Evolving Management Practices for Early Sepsis-induced Hypoperfusion

A Narrative Review

Evolving management practices for early sepsis-induced hypoperfusion: a narrative review

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Abstract

Sepsis causes significant morbidity and mortality worldwide. Resuscitation is a cornerstone of management. This review covers 5 areas of evolving practice in the management of early sepsis-induced hypoperfusion: fluid resuscitation volume, timing of vasopressor initiation, resuscitation targets, route of vasopressor administration, and use of invasive blood pressure monitoring. For each topic, we review the seminal evidence, discuss the evolution of practice over time, and highlight questions for additional research. Intravenous fluids are a core component of early sepsis resuscitation. However, with growing concerns about the harms of fluid, practice is evolving towards smaller-volume resuscitation, which is often paired with earlier vasopressor initiation. Large trials of fluid-restrictive, vasopressor-early strategies are providing more information about the safety and potential benefit of these approaches. Lowering blood pressure targets is a means to prevent fluid overload and reduce exposure to vasopressors; mean arterial pressure targets of 60-65mmHg appear to be safe, at least in older patients. With the trend toward earlier vasopressor initiation, the need for central administration of vasopressors has been questioned, and peripheral vasopressor use is increasing, though is not universally accepted. Similarly, while guidelines suggest use of invasive blood pressure monitoring with arterial catheters in patients receiving vasopressors, blood pressure cuffs are less invasive and often sufficient. Overall, the management of early sepsis-induced hypoperfusion is evolving towards fluid-sparing and less-invasive strategies. However, many questions remain, and additional data are needed to further optimize our approach to resuscitation. (Word Count: 236)

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Introduction

Sepsis causes significant morbidity and mortality worldwide, contributing to an estimated 49 million hospitalizations and 11 million deaths in 2017.(1) Resuscitation is a key component of sepsis management, but the optimal approach to resuscitation remains unclear. This review focuses on five key aspects of resuscitation where practice is evolving: fluid resuscitation volume, vasopressor timing, resuscitation targets, route of vasopressor administration, and use of invasive blood pressure monitoring. For each topic, we review the evidence and current guidelines, discuss practice evolution over time, and highlight questions for future research. In the Supplement, we address additional aspects of resuscitation.

Definitions and Scope

This review focuses on management of patients with early sepsis-induced hypotension and hyperlactatemia, drawing primarily from clinical trials. Pre-clinical and clinical physiological studies have also informed current practice, but are beyond the scope of this review.

Given the variety and overlap of terms used in practice, we present definitions in **Figure 1.** We use hypoperfusion to refer to hypotension and/or hyperlactatemia, acknowledging the limitations of this definition. Hypotension and hyperlactatemia are each associated with mortality in sepsis, making them important bedside clinical markers.(2) However, their relationship to tissue perfusion is not fully understood(3), as sepsis-induced inflammation can cause microcirculatory dysfunction and disrupt tissue perfusion and

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oxygen delivery independently of hemodynamics(4,5). However, given the clinical focus of this review, we define hypoperfusion as hypotension and/or hyperlactatemia, as these widely available clinical markers are used in practice and trials.

Fluid resuscitation: How much is enough?

- Conventional teaching: Intravenous (IV) fluids are a cornerstone of managing early sepsis-induced hypoperfusion.
- Current guidelines: Several guidelines recommend an initial resuscitation volume of 30ml/kg.(6) However, there are scant recommendations to guide ongoing fluid resuscitation.
- Evolving practice: Practice is evolving towards fluid-sparing approaches to ongoing resuscitation, and there is increasing equipoise about the necessity of the 30ml/kg initial resuscitation volume.

Fluid resuscitation has been a core component of managing early sepsis-induced hypoperfusion for several decades. After the 2001 Rivers, *et al*. trial(7), early goal-directed therapy (EGDT) for septic shock was recommended by the Surviving Sepsis Campaign (SSC) guidelines. The EGDT protocol includes invasive monitoring with central venous and arterial catheters, fluid resuscitation to maintain central venous pressure (CVP) 8-12 mmHg, vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg, and blood transfusions and inotropes to maintain central venous oxygen saturation ($ScvO_2$) ≥70%. In the Rivers trial, patients randomized to EGDT vs standard

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therapy received more fluid (4,981 vs 3,499ml within 6 hours, p<0.001), blood transfusions (64.1%. vs 18.5%, p<0.001), and inotropes (13.7% vs 0.8%, p<0.001).

Subsequently, three multicenter trials (ARISE, ProCESS, ProMISe) tested EGDT vs usual care, which had evolved over the preceding decade in response to the Rivers trial.(8–10) In these trials, patients randomized to EGDT vs usual care received 200-1,000ml more fluid within 6 hours post-enrollment. Yet, mortality outcomes were neutral in these individual trials and in both standard and individual patient-level meta-analyses.(11,12) (**Table 1**) Notably, patients in these trials had higher baseline $ScvO_2$ than patients in the Rivers trial (70% vs 49%; **Table 1**), suggesting they were less sick or enrolled after more resuscitation. However, there was no indication of benefit of EGDT across any of the 59 subpopulations examined in an individual patient-level meta-analysis of ARISE, ProCESS, and ProMISe, including subgroups defined by illness severity and time to randomization(11). Rather, these findings suggest that across all patient populations, usual care and EGDT had equivalent outcomes. Both are reasonable approaches to resuscitation, although EGDT is more invasive and labor-intensive.

Following ARISE, ProCESS, and ProMISe, the 2016 SSC Guidelines replaced the recommendation for EGDT with a pragmatic recommendation that patients with sepsis-induced hypoperfusion receive ≥30ml/kg crystalloids within 3 hours of presentation, with ongoing resuscitation guided by serial assessments of hemodynamic status. However, most trials have enrolled patients after some initial fluid administration, precluding

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rigorous evaluation of initial fluid volume. 30 ml/kg was chosen because most patients enrolled in ARISE, ProCESS, and ProMISe received around 30ml/kg pre-randomization (**Table 1**).(11) Additionally, 30ml/kg has been associated with benefit in observational studies. For example, in a multicenter study of sepsis patients with intermediate lactates (2-4 mmol/L), implementation of a treatment bundle including a 30 ml/kg bolus was associated with increased fluid delivery and decreased mortality over time.(13) Importantly, however, no randomized trials have evaluated 30ml/kg vs other initial fluid volumes, and the SSC downgraded its 30ml/kg recommendation to a suggestion in 2021.(6)

The SSC's evolution from recommending EGDT, to recommending 30ml/kg, to suggesting 30ml/kg is emblematic of broader shifts in thinking and practice. IV fluids help correct intravascular depletion and restore preload. However, sepsis-induced hypotension and hyperlactatemia do not necessarily imply true hypovolemia. Patients with community-onset sepsis often have decreased oral intake, fever, and insensible losses that may contribute to volume depletion(14), but sepsis also induces an inflammatory response that decreases systemic vascular resistance, increases vascular permeability, and lowers blood pressure in a manner that may not be improved by fluid resuscitation(15,16).

Over the past 15 years, there has been increasing concern about potential harms from over-resuscitation. In observational studies, fluid overload and positive fluid balance have been associated with higher mortality, although risk for confounding limits strong

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conclusions (17–20). More compellingly, three randomized controlled trials (RCTs) in lower-resource settings (where negative impacts of fluid overload may be less remediable) showed harm with larger-volume resuscitation, as detailed in **Table 2**.(21–23)

Several small trials have evaluated fluid-restrictive approaches to ongoing resuscitation, using three general approaches: 1) fluid boluses for limited clinical criteria; 2) fluid boluses guided by serial assessments of fluid-responsiveness; and 3) capped total fluid volume (**Table 3**). Meta-analysis of these trials did not favor fluid-liberal vs fluid-restrictive approaches (6,24), but the lack of difference should be interpreted with caution due to small sample sizes, differing approaches to fluid limitation, and lack of separation in fluid volume in some trials (25–28).

CLASSIC, the first multicenter trial of fluid-restrictive resuscitation powered to assess patient outcomes, enrolled 1,554 septic shock patients across 31 European ICUs after initial fluid resuscitation.(29) Patients were randomized to usual care vs fluid-restriction, where 250-500ml crystalloid boluses were allowed for select clinical markers of hypoperfusion (lactate ≥4 mmol/L, MAP <50 mmHg, skin mottling, oliguria within 2 hours), to correct fluid losses, dehydration, or electrolyte deficiencies, and to ensure a total intake of 1,000ml/day. Patients randomized to fluid-restriction received less fluid (median difference -813ml, day 1), but mortality and secondary outcomes were similar (**Table 3**). Interpretation of these results is complicated by several factors. First, while pre-randomization fluid volume was notably lower in this trial than in the pilot trial 6

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years earlier, indicative of recent trends towards fluid-restriction (median 3,000-3,200ml vs 4,200-4,790ml), it was still high. By comparison, the separation in fluid between arms was small and of uncertain clinical significance. Protocol deviations occurred in 21% of the fluid-restriction arm, and while small (median 97ml/day), further reduced the difference between arms. Subgroup analysis of patients on respiratory support revealed numerically lower 90-day mortality in the fluid-restriction arm (46.5% vs 52.0%, p-value for heterogeneity=0.03), suggesting a potential benefit of fluid-restriction in these patients that may have been masked by sub-optimal separation in study arms and heterogeneity of treatment effect.

In the recent CLOVERS trial, 1,563 patients with early sepsis-induced hypotension in 60 US hospitals were randomized to a fluid-restrictive, vasopressor-early vs fluid-liberal approach(30).The trial was stopped early in 2/2022 for futility. There was high protocol adherence (97% vs 96%) and good treatment separation between arms (24-hour median differences: fluids -2,134ml; vasopressors 21.7%). However, outcomes were similar (**Table 3**). Hypothesized effect sizes were large and led to early stopping for futility, which results in wide confidence intervals and difficulty interpreting adverse events and subgroup analyses.

The neutral results of CLASSIC and CLOVERS despite statistically significant separation between arms present a few possible interpretations: 1) fluid-restrictive, vasopressor-early strategies may not be better than traditional fluid-liberal strategies; 2) the clinical criteria used to guide fluid boluses and vasopressor initiation in these studies

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do not represent the optimal approach; 3) the magnitude of the treatment effect included in the sample size calculations was unrealistically large, particularly given limitations in clinically-meaningful group separation and patient heterogeneity.

Dynamic measures of fluid-responsiveness (e.g., changes in cardiac output or stroke volume in response to passive leg raise or fluid challenges) can help inform ongoing fluid administration and avoid under- or over-resuscitation. Meta-analyses have yielded conflicting results on whether these approaches improve clinical outcomes.(31,32) More recently, however, in a multicenter RCT of 124 patients with sepsis-induced hypotension, randomization to fluid boluses guided by stroke volume change after passive leg raise resulted in lower ICU fluid balance, less renal replacement therapy, and less mechanical ventilation than usual care(33). (**Table 3**).

Overall, recent trials comparing fluid resuscitation approaches in higher-resource settings have all yielded neutral results(8–10,29), suggesting any of the tested approaches are reasonable in these settings. In bedside practice, clinicians should consider individual conditions that may require more or less resuscitation (e.g., dehydration and respiratory failure, respectively) and assess dynamic measures of fluid-responsiveness through fluid challenges to target resuscitation to individual patient needs. 30m/kg is a reasonable rule of thumb for initial fluid volume, but should be tailored based on patient factors and clinical response to fluid administration. Finally, it is important to note that existing resuscitation trials enrolled patients after fluid volumes of ≥30ml/kg (**Table 1, 3**). Thus, while the evidence behind 30ml/kg fluid volume is weak

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and primarily drawn from observational studies, existing trials do not support limiting initial resuscitation to less than 30ml/kg. Two ongoing trials of early sepsis resuscitation are enrolling patients even earlier and will further inform practice: ARISE FLUIDS [NCT04569942] and EVIS [NCT05179499] (**Table 4**).

Resuscitation timing: When should we add vasopressors?

- Conventional teaching: Vasopressors are reserved for patients who remain hypotensive despite fluid resuscitation.
- Current guidelines: Guidelines recommend initiating vasopressors before completing initial fluid resuscitation in patients with severe hypotension.(34,35)
- Evolving practice: Earlier initiation of vasopressors, concurrent with initial fluids and often paired with fluid-restriction.

The most common vasopressors (e.g., norepinephrine) are potent catecholamines with side effects including tachyarrhythmias, myocardial cell damage, immunomodulation, and potential rare organ or limb ischemia.(36,37) There is theoretical concern that initiating vasopressors before IV fluids could mask ongoing volume deficits, if present.(38) Therefore, traditional practice has been to initiate vasopressors only if patients remain hypotensive after initial fluid resuscitation. In a 2017 survey of 839 physicians in Europe, only 12% used vasopressors “early, before complete resuscitation” in sepsis-induced hypotension.(34)

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However, vasopressors have potential benefits. They raise blood pressure by increasing preload (like fluids), cardiac contractility, and systemic vascular resistance, though their effect on microcirculation and tissue perfusion is less clear.(39,40) In animal models of shock, norepinephrine helps restore blood pressure, mesenteric blood flow, and tissue oxygenation, and limit fluid volume (41,42). Prompt restoration of blood pressure may be important because duration of low MAP in early sepsis is associated with increased mortality.(43) These pre-clinical and observational data have limitations, but have spurred interest in earlier vasopressor initiation to expedite shock resolution and minimize fluid resuscitation volumes.

Cohort studies and secondary analyses of trials have yielded conflicting results about the effects of early vasopressor initiation, (44–47) and interpretation is limited by high risk for confounding.

Before CLOVERS, only 3 small RCTs had evaluated early vasopressor initiation in sepsis-induced hypotension.(48–50) The largest, CENSER, was a single-center trial in Thailand that randomized 320 patients with sepsis-induced hypotension to early, fixed-dose norepinephrine (0.05 μg/kg/min for 24 hours) vs placebo infusion (**Table 3**).(49) Time to open-label norepinephrine and fluid administration within 6 hours were similar between study arms. However, patients randomized to early norepinephrine were more likely to achieve resuscitation targets (MAP >65 mmHg, urine output >0.5ml/kg, and decrease in lactate >10%) within 6 hours, suggesting early, low-dose norepinephrine is safe and may hasten resolution of shock. The impact of early vasopressors on patient-

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centered outcomes is unclear, with recent trials of fluid-restrictive, vasopressor-early regimens in sepsis (CLASSIC and CLOVERS) yielding neutral results, as discussed above.

When considering timing of vasopressor initiation, it is important to acknowledge the potential downstream impacts of vasopressor-early strategies. In CENSER, 47% of patients were managed on the general ward, but many institutions require ICU admission or central venous access for patients receiving vasopressors. In CLOVERS, patients randomized to the vasopressor-early arm were more likely to be admitted to an ICU than patients in the fluid-liberal arm (67.3% vs 59.2%, difference 8.1%, 95%CI: 3.3 to 12.8).(30) Therefore, earlier vasopressor initiation could impact ICU use and must be weighed against potential benefits of faster shock control and minimizing fluid volume.

While the benefit of early vasopressors is unclear, CLOVERS suggests a fluid-restrictive, vasopressor-early strategy is a safe and reasonable alternative to liberal fluids. Additional guidance on timing of vasopressor initiation may be provided by two ongoing multicenter trials: ARISE FLUIDS [NCT04569942] and EVIS [NCT05179499] (**Table 4**).

Moving the target: Reframing our resuscitation goals

- Conventional teaching: Maintain MAP ≥65 mmHg.
- Current guidelines: An initial MAP target ≥65 mmHg is broadly recommended.(6,34)

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- Evolving practice: Use of lower MAP goals and adjunctive resuscitation targets.

Lowering blood pressure targets is one way to prevent fluid overload while also avoiding vasopressors and associated line placement to facilitate vasopressor delivery.

MAP is the most widely accepted and studied target for resuscitation and vasopressor titration. However, tissue hypoperfusion may also occur in the absence of systemic hypotension and has independent implications for mortality.(2,4) Therefore, more direct markers of tissue perfusion (e.g, lactate, capillary refill time) are sometimes used as adjunctive resuscitation targets.

Most studies of MAP targets in sepsis have compared ≥65 mmHg to ≥75-85 mmHg, with the hypothesis that higher MAPs improve tissue perfusion and organ function. While higher MAPs may increase cardiac output and potentially microcirculation, they do not consistently improve renal function or lactate levels.(51,52) This finding may be explained by alternative, poorly-understood causes of sepsis-induced organ dysfunction. For example, animal models of sepsis suggest that acute kidney injury occurs independently of renal blood flow, oxygen delivery, or histologic injury.(53)

The SEPSISPAM trial was the first to evaluate the impact of MAP targets on mortality, randomizing 776 patients with septic shock to a MAP target 65-70 mmHg vs 80-85 mmHg.(54) There was significant separation in observed MAPs between arms (p=0.02). Among patients with chronic hypertension, randomization to the lower MAP target was

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associated with increased incidence of renal replacement therapy. However, overall patients randomized to the lower MAP target received less norepinephrine, had lower incidence of atrial fibrillation, and had similar 28-day mortality (**Table 3**). Based on these results, SSC guidelines recommend an initial MAP target of ≥65 mmHg over higher targets.(6)

Some experts have suggested further lowering MAP targets given the potential risks of fluids and vasopressors. While difficult to extrapolate to sepsis, permissive hypotension is guideline-recommended in trauma patients with hemorrhagic shock, where over-resuscitation and high MAPs may propagate bleeding and contribute to complications.(55) In sepsis, exploratory analyses of SEPSISPAM and the Ovation pilot trial found decreased mortality in older patients randomized to lower MAPs.(56,57) These findings motivated the 65 Trial, a pragmatic, multicenter RCT that randomized 2,600 ICU patients aged ≥65 years with vasodilatory shock to permissive hypotension (MAP target 60-65 mmHg) vs usual care.(58) There was separation between arms in observed MAP (median 66.7 vs 72.6 mmHg), and randomization to permissive hypotension resulted in less vasopressor exposure and lower adjusted 90-day mortality. Unadjusted 90-day mortality findings were neutral (**Table 3**). In a pre-specified subgroup analysis, patients with chronic hypertension randomized to permissive hypotension had lower 90-day mortality, suggesting lower MAP targets in chronically hypertensive older patients may be beneficial, or are at least unlikely to be harmful—a long-held concern bolstered by the SEPSISPAM trial. Overall, the 65 Trial suggests targeting a MAP of 60-65mmHg decreases vasopressor exposure, is likely safe, and

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may be beneficial in older patients. Indeed, a recent meta-analysis of SEPSISPAM, Ovation, and the 65 Trial, while negative overall, found lower MAP targets were associated with lower mortality in the sepsis subgroup (RR 0.91; 95%CI 0.83-0.99)(59).

Adjunctive markers of tissue perfusion, such as lactate and capillary refill time, provide additional data to guide resuscitation. A meta-analysis of 4 small RCTs found that targeting resuscitation to a 10-20% reduction in lactate, in addition to traditional hemodynamic targets, was associated with decreased mortality.(60) Capillary refill time may provide an even more direct bedside measurement of tissue perfusion than MAP or lactate.(61) The largest trial to assess capillary refill time was ANDROMEDA-SHOCK, a multicenter trial that randomized 424 patients with septic shock to receive fluids, higher MAPs, and inotropes if they failed to meet resuscitation targets by capillary refill vs serial lactate measurements despite maintaining MAP ≥65 mmHg.(62) Trial adherence was high (protocol deviations: 13.7% capillary refill arm, 10.8% lactate arm), though the difference in resuscitation was small: compared to the lactate arm, patients in the capillary refill arm received 408ml less fluid within 8 hours (p=0.01) with no difference in vasopressor-free days or inotrope use. The point estimate for 28-day mortality favored the capillary refill arm and—although 95% confidence intervals were wide and crossed the line of no effect (**Table 3**)—a Bayesian re-analysis found over 90% probability that capillary refill-guided resuscitation improved 28-day mortality vs lactate across all priors (63). We suggest that both lactate and capillary refill can be helpful to inform resuscitation, but that clinicians should be cognizant that they may be influenced by factors unrelated to perfusion, such as liver function and temperature respectively.(64)

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Clinicians should not rely on any single marker in isolation to guide resuscitation, but rather must consider the overall clinical picture to inform decision-making.

Beyond capillary refill time and lactate, markers of microcirculatory changes, such as sublingual orthogonal polarization spectral imaging, aim to measure tissue perfusion more directly at bedside, but are not widely available and their role in targeting resuscitation has not been established.(5) There are ongoing efforts to develop additional bedside measures to individualize resuscitation approaches by identifying which patients with sepsis-induced hypoperfusion need fluid, vasopressors, or both, for example by using diastolic shock index (ratio between heart rate and diastolic blood pressure)(65) or dynamic arterial elastance (calculated using bedside ultrasound)(66).

Overall, we suggest an initial MAP target of ≥65 mmHg in younger patients and 60-65 mg Hg in older patients. Clinician exam, lactate, capillary refill time, and other measures of end-organ function (e.g., mentation, urine output) should be monitored to assess the adequacy of resuscitation, guide additional resuscitation, and inform subsequent resuscitation targets (67). It should be noted that capillary refill time and lactate have only been tested for intensifying therapy in refractory shock. The use of these, and other markers, to evaluate adequacy of different MAP goals warrants further study. A large multi-national, multicenter trial (ANDROMEDA-2: NCT05057611) and a smaller trial (TARTARE-2S: NCT02579525), will provide more data about possible benefits of targeting resuscitation to multiple markers of tissue perfusion and fluid-responsiveness (**Table 4**).

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Challenging a paradigm: Must vasopressors be administered centrally?

- Conventional teaching: Vasopressors must be administered via central venous access.
- Current Guidelines: 2021 SSC guidelines suggest initiating vasopressors peripherally rather than delaying initiation until central access is obtained, but advise central administration as soon as feasible.(6)
- Evolving practice: Primary peripheral administration of vasopressors.

In the 1950s, several case reports described catastrophic tissue injury from peripheral extravasation of vasopressors.(68) Based on these reports, central administration became standard. After the 2001 Rivers trial of EGDT, placement of central venous catheters (CVCs) was further justified to facilitate $ScvO_2$ monitoring.

Over the past 5 years, however, the long-held teaching that vasopressors must be delivered centrally has been questioned. CVCs provide secure access for medication delivery and a means of hemodynamic monitoring that is critical for some patients. While $ScvO_2$ monitoring may be useful for some patients, ARISE, ProCESS and ProMISe indicate it is not required for all patients, eliminating one indication for routine CVC placement.(8–10) Further, requiring CVCs in all patients receiving vasopressors may cause more harm than benefit. CVC placement requires time and expertise, which can delay vasopressor initiation.(69) CVC placement also carries risk for mechanical complications, line infections, and thrombosis.(70) Given some patients need

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vasopressors for only short durations, requiring CVCs for vasopressor administration may introduce unnecessary risk for these patients.(71) Finally, modern medication pumps permit tight control of vasopressor infusion rates and ultrasound is widely available to confirm appropriate placement of peripheral venous access, lowering the risk of extravasation since the original case reports of harm.

Indeed, peripheral vasopressor administration seems to be increasing in practice. In ARISE, 42% of early vasopressor-treated patients had vasopressors initiated through a peripheral IV (PIV), which was associated with decreased time to vasopressor initiation compared to central administration (median 2.4 vs 4.9 hours from ED arrival, $p<0.001$)(69). Furthermore, trial protocols increasingly allow for peripheral vasopressor administration, such as CLOVERS(30); ARISE FLUIDS [NCT04569942]; EVIS [NCT05179499]).

Despite the increased use of peripheral vasopressors, only one RCT has indirectly addressed central vs peripheral vasopressor administration. In this trial, 266 patients in 3 French ICUs who needed venous access (70% for the indication of low-dose vasopressors) were randomized to receive peripheral vs central venous access.(72) Complications were more common among patients randomized to peripheral access, although PIV complications (e.g., erythema, extravasation) tended to be less serious than complications from central access (e.g., pneumothorax, arterial puncture). Importantly, 61 (47.7%) patients randomized to PIV never received central access,

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suggesting it may be feasible to avoid central access for at least some patients receiving low-dose vasopressors.

A growing body of literature supports the safety of peripheral vasopressor administration within certain limitations. In a review of 318 peripheral vasopressor adverse events (114 extravasations, 204 tissue injuries), few events were reported with short-term infusion (<24 hours) or with PIVs proximal to the antecubital or popliteal fossae.(73) In a meta-analysis of 11 studies including 16,055 adult patients receiving peripheral vasopressors, the pooled incidence of adverse events (infiltration, extravasation, or erythema) was 1.8% and there were no cases of tissue necrosis.(74) After excluding a large peri-operative study where patients received vasopressors in a controlled manner for short durations during surgery, the pooled incidence of adverse events remained low (2.1%). Two other systematic reviews of peripheral vasopressor use in emergency departments and ICUs estimated extravasation and infiltration rates closer to 3%, but likewise found no episodes of tissue necrosis.(75,76) The most important factor associated with extravasation was a lack of safety guidelines for IV monitoring, underscoring the importance of monitoring peripheral vasopressor infusions.(76) Notably, peripheral vasopressor complication rates with monitoring are similar to current complication rates of CVC placement, which ranged from 3.1-3.7% in a multicenter trial of CVC insertion.(70)

Overall, extravasation of peripheral vasopressors is uncommon and tissue injury is rare with monitored peripheral administration. Therefore, in patients with secure PIVs, we

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recommend initiating vasopressors peripherally to expedite vasopressor initiation and suggest vasopressors can be continued peripherally at lower doses and with regular monitoring for extravasation. Clinicians should consider the vasopressor dose, clinical trajectory, size/location of the PIV, and other indications for CVC placement when deciding whether to continue vasopressors peripherally vs transition to central access. There are no universally agreed upon thresholds dictating transition to central administration, so institutional policies and practice vary widely (77). More research is needed to understand the safety of longer-term and higher-dose peripheral vasopressor administration, as well as risks for complications other than extravasation and tissue injury (e.g. thrombosis).

Always necessary? The role of arterial catheters

- Conventional teaching: Patients receiving vasopressors should have arterial catheters for blood pressure monitoring.
- Current Guidelines: Multiple societies suggest invasive blood pressure monitoring with arterial catheters for patients receiving vasopressors.(6,34)
- Evolving practice: Use of non-invasive blood pressure (NIBP) monitoring with a blood pressure cuff, in absence of other indications for arterial catheters.

Despite recommendations for invasive blood pressure monitoring in septic patients requiring vasopressors, arterial catheter use varies widely in practice. In a 2017 survey of physicians in Europe, 84% of respondents “always” used arterial catheters to measure blood pressure in septic shock.(34) However, in a study of 168 US ICUs,

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arterial catheter placement among patients receiving vasopressors was lower (51.7% in the median hospital), and varied widely across hospitals (IQR 30.8%, 76.2%).(78)

Arterial catheters are more accurate than blood pressure (BP) cuffs and provide continuous measurements, facilitating vasopressor titration.(79) They also allow for arterial blood sampling. However, both BP cuffs and arterial catheters are susceptible to artifacts that can limit their interpretation, and NIBP monitoring is accurate in detecting MAPs <65 mmHg and clinically meaningful MAP changes.(80) Therefore, arterial catheters may not improve detection or treatment of hypotension over NIBP monitoring, particularly in less severely ill patients with reliable BP cuff readings.

While arterial catheters are generally considered safer than CVCs, they may carry risk for catheter-associated infections and colonization of similar magnitude to CVCs.(81) Arterial catheter placement also carries mechanical risks, including hematomas, thrombosis, and rare arterial complications such as ischemia and pseudo-aneurysms.(82) While complication rates are similar among all arterial catheter sites(82), complications occurring at central sites, such as femoral and axillary arteries, may have more serious consequences, which must be weighed against the potential increase in measurement accuracy of central vs radial arterial catheters(83).

The only study evaluating the clinical impact of arterial catheter use in vasopressor-treated patients was a propensity-matched cohort study, which did not find benefit.(84) Interpretation of these findings is limited by the observational design, but underscores

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the need for RCTs to assess the utility of arterial catheters and target invasive interventions to patients most likely to benefit.(85)

The field of NIBP monitoring is growing, and there may be alternatives to BP cuffs in the future. Ongoing trials are testing novel monitoring devices, though these devices are not yet widely available and will need to be tested in critically ill patients.(86)

In the meantime, we suggest that arterial catheter placement is not necessary for all patients receiving vasopressors, and should be prioritized in patients with labile vasopressor requirements, unreliable BP cuff readings, or other indications for arterial catheter placement (e,g, blood draws).

Future Directions

There is a growing body of literature informing management of early sepsis-induced hypoperfusion. While most trials discussed in this review yielded neutral results, they have informed practice by showing that less invasive or less intensive approaches to resuscitation often yield similar outcomes, at least in the overall study population. The next step in sepsis resuscitation research is to understand how we can individualize care. Advanced statistical approaches have been used post-hoc to identify patients most likely to benefit from tested interventions, which can help overcome heterogeneity of treatment effects inherent to existing ICU trials(87). Going forward, however, trials must prospectively consider the heterogenous nature of sepsis by identifying sepsis phenotypes and treatment-responsive subgroups to inform and test personalization of

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care within trials(88). Additionally, in defining subgroups it may be beneficial to shift from studying septic shock separately to focusing on broader shock phenotypes, e.g., defined by cardiac function, fluid status, or the presence of vasodilation, as in the 65 Trial(58). Future trials must be sufficiently large to detect small but clinically-meaningful differences in patient-important outcomes. Trials should avoid stopping early based on unrealistically large estimated effect sizes, which limits the power of subgroup analyses and ability to assess heterogeneity. Finally, to inform early resuscitation practices, trials of resuscitation must incorporate novel trial designs and consent structures that facilitate earlier enrollment(89), drawing on experiences with alterations to informed consent processes in cardiac arrest and brain injury trials (90).

Conclusion

Sepsis is a major driver of morbidity and mortality worldwide, and resuscitation is a critical component of management. In this review, we summarize the evidence behind current resuscitation practices, discuss practice evolution toward less intensive approaches, and highlight gaps and limitations of our current evidence base.

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Table 1. Trials of Early Goal-Directed Therapy

Study	**Population**	**Intervention**	**A. Fluids from presentation to study enrollment**†	**B. Fluids from study enrollment to study hour 6***,†	**C. Total fluids from presentation to study hour 6 (A+B)**†	**$ScvO_2$ at study enrollment**	**Outcomes**** (Intervention vs Control)
Rivers, *et al.,* 2001(7)	263 patients with septic shock in 1 US ED	EGDT vs usual care	n/a, pre-randomization fluids were included in total reported fluids from hours 0-6 (column B)	EGDT: 4,981ml Standard therapy: 3,499ml *(mean),* p<0.001	EGDT: 4,981ml Standard therapy: 3,499ml (*mean),* p<0.001	EGDT: 48.6 ± 11.2% Standard therapy: 49.2 ± 13.3% (*mean*), p=0.49	In-hospital mortality: 30.5% vs 46.5%, p=0.009
ARISE, 2014(8)	1,600 patients with septic shock in 51 hospitals in Australia and New Zealand	EGDT vs usual care	EGDT: 2,515ml Usual care: 2,591ml *(mean),* p-value not reported	EGDT: 1,964ml Usual care: 1,713ml *(mean),* p<0.001	EGDT: 4,479ml Usual care: 4,304ml (*mean),* p-value not calculated	EGDT: 72.7 ± 10.5% (*mean*) ScvO2 was not monitored in the usual care group	90-day mortality: 18.6% vs 18.8%, p=0.90
ProCESS, 2014(9)	1,341 patients with septic shock in 31 US hospitals	EGDT vs protocol-based "standard" therapy vs usual care	EDGT: 2,254ml Protocol: 2,226ml Usual care: 2,083ml (*mean)*, p=0.15	EGDT: 2,805ml Protocol: 3,285ml Usual care: 2,279ml *(mean),* p<0.001	EDGT: 5,059ml Protocol: 5,511ml Usual care: 4,362ml (*mean)*, p-value not reported	Overall: 71± 13% (*mean*) ScvO2 was not routinely monitored in usual care group	60-day in-hospital mortality: 21.8% vs 18.2% vs 18.9%, p=0.83
ProMISe, 2015(10)	1,260 patients with septic shock in 56	EGDT vs usual care	EDGT: 1,950ml Usual care: 2,000ml *(median)*, p-	EGDT: 2,000ml Usual care: 1,784ml	EDGT: 3,950ml Usual care: 3,784ml (*median)*, p-	Overall: 70 ± 12% (*mean*) ScvO2 was not routinely	90-day mortality: 29.5% vs 29.2%, p=0.90

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	hospitals in England		value not reported	*(median),* p value not reported	value not reported	monitored in usual care group	EGDT was associated with higher organ-failure scores, more days of cardiovascular support, and longer ICU stays

*Values do not include fluid received pre-randomization
**Listed as intervention vs usual care, p-value

†Rivers, *et al.*, reported the total fluid patients received from presentation to hour 6, whereas the ARISE, ProCESS, and ProMISe trials reported the fluid patients received before study enrollment and from study enrollment to study hour 6 separately, as denoted in columns A and B above. Column C is a summation of total fluid received pre-enrollment and during the first 6 hours of study enrollment in the ARISE, ProCESS, and ProMISe trials, to facilitate a comparison to the amount of fluid patients received in Rivers, *et al*.

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Table 2. Trials of sepsis resuscitation in lower-resource settings

Trial	Details	Interventions	Outcomes**
FEAST trial, 2011(21)	3,141 children with fever and organ dysfunction at 6 hospitals in Kenya, Tanzania, and Uganda	Albumin bolus vs saline bolus vs usual care	Stopped early due to increased mortality in the fluid bolus arms 48-hour mortality: 10.6% (albumin arm) vs 10.6% (saline arm) vs 7.3% (usual care, no bolus)
Simplified Severe Sepsis Protocol-1, 2014(22)	112 adults with sepsis and hypotension at a single center in Zambia	6-hours sepsis bundle (4,000ml IV fluids guided by jugular venous pressure, dopamine, and blood transfusion) vs usual care	Stopped early due to high mortality in patients with hypoxemic respiratory distress at baseline (8/8 intervention vs 7/10 control) In-hospital mortality: 64.2% vs 60.7% (RR 1.05, 95% CI 0.79-1.41)
Simplified Severe Sepsis Protocol-2, 2017(23)	209 adults with sepsis and hypotension at a single center in Zambia	6-hour sepsis bundle (IV fluid boluses guided by jugular venous pressure, vasopressors, and blood transfusions) vs usual care	In-hospital mortality: 48.1% vs 33.0%, p=0.03 Fluid received within 6 hours (median): 3,500ml vs 2,000ml, p<0.001 Fluid received within 24 hours (median): 4,000ml vs 3,000ml, p<0.001 Vasopressors received: 14.2% vs 1.9%, p<0.001

**Listed as intervention vs usual care, p-value

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Table 3. Trials of fluid-restrictive approaches to ongoing resuscitation, early vasopressors, and lower resuscitation targets.

Study	Population	Time to Enrollment	Intervention	Differences Between Study Arms**,§	Outcomes**, §
Fluid Resuscitation, strategy 1: Fluid boluses based on select clinical criteria					
Meyhoff *et al.* 2022(29) / CLASSIC	1,554 patients with septic shock in 31 European ICUs	Enrollment after at least 1,000mL IV fluid, within 12 hours of septic shock diagnosis • Time from ICU admission to enrollment (median): 3 hours • Fluid pre-enrollment (median): 3,200mL in intervention vs 3,000mL in control	Intervention: 250-500ml boluses for 4 clinical criteria: (1) Lactate ≥4mmol/L; (2) MAP <50 mm Hg despite vasopressors; (3) Skin mottling; (4) Oliguria within 2 hours of randomization. Fluids were also allowed to correct fluid losses, dehydration, or electrolyte deficiencies and to ensure a total intake of 1,000ml/day. Control: Usual care	IV fluids within 5 days (median): 1,450 mL vs 3,077 mL, p-value not reported	*90-day mortality:* 42.3% vs 42.1%, p=0.96 Serious adverse events (including ischemia and kidney injury): 29.4% vs 30.8%, p=0.46
Jessen *et al.* 2022(103) / REFACED feasibility trial	123 patients with sepsis without shock in 2 Denmark EDs	Enrollment after no more than 500ml of IV fluid • Time from ED arrival to enrollment (median): 140 minutes • Fluid pre-enrollment (median): 0ml	Intervention: 250ml bolus for lactate ≥4mmol/l, hypotension, mottling, severe oliguria within 4 hours of randomization Control: Usual care	*IV fluids within 24 hours (mean):* 562 ml vs 1,370ml, p=0.001	No difference in use of mechanical ventilation, vasopressors, or new kidney injury
Hjortrup, *et al*., 2016(104) / CLASSIC feasibility trial	151 patients with septic shock in 9 Scandinavian ICUs	Enrollment after 30ml/kg bolus, within 12 hours of septic shock diagnosis • Time to enrollment not reported • Fluid pre-enrollment (median): 4,200ml in intervention vs	Intervention: 250-500ml boluses for 4 clinical criteria: (1) Lactate ≥4mmol/L; (2) MAP <50 mm Hg despite vasopressors; (3) Skin mottling; (4) Oliguria within 2 hours of randomization Control: Usual care	*Fluids within 5 days (median)*: 500ml vs 2000ml, p<0.001	90-day mortality: 33% vs 41%, p=0.32 Acute Kidney Injury (AKI): 37% vs 54%, p=0.03

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		4,790ml in control			
Semler, *et al*., 2020(25) / BALANCE pilot trial†	30 patients with SIRS and shock or respiratory insufficiency in 1 US medical ICU	Enrollment within 12 hours of ICU admission • Time from ICU admission to enrollment (median): 13.8 hours • Fluid pre-enrollment (median): 1,496ml in intervention vs 2,740ml in control	Intervention: IV fluid only for oliguria or increasing vasopressor requirement Control: Usual care	*Difference in daily fluid balance (mean):* -398 ml, p=0.33	In-hospital mortality: 30.0% vs 26.7%, p>0.99 Neutral results for secondary outcomes, including mortality, support-free days, AKI
Fluid Resuscitation, strategy 2: Fluid boluses based on evaluation of fluid responsiveness					
Douglas, *et al*., 2020(33)	124 patients with septic shock at 13 hospitals in the US and UK	Enrollment within 24 hours of hospital arrival • Time from hospital arrival to enrollment (median): 3.6 hours in intervention vs 3.3 hours in control • Fluid pre-enrollment (median): 2,500 ml in intervention vs 2,200 ml in control	Intervention: PLR assessment before any clinician-desired fluid bolus; fluids given only if PLR positive Control: Usual care (2:1 randomization)	*Fluid balance at 72 hours or ICU discharge (mean):* 650ml vs 2,020ml, p=0.021	30-day mortality: 15.7% vs 22.0%, not significant RRT: 5.1% vs 17.5%, p=0.04 Mechanical ventilation: 17.7% vs 34.1%, p=0.04
Lanspa, *et al*., 2018(26) / feasibility trial†	30 patients with septic shock in 1 US medical ICU	Enrollment within 6 hours of septic shock diagnosis • Time from sepsis diagnosis to enrollment (median): 3.1 hours in intervention vs 4 hours in control • Fluid pre-enrollment (median): 3,330ml in intervention vs	Intervention: Echo-guided resuscitation every 1 hour for 6 hours Control: Modified EGDT for 6 hours	Fluids received during study (median): 0 ml vs 1,000ml, p=0.61	*Change in SOFA score at 48 hours:* -4 vs -6 points, p=0.10 28-day mortality: 33% vs 20%, p=0.68

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		3,380ml in control			
Cronhjort, *et al*., 2016(28)†	34 patients with septic shock in 1 Swedish surgical ICU	Enrollment within 12 hours of septic shock diagnosis • Time from ICU admission to enrollment (mean): 5 hours • Fluid pre-enrollment not reported	Intervention: PLR assessment before any clinician-desired fluid bolus; fluids given only if PLR positive Control: Usual care	Fluids during study (median): 2,103ml vs 2,408ml, p=0.38	*Weight difference from enrollment to day 3 (mean):* 0.6kg vs 1.3kg, p=0.59 30-day mortality: 12.5% vs 11.1%, p=1.00
Chen and Kollef, 2015(27) / pilot trial†	82 patients with septic shock in 1 US medical ICU	Enrollment within 12 hours of initial fluid bolus • Time to enrollment and fluid pre-enrollment not reported	Intervention: Targeted Fluid Minimization, defined as daily PLR assessments with fluids only if positive Control: Usual care	*Fluid balance by day 3 (median)*: 1,952ml vs 3,124 ml, p=0.20 *Fluid balance by day 5 (median)*: 2,641ml vs 3,616 ml, p=0.40	In-hospital mortality: 56.1% vs 48.8%, p=0.51 Neutral results for other secondary outcomes, including ventilator days, need for RRT
Richard, *et al*., 2015(105)	60 patients with septic shock in 1 French medical ICU	Enrollment within 12 hours of initial hypotension • Time from hypotension to enrollment (median): 10 hours in intervention vs 9 hours in control • Fluid pre-enrollment (median): 3,500ml in intervention vs 3,000ml in control	Intervention: Fluids guided by preload dependence indices (pulse pressure variation or PLR) every 1 hour for 6 hours, then every 4 hours until vasopressor weaning Control: CVP-guided fluids every 1 hour for 6 hours, then every 4 hours until vasopressor weaning	Daily fluids (median): 383 ml/day vs 917ml/day, p=0.04	*Time to shock resolution:* 2.3 days vs 2.0 days, p=0.29 28-day mortality: 23% vs 47%, p=0.10
Fluid Resuscitation, strategy 3: Restricting total fluid volume					
Corl, *et al*.,	109 patients	Enrollment after	Intervention: Limit of ≤60 ml/kg	Fluids within 72	*30-day mortality:*

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2019(106) / RIFTS pilot trial	with septic shock in 2 US medical ICUs	1,000ml initial bolus • Time from ED presentation to enrollment (median): 8.8 hours in intervention vs 9.1 hours in control • Fluid pre-enrollment (mean): 34.4 ml/kg in intervention vs 36.2ml/kg in control	fluid within 72hours Control: Usual care	hours of enrollment (mean): 47ml/kg vs 61ml/kg, p=0.01	21.8% vs 22.2%, p>0.99
Early Vasopressor Initiation					
NHLBI Trial Network, 2023(30) / CLOVERS	1,563 patients with sepsis-induced hypotension across 60 US hospitals	Enrollment after 1,000-3,000ml initial bolus • Time from qualifying hypotension to randomization (median): 61 minutes in intervention vs 60 minutes in control • Fluid pre-enrollment (median): 2,050 ml in both groups	Intervention: Fluid restriction, with vasopressors for ongoing hypotension and rescue fluid boluses only for select clinical criterial Control: Fluid liberal, with fluid boluses for ongoing hypotension and rescue vasopressors only for select clinical criteria	Fluids in first 24 hours: 1,267ml vs 3,400 ml, difference -2,134 [95%CI: -2,318 to -1,949ml] Vasopressor administration in first 24 hours: 59.0% vs 37.2%, difference 21.7% [95CI: 16.9 to 26.6%].	*90-day mortality:* 14.0% vs 14.9%, difference -0.9 [95% CI: -4.4 to 2.6]).
Permpikul et al., 2019(49) / CENSER	320 patients with sepsis-induced hypotension in 1 Thailand hospital	Enrollment within 1 hour of hypotension • Time from ED arrival to any norepinephrine (median): 1 hour 33 minutes in intervention vs 3 hours 12 minutes in control	Intervention: Fixed-dose norepinephrine (0.05 μg/kg/min for 24 hours) Control: Placebo infusion	Total fluids within 6 hours (median): 2,450ml vs 2,600ml, p=0.33	*Resuscitation targets achieved within 6 hours:* 76.1% vs 48.4%, p <0.001 28-day mortality: 15.5% vs 21.9%, p=0.15
MacDonald, *et al*., 2018(48) / REFRESH pilot	99 patients with sepsis-induced	Enrollment after 1,000ml initial bolus • Time from ED arrival	Intervention: Vasopressors for MAP <65 mmHg; 250ml boluses at physician discretion	*Total fluids within 6 hours (median):* 2,387ml (30ml/kg)	90-day mortality: 8% vs 6%, p-value not

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trial	hypotension in 8 Australian ED	to enrollment (median): 140 minutes in intervention vs 143 minutes in control • Fluid pre-enrollment (median): 1,450 ml in intervention vs 1,250 ml in control	Control: Usual care, defined as 1,000ml initial fluid bolus and further 500ml boluses at physician discretion, vasopressors for sustained MAP <65 mmHg despite fluids	vs 3,000ml (43ml/kg), p<0.001	reported Neutral results in other secondary outcomes, including ICU admission, LOS, vasopressor-free, ventilator-free, and RRT-free days
Resuscitation Targets§					
SEPSISPAM 2014(54)	776 patients with septic shock across 29 hospitals in France	Enrollment after at least 30ml/kg fluids and within 6 hours vasopressor initiation	Low-target arm: 65-70 mmHg High-target arm: 80-85 mmHg	Norepinephrine dose (day 1, median): 0.45 vs 0.58 μg/kg/min, p<0.001 Norepinephrine duration (mean): 3.7 vs 4.7 days, p<0.001	*28-day mortality*: 34.0% vs 36.6%, p=0.57 Atrial fibrillation: 2.8% vs 6.7%, p=0.02 Among patients with chronic hypertension, rate of renal replacement therapy: 42.2% vs 31.7%, p=0.046
Ovation Pilot Trial 2016(56)	118 patients with vasodilatory shock across 11 ICUs in Canada and the US	Enrollment after "adequate fluid resuscitation" per treating physician and within 24 hours of vasopressor initiation	Low-target arm: 60-65 mmHg High-target arm: 75-80 mmHg	Vasopressor dose (norepinephrine-equivalents, median): 10mg vs 14 mg, p=0.017 Vasopressor duration (median): 3 vs 5 days, p=0.0075	*Separation in MAP between groups*: 9mmHg (95% CI 7-11mmHg) Composite mortality or persistent organ-

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					dysfunction at 28 days: 44% vs 46%, p=0.21 Cardiac arrhythmia: 20% vs 26%, p=0.07
The 65 Trial 2020(58)	2,600 patients ≥ 65 years old with vasodilatory shock across 65 ICUs in the UK	Enrollment after "adequate fluid resuscitation" per treating physician and within 6 hours of vasopressor initiation	Low-target arm: 60-65 mmHg High-target arm: Usual care	Vasopressor dose (norepinephrine-equivalents, median): 17.7mg vs 26.4mg, difference -8.7mg [95% CI -12.8 to -4.6mg] Vasopressor duration (median): 33 hours vs 38 hours, difference -5 hours [95%. CI -7.8 to -2.2 hours]	*Unadjusted 90-day mortality:* 41.0% vs 43.8%, p=0.15 (OR 0.89, 95% CI: 0.76-1.04) Adjusted 90-day mortality: aOR 0.82, 95% CI: 0.68-0.98 90-day mortality in patients with chronic hypertension: 38.2% vs 44.3%, p=0.047 (aOR 0.67, 95% CI: 0.51-0.88)
ANDROMEDA-SHOCK 2019(62)	424 patients with septic shock and lactate ≥2.0 mmol/L across 28 ICUs in 5 countries	Enrollment after at least 20ml/kg fluids and within 4 hours of vasopressor initiation	MAP ≥65 mmHg with additional fluids, higher MAP targets, and inotropes in patients who failed to meet the randomized resuscitation target Arm 1: Capillary refill time normalization	Vasopressor doses not reported Vasopressor-free days within 28 days (mean): 16.7 vs 15.1 days, p=0.18	*28-day mortality*: 34.9% vs 43.4%, p=0.06 28-day mortality among patients with APACHE II scores<25: 24.6% vs 36.3%;

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			Arm 2: Decrease in serum lactate of 20%		(HR 0.61, 95% CI: 0.39-0.96)

**Results listed as intervention vs control, p-value
† Denotes studies that did not meet pre-specified targets for separation in fluid delivery between study arms
§ Results presented as lower-MAP target arm vs higher-MAP target arm for SEPSISPAM, Ovation, and the 65 Trial and as capillary refill time arm vs lactate arm for ANDROMEDA-SHOCK
Primary outcomes are reported in italics
PLR=Passive Leg Raise, AKI=Acute Kidney Injury, RRT=Renal Replacement Therapy, LOS=Length of stay, CI= Confidence Interval

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Table 4. Outstanding clinical questions in the management of early-sepsis induced hypoperfusion, related to topics covered in this review

Topic	Outstanding Clinical Questions	Ongoing Trials	Trial Details	Status
Fluid Resuscitation	1. Should patients with sepsis-induced hypoperfusion receive an initial fluid bolus volume of 30ml/kg vs other volumes (e.g., 20ml/kg) vs initial vasopressors without IV fluid?	None		
Fluid Resuscitation	2. For patients with ongoing sepsis-induced hypoperfusion despite an initial fluid bolus, should subsequent fluid boluses be guided by total volume goals, clinical criteria, serial evaluations of fluid responsiveness, or all of the above?	None		
Vasopressor Timing	3. For patients with sepsis-induced hypotension should blood pressure be treated with additional fluid resuscitation vs initiation of vasopressors?	CLOVERS [NCT03434028]	1,563 patients with sepsis-induced hypotension in US EDs and ICUs randomized to early vasopressors and restrictive fluids vs liberal fluids	Completed, see Table 3
		ARISE FLUID [NCT04569942]	1,000 patients with sepsis-induced hypotension in New Zealand and Australia EDs randomized to early vasopressors and restrictive fluids vs liberal fluids	Recruiting
Vasopressor Timing	4. For patients with sepsis-induced hypotension, should vasopressors be started before an initial fluid bolus, concurrently with an initial fluid bolus, or only if blood pressure fails to respond to	EVIS [NCT05179499]	3,286 patients with sepsis-induced hypotension in the UK randomized to early, peripheral vasopressors	Recruitment starting

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	an initial fluid bolus?		vs standard care	
Resuscitation Targets	5. For patients with sepsis-induced hypotension, should the target MAP be ≥65 mmHg, 60-65 mmHg, or another target?	None		
Resuscitation Targets	6. For patients with sepsis-induced hypoperfusion, should resuscitation be guided by targets other than MAP, such as diastolic blood pressure or tissue perfusion markers?	ANDROMEDA-2 [NCT05057611]	1500 patients with septic shock across multiple hospitals on 4 continents randomized to resuscitation guided by capillary refill time combined with clinical hemodynamic phenotyping (using pulse pressure variation to guide additional fluid and diastolic blood pressure to guide vasopressors) vs usual care	Recruiting since 2021
		TARTARE-2S [NCT02579525]	200 patients with septic shock in 4 European ICUs randomized to tissue perfusion targeted resuscitation (capillary refill time, skin mottling, lactate, peripheral temperature, urine output, MAP, and $ScvO_2$) vs standard MAP targets	Recruiting since 2016
Route of Vasopressor	7. For patients with sepsis-induced hypotension on vasopressor therapy,	None		

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Administration	under what circumstances should central venous access be obtained?			
Blood Pressure Monitoring	8. For patients with sepsis-induced hypotension on vasopressors, should blood pressure be monitored invasively with an arterial catheter vs non-invasively with a blood pressure cuff vs non-invasively with other novel blood pressure monitoring strategies?	None		

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Figure 1. Conceptual diagram of review concepts and their definitions

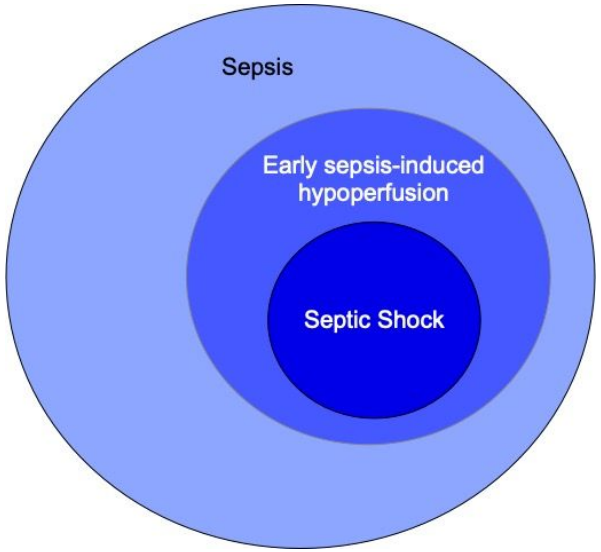

Figure 1 Definitions(2)	
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Early	Occurring within the first few hours of a patient's presentation with sepsis
Sepsis-induced	Related to a patient's presentation with sepsis and without another clear cause
Hypoperfusion	No clear definition. Generally conceptualized as reduced blood flow leading to inadequate delivery of oxygen and nutrients to tissues. Often denoted clinically by the presence of hypotension or hyperlactatemia.
Hypotension (*Sepsis-3)*	MAP <65 mmHg or vasopressor therapy
Hyperlactatemia (*Sepsis-3)*	Serum lactate level >2mmol/L (18mg/dL)
Septic shock *(Sepsis-3)*	Sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation

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Adequate volume resuscitation	No explicit definition provided in Sepsis-3, topic of debate

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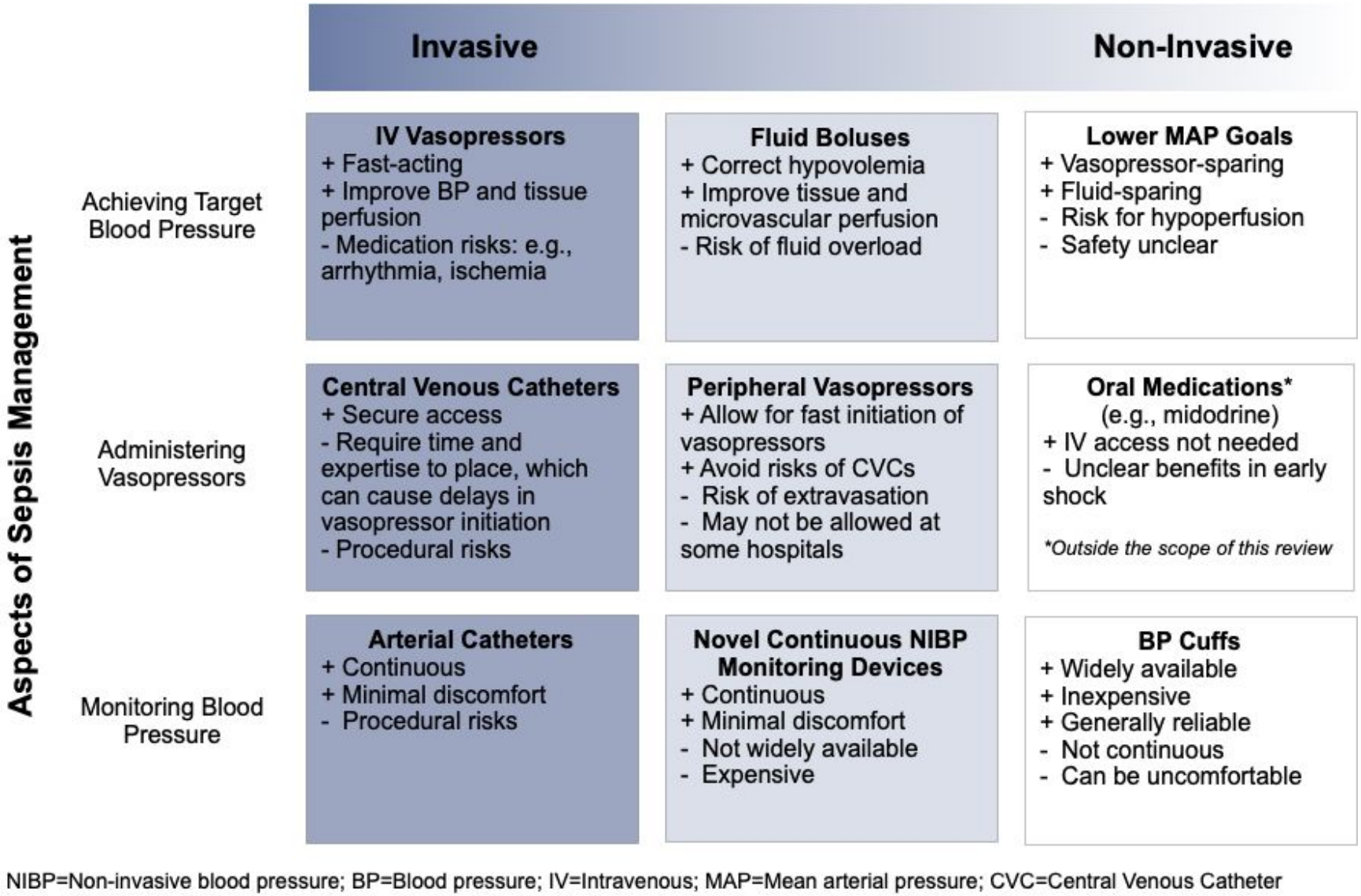
Figure 2. Overview of invasive vs non-invasive approaches to the management of early sepsis-induced hypoperfusion



NIBP=Non-invasive blood pressure; BP=Blood pressure; IV=Intravenous; MAP=Mean arterial pressure; CVC=Central Venous Catheter

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Evolving management practices for early sepsis-induced hypoperfusion: a narrative review

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ONLINE DATA SUPPLEMENT

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Supplement: Other Aspects of Resuscitation

Here we list other important management questions that are beyond the scope of this review, several of which are well-covered in other reviews.

What is the best fluid for resuscitation? Apart from the SMART trial, which favored balanced crystalloids, most large trials comparing balanced crystalloids vs normal saline have yielded neutral results for mortality and kidney injury.(91) However, a Bayesian meta-analysis combining 13 large RCTs with 35,884 patients found a high probability that balanced fluid reduces mortality over normal saline, suggesting balanced crystalloids are preferred in critically ill patients without brain injury(92). There are few data comparing the different balanced crystalloids.

Should IV fluids be administered as rapid boluses or slower infusions? There is concern that rapid fluid boluses may increase the negative consequences of fluids compared to slower fluid infusion, though there are limited data comparing these two fluid administration approaches. The largest RCT of fluid rate, the BaSICS trials, could not provide conclusive results on mortality difference by fluid infusion rate (333ml/hr vs 999ml/hr).(93) However, the ability to detect a meaningful difference in outcomes was limited given randomization occurred upon ICU admission, after initial fluid resuscitation in the ED, and patients received low fluid volumes during the study period. A secondary analysis of BaSICS using probabilistic conditional average treatment effects showed a fluid rate could be recommended for 19% of patients, with younger patients admitted

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after elective surgery potentially benefiting from slower infusions vs older patients with sepsis benefiting from rapid infusions.(94) Rapid boluses remain standard practice.

Should albumin be incorporated into resuscitation to facilitate fluid-restriction and improve patient outcomes? The addition of albumin during resuscitation has been suggested, particularly after large amounts of crystalloids, based on the theoretical benefit of improved oncotic pressure. The largest clinical trial of albumin in sepsis, the ALBIOS trial, found neutral results for mortality with the addition of 20% albumin to standard crystalloid resuscitation vs crystalloid resuscitation alone in patients with severe sepsis.(95) However, the addition of albumin resulted in lower 90-day mortality in a post-hoc analysis of patients in shock. Therefore, adding albumin in patients with septic shock who require large volume resuscitation may be warranted, though more work is needed to understand indications for albumin and optimize its use. The ongoing ALBIOSS-BALANCED trial [NCT03654001] is a 2-by-2 factorial RCT comparing resuscitation with balanced crystalloid vs normal saline with or without 20% albumin in patients with septic shock.

What are the optimal initial and subsequent vasopressors? Supported by the literature, guidelines recommend norepinephrine followed by the addition of vasopressin(6).There is evidence for a relative vasopressin deficiency in septic shock(96) and adding vasopressin may help spare catecholamine use (97,98), though pre-clinical studies suggest vasopressin can cause vasoconstriction and decreased cardiac output(99) which have not been measured in existing trials. While the three

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major trials comparing adding vasopressin vs increasing norepinephrine doses in patients with septic shock have yielded neutral results overall, in the largest trial (VASST), mortality was lower in the vasopressin group in patients with less severe shock, with no difference in more severe shock(97,98,100). However, at this time, the optimal threshold for adding vasopressin and when to incorporate the novel catecholamine-sparing agent angiotensin II are unclear based on available evidence.

What role do corticosteroids play in early resuscitation? Several large trials—ADRENAL, APROCCHSS, and VANISH—have found that the addition of corticosteroids in patients with persistent sepsis-induced hypotension and vasopressor requirements may accelerate shock resolution.(97,101,102) However, in these trials, corticosteroids were only added in patients who had been on vasopressors for several hours, leading the SSC to suggest adding corticosteroids in patients on vasopressors for at least 4 hours.(6) The benefit of starting corticosteroids earlier, closer to the time of vasopressor initiation, is unknown.

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