ScvO2) within the first six hours of emergency department presentation 17. However, the initial enthusiasm for EGDT was subsequently challenged by three large-scale, multicenter RCTs (ProCESS, ARISE, and ProMISe) and corroborating patient-level meta-analyses 3, 10. These modern trials explicitly refuted the benefits of EGDT, demonstrating no significant difference in 90-day or 1-year mortality between the protocolized EGDT group and the usual care group 3, 10, 28. Furthermore, trials revealed that rigid EGDT protocols paradoxically resulted in patients receiving significantly

higher intensities of treatment---including larger volumes of intravenous fluids and more frequent administration of vasoactive drugs---which translated into extended ICU admissions and an increased requirement for advanced cardiovascular support 22, 28.

The risks associated with aggressive, protocolized, early fluid bolus administration are particularly pronounced in resource-limited settings lacking advanced organ support. The FEAST trial, evaluating African children with severe infections, and the SSSP and SSSP-2 trials, assessing adults with severe sepsis in Zambia, both identified increased mortality associated with early fluid bolus regimens 17, 28. In the SSSP trial, the protocolized administration of intravenous fluids resulted in significantly more fluid administration in the first six hours but paradoxically increased the rate of respiratory decline and in-hospital mortality (48.1% versus 33.0%) compared to standard care, likely due to the exacerbation of pulmonary edema in patients without access to mechanical ventilation 17. In light of the accumulating evidence challenging rigid volume mandates, the 2021 SSC guidelines officially downgraded the recommendation for an initial 30 mL/kg bolus from a strong to a weak recommendation based on low-quality evidence 10, 24.

Volume and Dosing: Liberal versus Restrictive Strategies and Weight Adjustments

Fluid resuscitation is the cornerstone of managing sepsis-induced hypoperfusion, yet the transition from initial volume expansion to fluid overload presents a clinical challenge. Prompt intervention is crucial following the early recognition of bloodstream infections and sepsis using tools like the quick Sequential Organ Failure Assessment scale, but aggressive volume administration is associated with iatrogenic complications 32, 33. Following the initial acute resuscitative phase, the determination of total fluid volume and continuous dosing strategies represents a pivotal clinical challenge characterized by the delicate balance between restoring tissue perfusion and preventing clinically significant fluid overload. The physiological trajectory of fluid management is currently conceptualized through the ROSE framework, which delineates four distinct phases: Resuscitation (salvage therapy via immediate boluses), Optimization (titrated fluid administration), Stabilization (conservative fluid maintenance), and Evacuation (active de-escalation and de-resuscitation) 28, 30. Prolonged adherence to liberal fluid strategies leads to massive positive fluid balances, which are consistently correlated with deleterious clinical sequelae including damage to the endothelial glycocalyx, capillary leak syndrome, marked tissue edema, and increased overall mortality 17, 30.

To systematically address the dangers of fluid overload, landmark RCTs, including the CLASSIC and CLOVERS trials, were designed to compare liberal fluid administration against highly restrictive fluid protocols. In both of these rigorously controlled studies, the investigators found no statistically significant difference in the primary outcome of 90-day mortality between the restrictive and liberal strategies. 24, 28. However, comprehensive meta-analytical data provide nuanced evidence favoring restriction. A systematic review and meta-analysis evaluated the impact of restrictive fluid resuscitation specifically on renal function in sepsis-associated hypotension and shock across 3,718 participants. Their analysis demonstrated that a restrictive fluid strategy significantly reduces the incidence of severe AKI (Risk Ratio 0.87) and significantly shortens the required duration of mechanical ventilation compared to liberal usual care 14. The reduction in ventilation hours decreases the incidence of ventilator-associated pneumonia and indicates a profound protective effect against fluid-induced pulmonary edema. This is corroborated by the FACTT trial in ARDS patients, which showed that conservative fluid management significantly increases ventilator-free days 17, 30.

Volume dosing protocols present unique complexities in specialized demographic groups, particularly obese patients, where standardized algorithms risk severe miscalculation. The current SSC guidelines lack specific dosing recommendations for the obese population, leading to significant variations in clinical practice regarding the use of Actual Body Weight (ABW) versus Ideal Body Weight (IBW) 4. Calculating a 30 mL/kg bolus based on ABW in obese or morbidly obese patients may increase the risk of iatrogenic fluid overload and potential pulmonary edema. In a prospective observational study incorporating advanced hemodynamic monitoring via trans-pulmonary thermodilution, it was revealed that calculating the initial fluid load based on IBW allowed 70.4% of patients to safely receive the targeted physiological fluid volume without increasing the persistence of sepsis-induced AKI 26. The complexities of fluid dosing extend beyond adult body mass index categories into pediatric populations, where administering the standard 30 mL/kg bolus with balanced crystalloids like Ringer lactate has been associated with significant reductions in biomarkers of acute kidney injury compared to normal saline 12. Furthermore, deresuscitation of the active Evacuation phase of the ROSE model is increasingly advocated to restore negative fluid balance 30. This phase utilizes potent loop diuretics (e.g., furosemide) or renal replacement ultrafiltration to actively remove accumulated fluids. The efficacy of deresuscitation can be pharmacologically enhanced by the co-administration of hyperoncotic human albumin, which mobilizes interstitial fluid back into the intravascular space, thereby increasing hemodynamic stability

and diuresis simultaneously, reinforcing that negative fluid balances in the later phases of critical illness are strongly associated with improved survival 30.

Impact on Patient Prognosis: Hemodynamic Guidance, Organ Function, and Outcomes

The selection of resuscitation fluids in septic shock significantly influences patient-centered clinical outcomes, including mortality, the incidence of acute kidney injury, and the requirement for renal replacement therapy 19. Optimizing patient prognosis in the context of septic shock fundamentally relies on the accurate, real-time bedside assessment of fluid responsiveness to prevent the transition from beneficial preload augmentation to deleterious fluid overload. Historical reliance on static macro-hemodynamic parameters such as central venous pressure, heart rate and systolic blood pressure have been frequently shown to be unreliable predictors of true intravascular volume status and incapable of reliably forecasting whether a patient's cardiac output will increase following a fluid bolus 10, 27, 28. Consequently, modern critical care guidelines strongly recommend prioritizing dynamic physiological indices. Dynamic measures utilize cardiopulmonary interactions or postural changes to assess preload dependence; these include passive leg raising (PLR), stroke volume variation (SVV), pulse pressure variation (PPV) and echocardiographic assessments 1, 10, 28. The systematic review and GRADE-assessed meta-analysis synthesized data from multiple RCTs, concluding that utilizing dynamic measures of fluid responsiveness to guide intravenous fluid administration probably reduces 28-day mortality, significantly reduces the risk of AKI and decreases the cumulative fluid balance on day 3 1. This was corroborated by the FRESH trial, which demonstrated that guiding fluid therapy primarily via PLR and non-invasive bioreactance stroke volume changes resulted in a significantly lower net fluid balance and reduced the necessity for both RRT and mechanical ventilation 28.

Beyond optimizing hemodynamic flow, contemporary resuscitation paradigms are increasingly prioritizing the direct assessment of peripheral tissue perfusion and microcirculatory integrity as the ultimate determinant of patient prognosis. The ANDROMEDA-SHOCK trial fundamentally shifted the resuscitative landscape by comparing a standard strategy aimed at normalizing serum lactate levels against a personalized, hemodynamically guided strategy targeting the normalization of capillary refill time (CRT). The trial established that a personalized hemodynamic resuscitation strategy targeting CRT normalization improved the composite hierarchical outcome comprising mortality, duration of vital support, and length of stay (win ratio 1.16) 29. It is further emphasized that integrating the Oxygen Extraction Ratio (OER) into early-stage management is critical, as an initially low OER strongly predicts severe organ dysfunction and high in-hospital mortality 22. To further

refine microcirculatory assessment, the use of hand-held vital microscopes (HVM) and contrast-enhanced ultrasound (CEUS) is reviewed to directly visualize the sublingual capillary network and assess organ-specific microvascular flow and glycocalyx integrity at the bedside for the assessment of the effects of fluid resuscitation 28.

Slipping into hypervolemia due to inadequately guided fluid therapy can be highly detrimental to end-organ function.. When the patient reaches the plateau of the Frank-Starling curve, further fluid administration produces a negligible increase in stroke volume but is often associated with a significant elevation in central venous and right atrial pressures. This retrograde venous congestion is delineated as the primary driver of fluid-induced organ failure 27. In the pulmonary system, it dramatically increases extravascular lung water (EVLW), disrupting gas exchange and precipitating or exacerbating acute respiratory distress syndrome (ARDS), while simultaneously risking acute right ventricular dilation. In the renal system, elevated central venous pressure directly increases renal subcapsular pressure, causing interstitial renal edema; this physical distortion increases resistance to capillary blood flow, drastically decreases the glomerular filtration gradient, and is a primary physiological mechanism driving sepsis-associated AKI 28. Furthermore, large-volume chloride-rich crystalloid administration often leads to hyperchloremia, which appears to be independently associated with severe AKI in septic shock 7, 34. Meticulous fluid stewardship appears to play a critical role in mitigating organ failure, limiting hemodilution, and potentially improving the long-term survival of patients suffering from septic shock 27,28.

Summary

Sepsis induces profound microvascular derangements, mandating prompt fluid resuscitation. However, rigid Early Goal-Directed Therapy (EGDT) protocols, which dictated aggressive static parameter targets, have largely been supplanted following major trials including ProCESS, ARISE, and ProMISe. Modern paradigms have firmly transitioned toward individualized, dynamically guided hemodynamic resuscitation.

Regarding fluid composition, crystalloids remain the strongly recommended first-line therapy. Guidelines strongly recommend against the use of synthetic colloids due to their association with increased acute kidney injury (AKI) and mortality. While major trials such as BaSICS and PLUS demonstrated no significant mortality differences between normal saline and balanced crystalloids, network meta-analyses suggest balanced crystalloids may offer prognostic advantages, warranting further investigation into personalized fluid selection. Furthermore, hyperoncotic human albumin demonstrates a highly favorable physiological

profile, representing the most efficacious fluid intervention for mitigating renal injury and aiding active deresuscitation.

The rigid SEP-1 mandate, dictating a 30 mL/kg crystalloid bolus within three hours, faces intense professional scrutiny, as non-individualized strategies severely risk iatrogenic fluid overload. To prevent massive volume miscalculations, particularly in obese patients, Ideal Body Weight must be strictly utilized instead of actual body weight. Contemporary fluid stewardship is conceptually structured through the ROSE framework---Resuscitation, Optimization, Stabilization, and Evacuation---which actively emphasizes active de-escalation. Meta-analytical data suggest that restrictive fluid strategies may significantly decrease the incidence of severe AKI and curtail mechanical ventilation duration compared to liberal approaches.

Preventing pathological fluid overload is clinically paramount. Reaching the Frank-Starling plateau induces severe retrograde venous congestion, directly precipitating extravascular lung water accumulation, acute respiratory distress syndrome, and interstitial renal edema. Consequently, static indices like central venous pressure are deemed poorly predictive. Critical care guidelines strongly recommend utilizing dynamic physiological measures, such as passive leg raising and stroke volume variation, which demonstrably reduce AKI incidence and cumulative fluid balances. Moreover, the ANDROMEDA-SHOCK trial established that dynamically targeting capillary refill time significantly improves composite hierarchical clinical outcomes. Meticulous, dynamically guided fluid stewardship appears to be a critical component in mitigating organ failure and maximize long-term survival in septic shock.

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Author Contributions

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