



# How to avoid fluid overload

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## Purpose of review

This review highlights the recent evidence describing the outcomes associated with fluid overload in critically ill patients and provides an overview of fluid management strategies aimed at preventing fluid overload during the resuscitation of patients with shock.

## Recent findings

Fluid overload is a common complication of fluid resuscitation and is associated with increased hospital costs, morbidity and mortality.

## Summary

Fluid management goals differ during the resuscitation, optimization, stabilization and evacuation phases of fluid resuscitation. To prevent fluid overload, strategies that reduce excessive fluid infusions and emphasize the removal of accumulated fluids should be implemented.

## Keywords

fluid overload, fluid resuscitation, shock

## INTRODUCTION

Fluid overload is a relatively frequent occurrence in critically ill patients and is often a consequence of critical care intervention. Despite a common perception that it is benign, fluid overload in the critically ill is independently associated with increased morbidity and mortality. Thus, intravenous fluids need to be dosed appropriately to reduce the risk of harm associated with this potentially life-saving therapy. This review presents the recent evidence relevant to fluid overload in critically ill patients and provides an overview of fluid management strategies aimed at preventing fluid overload during the resuscitation of patients presenting with shock.

## OUTCOMES ASSOCIATED WITH FLUID OVERLOAD

Fluid extravasation into the interstitial space can adversely affect multiple organ systems (Table 1). Although characterizing fluid overload in every organ system is difficult (that is some systems lend themselves to fluid measurement and correlation with function more than others), increasing evidence has been noted in the pulmonary, cardiac, renal and gastrointestinal systems. Graded increases in extravascular lung water impair oxygenation and are independently associated with mortality [1]. Increased renal interstitial fluid may reduce capillary blood flow and lead to renal ischemia, which

can cause or worsen acute kidney injury (AKI). Fluid overload can also worsen myocardial and liver function, impair coagulation, delay wound healing and is a risk factor for intra-abdominal hypertension [2]. In the gastrointestinal system, diffuse intestinal wall edema can cause malabsorption and ileus. Other organ systems, such as the neurologic system, are more difficult to assess for fluid overload and associated complications.

The effect of tissue edema on organ function likely contributes to the association between fluid overload and increased morbidity and mortality. This association has been demonstrated in multiple studies involving patients with severe sepsis and the acute respiratory distress syndrome (ARDS) [1,3<sup>a</sup>,4–6]. In addition, Silversides *et al.* [7<sup>a</sup>] analyzed data from a prospectively collected registry of 492 ICU patients with AKI who received more than 2 days of renal replacement therapy. The study identified that a higher mean daily fluid balance independently increased the odds of hospital mortality [odds ratio

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**KEY POINTS**

- Fluid overload is associated with increased morbidity and mortality in critically ill patients.
- Aggressive fluid resuscitation increases the risk of excessive fluid administration and fluid overload.
- Fluid responsiveness should be assessed prior to fluid administration to reduce the risk of excessive fluid administration.
- Fluid resuscitation strategies should include clear limits and individualized end-points to reduce the risk of excessive fluid administration.
- Interventions aimed at achieving a negative fluid balance should be considered after adequately resuscitating patients with shock.

(OR) (95% confidence interval [CI]): 1.36 per 11 positive (1.18–1.57)].

Similar results have been shown among surgical and trauma patients. In a prospective observational study of 144 acute care surgery patients admitted to a surgical ICU, those patients who had a negative fluid-balance on the fifth ICU day had an independently lower odds of hospital mortality [OR (CI), 0.31 (0.13–0.76); *P* = .010] [8<sup>■</sup>]. A recent meta-analysis of

three randomized controlled trials and seven observational studies comparing liberal with restrictive fluid management strategies in trauma patients concluded that liberal fluid resuscitation may be associated with higher mortality [9<sup>■</sup>].

Fluid overload is also associated with increased hospital costs and greater hospital resource utilization. A single center study by Kelm *et al.* [10<sup>■</sup>] found that 77% of patients with sepsis had signs of persistent fluid overload on the third day after receiving a standardized early goal-directed therapy protocol. Fluid overload independently increased subsequent diuretic use [OR (CI): 1.66 (1.01–2.74)], thoracenteses [OR (CI): 3.83 (1.74–9.15)] and hospital death [OR (CI): 1.92 (1.16–3.22)]. A retrospective matched cohort study of 63 974 adult patients from a multi-center ICU database found that patients with fluid overload had statistically significant increases in the average total hospital costs per visit (56.7%) and the average total ICU cost per visit (92.6%) compared with patients without fluid overload (*P* < 0.001) [11<sup>■</sup>]. Patients with fluid overload also had a two-fold longer ICU stay, 4% higher hospital mortality and 0.5% higher risk for 30-day readmissions.

**HOW TO PREVENT FLUID OVERLOAD**

Fluid management strategies including two elements appear to be helpful in preventing fluid

**Table 1.** The pathophysiologic effects of fluid overload on organ systems

Body system	Effect of fluid overload	Clinical manifestation
Central nervous system	Cerebral edema	Impaired cognition Delirium
Respiratory system	Pulmonary edema Pleural effusions	Increased work of breathing Impaired gas exchange Decreased lung compliance Increased extravascular lung water
Cardiovascular system	Myocardial edema Pericardial effusions	Impaired contractility Diastolic dysfunction Conduction abnormalities
Gastrointestinal system	Gut wall edema Ascites	Malabsorption Ileus Bacterial translocation Intra-abdominal hypertension
Hepatobiliary system	Hepatic congestion	Cholestasis Impaired synthetic function
Renal system	Renal interstitial edema Elevated renal venous pressure	Acute kidney injury Uremia Salt and water retention
Skin and musculoskeletal system	Tissue edema Impaired lymphatic drainage Deranged microcirculation	Poor wound healing Pressure ulcers Wound infection

overload in patients with shock. First, during resuscitation, excessive fluid administration should be avoided. Aggressive fluid resuscitation is associated with a high incidence of fluid overload. This was recently demonstrated in a retrospective cohort study of 405 patients with severe sepsis or septic shock who received early goal-directed therapy [10<sup>¶</sup>]. There was clinical evidence of fluid overload 24 h after admission in 67% of patients, and this persisted until day 3 of admission in 48% of patients. Patients with fluid overload on days 1 and 3 had a higher risk of hospital mortality compared with patients without fluid overload, highlighting the possible dangers of over-resuscitation with intravenous fluids. Second, removal of excess fluids should be promoted in patients whose shock has resolved. In patients with septic shock who have been adequately resuscitated, conservative fluid management leading to negative fluid balances is associated with a decrease in hospital mortality [4].

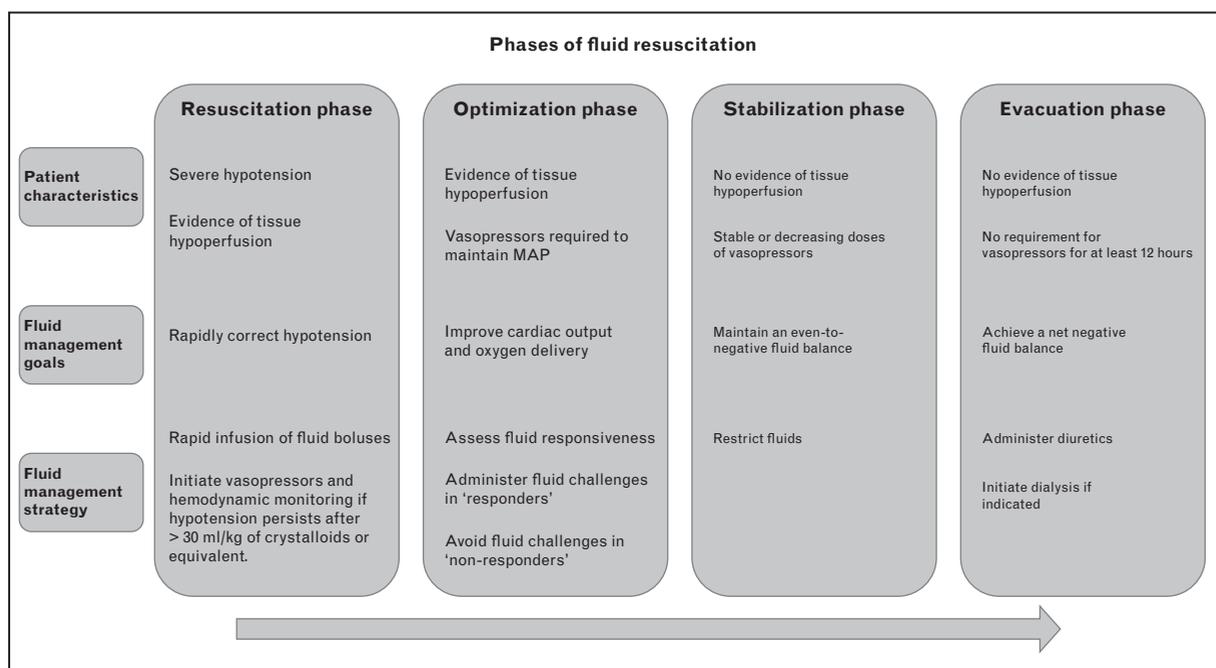
These principles can be applied during the resuscitation of patients with shock which can be viewed as occurring in four phases corresponding to the acronym 'ROSE': resuscitation, optimization, stabilization and evacuation [12<sup>¶</sup>]. The goals of fluid administration as well as the associated risk and benefits will vary depending on phase of resuscitation (Fig. 1). The primary goal of fluid administration during the resuscitation phase is to rapidly correct systemic hypotension. During the optimization phase, the goal of fluid administration is to improve oxygen delivery to the tissues. In the

stabilization phase, patients are hemodynamically stable and fluid administration should be restricted. In the evacuation phase, interventions are targeted at fluid removal.

## RESUSCITATION PHASE

This is the initial phase of resuscitation in patients with severe systemic hypotension and evidence of tissue hypoperfusion, such as an elevated serum lactate. In this phase, the immediate goal is to correct the hypotension, and intravenous fluids are typically first-line therapy [13]. The volume of fluid required during this phase must be individualized and will necessarily vary between patients and according to fluid type. In sepsis-induced hypotension, the Surviving Sepsis Campaign guidelines recommend an initial minimum crystalloid fluid bolus of 30 ml/kg of body weight [13]. Multiple fluid boluses are often given to achieve a predefined BP target and frequently with limited hemodynamic monitoring such as routine bedside vital signs. Fluids should be given quickly as earlier resuscitation is associated with better outcomes. This was recently demonstrated in a study of 594 with severe sepsis and septic shock that examined the proportion of total fluids received during the first 3 h compared with the later 3 h and found that a higher proportion of total fluids received within the first 3 h of resuscitation was associated with improved survival [14<sup>¶</sup>].

The BP targets will depend on the patient's underlying diagnosis. The recommended mean



**FIGURE 1.** The phases of fluid resuscitation in patients with shock. MAP, mean arterial blood pressure.

arterial pressure in the majority of patients with septic shock is 65 mmHg. This recommendation is supported by a recent randomized controlled trial that compared the effect of a high mean arterial pressure target (80–85 mmHg) with a low mean arterial pressure target (65–70 mmHg) in patients with septic shock [15<sup>■</sup>]. There were no significant differences in 28-day or 90-day mortality between both groups. However, patients with chronic hypertension in the group targeting a higher mean arterial pressure required less renal-replacement therapy than those in the group targeting a mean arterial pressure between 65 and 70 mmHg. This suggests that BP targets must be individualized, as a higher mean arterial pressure may confer benefit to specific populations of critically ill patients with shock.

Although the initial focus of resuscitation should be on fluid administration, vasopressor support should not be delayed in those with persistent hypotension. There is no consensus on the optimal timing of vasopressor use during this phase. However, the administration of vasopressors prior to adequate fluid resuscitation in hypovolemic patients can worsen organ perfusion and function. A retrospective study of 2849 patients with septic shock that examined the influence of the timing of fluid and vasopressor therapy as well as the total volume of fluids given on hospital mortality suggested that starting vasopressors within the first hour of resuscitation may be harmful [16<sup>■</sup>]. Conversely, delayed initiation of vasopressors in patients with persistent hypoperfusion despite fluid administration can also worsen end-organ damage and is associated with increased mortality [17<sup>■</sup>,18<sup>■</sup>]. Ongoing or unmonitored volume resuscitation in patients with persistent hypotension increases the likelihood of excessive fluid administration. A reasonable approach for patients whose hypotension has not resolved after receiving a volume of crystalloid fluid equivalent to 30 ml/kg of body weight is to start a vasopressor while continuing fluid therapy guided with the aid of hemodynamic monitoring.

### Optimization phase

The primary problem during the optimization phase of resuscitation is ongoing or occult tissue hypoperfusion. In this phase, the goal of fluid administration is to increase oxygen delivery to the tissues in order to meet cellular oxygen demands. Oxygen delivery ( $DO_2$ ) is primarily a function of cardiac output (heart rate  $\times$  stroke volume), hemoglobin concentration and arterial oxygen saturation. The purpose of administering a fluid challenge is to increase oxygen delivery by increasing stroke volume and thus,

cardiac output. Not all critically ill patients will respond in this manner to fluid bolus therapy (that is an increase in cardiac output, known as a fluid ‘responder’). It is estimated, however, that 50% of patients are not fluid responders (‘nonresponders’) and will not increase stroke volume in response to a fluid challenge [19]. Further fluid challenges in such patients potentially expose them only to the harmful effects of fluid accumulation without providing any of the potential benefits. Consequently, fluid therapy aimed at improving oxygen delivery should be avoided in patients who are fluid nonresponders and a greater emphasis put on the use of vasoactive agents.

There is no gold standard for determining fluid responsiveness, but there is growing consensus favoring the use of dynamic measures of fluid responsiveness over static measures such as central venous pressure (CVP) or central venous oxygen saturation ( $ScvO_2$ ) [20<sup>■</sup>]. Multiple studies have shown that CVP is a poor measure of volume status and does not reliably predict fluid responsiveness, with the possible exception of tracking changes in CVP induced by passive leg raising [21,22]. Using CVP to guide fluid administration may easily lead to excess fluid administration and fluid overload. There are several available methods to accurately assess fluid responsiveness in both spontaneously breathing and mechanically ventilated patients [20<sup>■</sup>]. Pulse pressure variation, stroke volume variation, as well as respiratory variations in the inferior vena cava, superior vena cava and internal jugular vein as measured by ultrasound have all been shown to accurately predict fluid responsiveness in mechanically ventilated patients [23<sup>■</sup>,24–27,28<sup>■</sup>]. The passive leg raise technique in combination with measurement of cardiac output, stroke volume or aortic blood flow is effective in spontaneously breathing patients [29,30]. In practice, the use of these techniques varies widely. A prospective multicenter study of adult patients with shock in 19 French ICUs showed significant between-center differences in the use of hemodynamic monitoring to guide fluid administration along with differences in both the total volume of fluids given during the first 4 days and the average size of individual fluid boluses [31<sup>■</sup>].

During the resuscitative phase, fluids must be administered in a timely and targeted manner with appropriate limits to fluid administration. Surrogate marker of tissue perfusion, such as serum lactate and  $ScvO_2$ , is often used to determine the end-point of resuscitation. Three recent large multicenter randomized controlled studies in sepsis showed no benefit in using protocols that required continuous  $ScvO_2$  monitoring over usual care. The American

Protocolized Care for Early Septic Shock trial, the Australasian Resuscitation in Sepsis Evaluation trial and the UK Protocolized Management in Sepsis trial all showed no difference in 90-day mortality when comparing early goal-directed therapy with usual care in the management of severe sepsis and septic shock [32<sup>■</sup>–34<sup>■</sup>]. These findings argue against routinely targeting absolute values of measures such as ScvO<sub>2</sub> during the resuscitation of patients with septic shock. The adequacy of resuscitation should be monitored using clinical judgment as well as physiologic and biochemical parameters and should be individualized to the patient. Clear criteria, such as the absence of fluid responsiveness or the presence of clinical evidence of fluid overload, should be used to determine when to stop giving fluid challenges in patients who fail to achieve their resuscitation goals.

### Stabilization phase

Patients in the stabilization phase of resuscitation have adequate tissue perfusion and may still require hemodynamic support with vasopressors, although the doses of these medications will be stable or decreasing. In this group, careful weighing of the potential risks and benefits of further fluid administration is required and further fluid administration should be restricted in patients without ongoing losses. In patients who are fluid responsive, a fluid challenge may be reasonable with the goal of decreasing vasopressor requirements. This must be balanced against the evidence that late goal-directed therapy may be associated with worse outcomes [35].

Fluids should be restricted in patients not requiring hemodynamic support. In the absence of evidence suggesting hypoperfusion, fluid challenges should not be given, even in those who are fluid responsive. Careful attention must be paid to assess hypoperfusion, whether physiologically or with clinical laboratory tests. Maintenance fluids are usually not required and should be discontinued when possible as critically ill patients frequently receive sufficient fluids with medications and nutrition to account for insensible losses.

### Evacuation phase

In this phase, the goal is to remove excess fluids in patients who are hemodynamically stable and do not have evidence of tissue hypoperfusion. Recent studies have demonstrated that protocols aimed at achieving a negative fluid balance are feasible and are associated with decreased morbidity. The Fluid and Catheter Treatment Trial (FACTT trial) enrolled 1000 patients with ARDS who were managed with

either a conservative or liberal fluid strategy [36]. Patients with a mean arterial pressure more than 60 mmHg, no vasopressor support for more than 12 h, adequate urine output and circulation were either given furosemide targeted to achieve a CVP less than 4 mmHg or pulmonary artery occlusion pressure (PAOP) less than 8 mmHg (fluid conservative group) or CVP (< 10 mmHg) and PAOP (< 14 mmHg) (fluid liberal group). In this study, there was no difference in mortality but the conservative fluid strategy led to a more negative fluid balance at 7 days, 2.5 more days alive and free of mechanical ventilation and a shorter ICU length of stay.

In order to more easily operationalize a fluid restrictive strategy, a simplified version of the FACTT fluid management protocol was evaluated in a recent study [37<sup>■</sup>]. Using the 'FACTT lite' protocol, patients with MAP more than 60 mmHg and who were off vasopressors for more than 12 h were given furosemide to target a CVP less than 4 mmHg or PAOP less than 8 mmHg if they had adequate urine output [37<sup>■</sup>]. A total of 1124 patients who were managed with the FACTT lite protocol were retrospectively compared with the 497 patients managed with the FACTT liberal fluid strategy and the 503 patients who were managed with the FACTT conservative fluid strategy. The investigators found that management with the FACTT lite protocol resulted in a significantly lower fluid balance than the FACTT liberal protocol and no difference in the number of ventilator-free days compared with the FACTT conservative protocol. It appears that this simplified version of a fluid conservative approach achieves similar fluid balance, and we believe it would result in similar improved outcomes if compared with a historical liberal approach to fluid management.

Biomarkers may also be used to guide fluid removal in critically ill patients. In the B-type Natriuretic Peptide for the Fluid Management of Weaning (BMW) study, 304 mechanically ventilated patients were randomized to a B-type natriuretic peptide (BNP)-driven fluid management strategy or usual care [38,39]. Patients in the BNP-driven group received diuretics and had fluid restricted on days when their BNP was at least 200 pg/ml. Duration of weaning was significantly shorter in the BNP-driven group, and there was a decreased incidence of ventilator-associated pneumonia and ventilator-associated events.

There is no consensus about the optimal timing of fluid removal, and there are limited data to guide a specific recommendation. In both the FACCT trial and the BMW trial, patients were required to have been off vasopressor therapy for at least 12 h before

diuretics were administered. A reasonable approach is to begin restricting fluids when patients achieve hemodynamic stability and/or normal tissue perfusion, and to consider initiating diuresis in patients who are hemodynamically stable with clinical evidence of fluid overload and unable to achieve a negative fluid balance spontaneously. An expert discussion of the pharmacologic management of fluid overload and the indications and management of mechanical fluid removal in critically ill patients was recently published [40<sup>a</sup>,41<sup>a</sup>].

There are understandable concerns about the risk of organ hypoperfusion associated with fluid removal. The data in this regard are inconclusive. The development of shock in patients managed with the FACTT lite protocol was not significantly different compared with patients managed with the FACTT liberal protocol [37<sup>a</sup>]. There are conflicting results regarding organ dysfunction with conservative fluid management in ARDS: greater cardiovascular dysfunction, and less acute neurological dysfunction [36], although a subsequent report found a higher incidence of long-term cognitive dysfunction with conservative fluid therapy [42]. In the BMW trial, there was no difference in the incidence of renal failure between the intervention and control groups [38]. The impact of fluid conservative strategies on organ function requires additional study, particularly as it relates to the ebb and flow of fluid therapy in sepsis. Given these concerns, fluid removal should be performed cautiously with clear limits and appropriate safety monitoring to avoid inducing hypovolemia.

## CONCLUSION

Fluid overload in the critically ill is a potentially preventable complication that is associated with increased morbidity and mortality. Specific fluid management strategies can be implemented during each phase of resuscitation to help mitigate the effects of fluid overload and thus, improve outcomes. Ultimately, the most effective fluid management strategy is the one that is individualized and emphasizes adequate early resuscitation and a more restrictive approach to fluid administration in the latter phases. Further research on how best to personalize fluid therapy in the critically ill is needed, particularly in the dynamic critically ill patient.

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## Conflicts of interest

Dr O.C.O. and Dr D.J.M. have no conflicts to disclose. Dr G.S.M. conducts research on fluid management in critically ill patients and his institution (Emory University) has received funding from Abbott Laboratories and Baxter Healthcare for research, and Dr G.S.M. has served as a medical advisor to CSL Behring and Grifols.

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