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REVIEW

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Fluid management strategies in critically ill patients with ARDS: a narrative review

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Abstract

Hypervolemia is associated with worse outcomes in critically ill patients with acute respiratory distress syndrome (ARDS), with early positive fluid balance linked to longer intensive care unit (ICU) stays, prolonged ventilatory support, and increased mortality risk due to cardiopulmonary complications, lung edema, and extrapulmonary organ dysfunction. However, a restrictive fluid management strategy is associated with hypoperfusion and distal organ dysfunction, including acute renal failure and cognitive impairment. Indeed, fluid administration in patients with ARDS represents a challenge, as it must take into account the underlying condition, such as sepsis or acute brain injury (ABI), where optimal fluid management is a major determinant of disease outcome. In such cases, the approach to fluid administration should be individualized based on hemodynamic and clinical parameters according to the course of the disease. The strategy of "salvage, optimization, stabilization, and de-escalation" can guide fluid administration in the initial therapeutic approach, whereas negative fluid balance with the use of diuretics or renal replacement therapy (RRT) should be the goal once hemodynamic stabilization has been achieved.

Keywords Acute respiratory distress syndrome, Acute brain injury, Fluid management, Fluid overload, Fluid responsiveness, Sepsis

Introduction

The term ARDS refers to the acute onset of severe respiratory failure of non-cardiogenic origin, characterized by excessive hypoxemia, bilateral pulmonary infiltrates, and pulmonary inflammation with alveolocapillary hyperpermeability [1]. Since its initial description ~ 60 years ago [2] and its first definition in 1988 [3], the definition of ARDS has been re-evaluated over time. The first revision occurred in 1992 during an American–European consensus conference by the American Thoracic Society and the European Society of Intensive Care Medicine [4], followed by the ARDS Definition Task Force in Berlin in 2012 [5–7]. Recently, in light of advances in ARDS research and management, such as the use of noninvasive pulse oximetry to assess oxygenation, high-flow nasal oxygen for managing severe hypoxemic respiratory failure, and challenges in diagnosis and treatment in resource-limited settings, a revised definition has been proposed. This expanded definition includes non-intubated patients, allows the use of oxygen saturation to assess hypoxemia, and incorporates lung ultrasound as an imaging modality [8].

Fluid overload has been shown to negatively impact outcomes in ARDS patients, with early positive fluid balance during critical illness being associated with the onset of ARDS, prolonged mechanical ventilation, longer ICU stay, and an increased risk of death [9, 10]. Besides excessive inflammation, a major pathophysiological issue in the pathophysiology of ARDS is the compromised lung microvascular barrier resulting from elevated endothelial and epithelial permeability, leading to the retention of protein-rich edema fluid in both the interstitial and alveolar spaces. [11–13]. The influx of protein-rich fluid into the interstitium reduces the normal oncotic pressure

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differential between the intravascular and interstitial spaces, making ARDS patients more susceptible to the hydrostatic forces linked to elevated pulmonary capillary wedge pressure (PCWP) than those with cardiogenic pulmonary edema [14]. Recognizing that patients with ARDS are especially sensitive to hydrostatic forces related to intravascular volumes, a conservative fluid management strategy that minimizes intravenous fluid administration and includes diuretics may help lower hydrostatic pressure and increase serum oncotic pressure, potentially reducing the risk of pulmonary edema [15]. In 2007, Wiedemann et al. conducted the Fluids and Catheters Treatment Trial (FACTT), which showed that a conservative fluid management strategy for ARDS patients, guided by hemodynamic and clinical parameters, resulted to a reduced fluid balance and improved outcomes, such as improved oxygenation and an increased number of ventilator-free days [16]. A subsequent, less restrictive protocol (FACTT Lite) further supported these findings, showing similarly improved outcomes [17].

Although conservative fluid strategy is an essential aspect of ARDS management, it is also linked to detrimental effects, including the development of acute renal failure, which may require RRT [16, 18], and cognitive dysfunction [19]. In addition, it should not be overlooked that fluid management in patients with ARDS must consider its etiology, particularly in cases of sepsis or ABI, where a suboptimal fluid strategy can significantly affect the patient's prognosis [20, 21]. Indeed, extensive research highlights that mortality is lower in critically ill septic patients when appropriate fluid volumes are administered during the initial stages of resuscitation, followed by restrictive fluid management once hemodynamic stability is achieved, compared to patients who receive either insufficient or excessive fluid volumes [22]. In addition, the frequent need for positive-pressure mechanical ventilation (PPMV) in those patients underscores the critical importance of maintaining adequate cardiac preload, as sepsis commonly results in a combination of vasodilatory shock and reduced cardiac output (CO), complicating patient management [23]. Moreover, in neurocritical care patients with brain injury, hypotension and hypovolemia are associated with reduced cerebral perfusion pressure (CPP), particularly important in those with symptomatic vasospasm, acute cerebrovascular occlusions, high-grade stenoses, or impaired cerebral autoregulation, leading to exacerbation or triggering of brain injury, resulting in higher mortality and worse outcomes [24–32].

Given the complex pathophysiology of ARDS and the limited research available, this review aims to comprehensively summarize the current evidence on fluid management in patients with ARDS and to clarify resuscitation strategies for this patient population. Our work explores fluid therapy in relation to ARDS pathophysiology and examines cardio-pulmonary–renal interactions, particularly within the context of invasive mechanical ventilation (MV). It also reviews the evidence on conservative vs. liberal fluid strategies, discusses the general principles of fluid management in critical illness, including types of fluids and approaches to hemodynamic monitoring, and addresses specific clinical contexts, such as ABI and sepsis. Finally, we identify current knowledge gaps and outline potential avenues for future research.

Methods

A comprehensive literature search was conducted using PubMed to identify relevant studies focusing on fluid management in ARDS. The search terms included"acute respiratory distress syndrome,""fluid management,""fluid resuscitation,""early goal-directed therapy,""fluid responsiveness,""hemodynamic monitoring,""sepsis,""acute brain injury,"and"critical care."Boolean operators (AND, OR) and truncations were applied to refine and optimize search results. The search was focused on articles published in English over the past 20 years (2004–2024), while key seminal works predating this period were included to ensure historical context and foundational understanding. Manual screening of references from selected studies was performed to identify additional relevant literature.

Fluid management in the context of ARDS pathophysiology

Multiple factors contribute to the cumulative fluid balance in ARDS patients, especially in situations, where concurrent circulatory failure is present, characterized by low systemic vascular resistance that demands fluid resuscitation. In patients with ARDS undergoing MV, positive airway pressure significantly influences positive fluid balance. Increased airway pressure elevates intrathoracic pressure, which in turn reduces central arterial blood volume [10]. Pathological conditions can exacerbate the negative impact of PPMV on both CO and venous return, especially with the use of high levels of positive endexpiratory pressure (PEEP). In situations, where effective blood volume is decreased, whether absolutely or relatively, such as in cases of sepsis, hypovolemia, obstructive and distributive shock, and dynamic hyperinflation, it is often necessary to administer intravenous fluids to facilitate volume expansion. This approach helps to elevate mean systemic filling pressure and enhance venous return, potentially in conjunction with vasopressors and/or inotropic agents during MV [33–36]. Nevertheless, the pathophysiology of normal pressure

pulmonary edema suggests that administering fluids can elevate left atrial and pulmonary venous pressures, which may aggravate alveolar flooding and reduce arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2). Moreover, research indicates that induced hypotension, along with reduced CO and pulmonary blood flow, as seen in hemorrhagic shock, increases alveolar and physiological dead space, thereby impairing gas exchange and leading to hypercapnia [37, 38]. PPMV not only reduces ventricular preload but also elevates endogenous levels of antidiuretic hormone (ADH), renin, aldosterone, and angiotensin II, which together increase the likelihood of fluid retention and volume overload [39–41].

Hypoalbuminemia is frequently seen in inflammatory conditions and is a typical characteristic of all critically ill patients [42]. ARDS is frequently linked to hypoproteinemia, which results from hemodilution and the leakage of proteins into the interstitial and alveolar spaces, leading to decreased serum oncotic pressure that can worsen the non-cardiogenic pulmonary edema and limit diuresis [15]. Moreover, it is related to both enhanced vascular permeability, which increases the distribution volume of albumin, and a reduced half-life of albumin, ultimately resulting in a lower total albumin mass, even though there is an increase in fractional synthesis [43].

Cardio-pulmonary–renal interactions in ARDS and invasive mechanical ventilation

Acute kidney injury (AKI) affects approximately one-third of mechanically ventilated patients and is associated with worse short- and long-term outcomes, as well as high mortality [44–46]. The pathophysiology of AKI in mechanically ventilated patients is multifactorial, including MV-associated hemodynamic alterations impairing venous return and CO, neurohormonal pathways, inflammatory cascades associated with lung injury (LI) and MV, and gas exchange disturbances, such as hypoxemia and hypercapnia (Fig. 1) [47–49].

PPMV fundamentally differs from the physiology of spontaneous ventilation, where positive intrathoracic pressures occur only transiently, particularly during coughing or the Valsalva maneuver [50]. PPMV is associated with significant hemodynamic consequences,

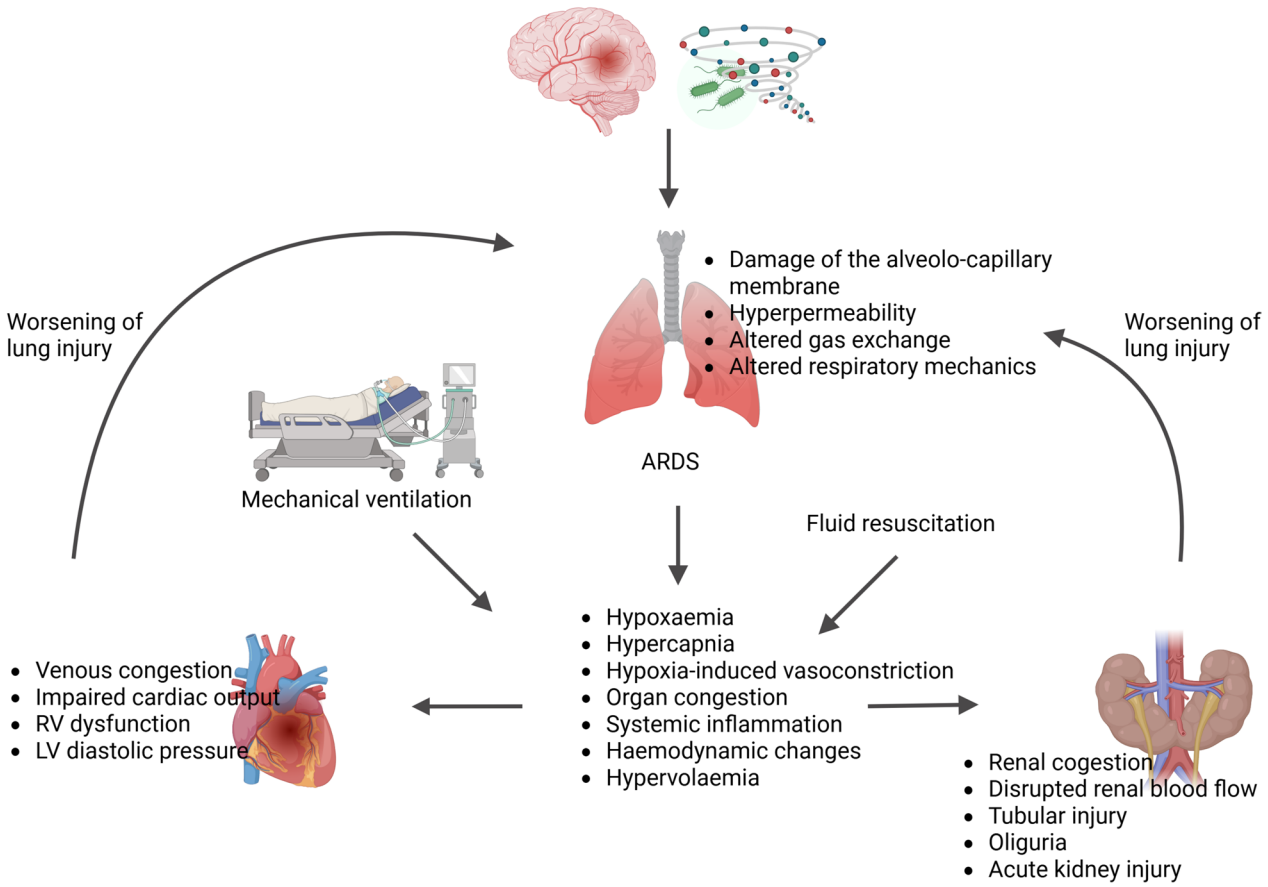

Fig. 1 Cardio-pulmonary–renal interactions in ARDS and invasive mechanical ventilation. *ARDS* acute respiratory distress syndrome, *LV* left ventricle, *RV* right ventricle

including increased right atrial pressures due to elevated intrathoracic pressures, which subsequently reduce the pressure gradient for venous return. As a result, altered venous return leads to decreased right ventricular (RV) preload and impaired organ perfusion. In addition, increased pulmonary vascular resistance may further impact RV stroke work, while a reduced intrathoracic-to-extrathoracic aortic pressure gradient lowers left ventricle (LV) afterload and stroke work, ultimately leading to a decrease in CO proportional to mean airway pressure (Fig. 1) [51, 52]. In the kidneys, elevated intrathoracic pressures, impaired CO due to impeded venous return, and atrial stretch lead to MV-related reductions in renal blood flow [53]. Moreover, elevated intrathoracic pressures and compromised RV function contribute to increased renal congestion due to reduced venous return, which manifests as elevated central venous pressure (CVP) and pulmonary vascular resistance [48, 54]. In addition, PEEP levels—a key component of the ventilatory strategy in patients with ARDS—are an additional factor leading to increased intra-abdominal pressure, depending on the level of positive pressure, respiratory system elastance, and pre-existing abdominal pressure. In combination with the caudal movement of the diaphragm, this may further worsen venous congestion and impair renal perfusion [44, 55, 56]. On the other hand, critically ill patients with AKI are at a significantly higher risk of developing severe respiratory failure requiring MV [57, 58].

Even with contradictory results, research highlights that PPMV may activate neurohormonal mechanisms influencing renal function, including the renin–angiotensin axis, secretion of ADH, atrial natriuretic peptide (ANP) production, and sympathetic activation. ADH secretion leads to a redistribution of intrarenal blood flow from the cortex to the medulla, resulting in prerenal vasoconstriction and greater fluid retention at any level of renal perfusion [59–62]. Moreover, the secretion of ADH can occur in response to PEEP [63], further exacerbating fluid retention and hypervolemia. Although the underlying pathophysiologic mechanisms behind this paradoxical effect are not fully understood, it is hypothesized that multiple factors contribute, including arterial baroreceptor activity [64, 65]. Furthermore, clinical and experimental research has shown that sympathetic activity related to PPMV is associated with increased renin activity, stimulation of the renin–angiotensin axis, impaired renal function, fluid and salt retention, and oliguria [40, 48, 63, 65–67]. In contrast, atrial and cerebral natriuretic peptides counteract these effects by promoting natriuresis through the direct inhibition of renin secretion from juxtaglomerular cells and the suppression of aldosterone production and release [63, 68, 69].

Although MV is a life-saving intervention for patients with ARDS, it can also aggravate LI, a phenomenon known as ventilator-induced lung injury (VILI) [70]. The pathophysiology of VILI is complex and involves multiple mechanisms, including increased trans-alveolar (transpulmonary) pressures (barotrauma), alveolar distension (volutrauma), and cyclic alveolar opening and closure (atelectrauma). In addition to structural consequences, these mechanical forces activate complex inflammatory pathways, triggering regional and systemic inflammatory responses (biotrauma) that can extend to extrapulmonary organs, including the kidneys [7, 71]. MV-associated inflammatory cascades can spread through the systemic circulation due to increased alveolar–vascular permeability, leading to the decompartmentalization of the inflammatory response and affecting extrapulmonary organs and systems [7, 72]. These inflammatory mediators include tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, soluble TNF-α receptor 75, IL-1β, and IL-1 receptor antagonist (IL-1ra), detected in both plasma and bronchoalveolar lavage fluid of mechanically ventilated patients, as well as in experimental models of MV [73–76]. Among these mediators, some have been implicated in kidney injury by inducing epithelial cell apoptosis and reducing renal blood flow, with these effects being more pronounced in individuals who received lung-injurious MV [49, 77].

Arterial blood gas abnormalities, such as systemic acidosis, hypoxemia, and hypercapnia, may impact renal function and contribute to AKI by reducing renal perfusion pressure and altering renal vascular resistance (Fig. 1). These effects occur through various pathogenic mechanisms, including adrenergic stimulation and disruptions in nitric oxide metabolism [48, 78]. Although it is well-established that lung-protective ventilation with low tidal volumes (6 mL/kg) and PEEP improves prognosis in patients with ARDS, it may also lead to hypercapnia and acidemia [79]. Indeed, a retrospective cohort study of ARDS patients with normal renal function prior to ARDS onset highlighted that acidosis on day 1 was significantly related to the occurrence and severity of AKI [80] and is associated with elevated oxygen consumption in the proximal tubule [81, 82]. Moreover, hypercapnia may promote vasoconstriction of the renal vasculature, resulting in elevated vascular resistance, decreased renal blood flow (RBF) and glomerular filtration rate (GFR), and reduced natriuresis [48, 83]. Finally, in patients with severe LI, hypoxia-related renal ischemia with PaO_2 levels below 75 mmHg contributes to an imbalance between renal oxygen supply and demand, the formation of harmful metabolic byproducts, necrosis of tubular epithelial cells, and impairment of renal function [84].

Conservative vs. liberal fluid strategies

A fluid administration strategy in critically ill patients is a real challenge in daily clinical practice, given the need to achieve adequate oxygen delivery and tissue perfusion while reducing the development or worsening of potential LI [85]. An unrestricted fluid administration strategy during the initial resuscitation phase is referred to as liberal and is also characterized by the absence of targeted fluid removal after the patient achieves hemodynamic stabilization. The rationale behind this approach is that increasing stroke volume can improve end-organ perfusion and enhance oxygen delivery [86]. About 40 years ago, observational studies found that liberal fluid strategies were linked to poorer clinical outcomes in ARDS patients [87]. Indeed, early in critical illness, a positive fluid balance significantly increases the risk of developing ARDS and contributes to higher mortality rates. In addition, despite careful monitoring, the majority of ARDS patients present with a positive fluid balance at onset, which not only exacerbates LI but also predicts prolonged MV, extended ICU and hospital stays, and an overall increase in mortality [9, 88, 89]. Moreover, hypervolemia is linked to organ failure and is identified as an independent predictor of adverse outcomes in critically ill patients [90–93]. The clinical effects of hypervolemia are particularly evident in lung function, where respiratory failure becomes apparent early. However, fluid overload can also impact other organs and systems, such as the kidneys, which, being encapsulated organs, are especially prone to developing AKI. Additional complications include delirium, abdominal compartment syndrome, and impaired wound healing [94–97]. Furthermore, it should be kept in mind that the interaction between fluid administration and MV strategies may contribute to VILI, potentially aggravating the damage. For example, in experimental models of LI, combining a high volume of fluids with pressure–support ventilation, rather than pressure control ventilation, has been associated with worse LI. Furthermore, it has been highlighted that endothelial damage in the lungs is aggravated when a large volume of fluid is administered, especially with the use of high PEEP or a sudden reduction in PEEP [98].

In general, hypervolemia results in tissue and interstitial edema, hinders blood flow and lymphatic flow, impairs metabolism, alters oxygen diffusion, and disrupts cell-to-cell interactions [99, 100]. While the pathophysiologic mechanisms of delirium in critically ill patients are multifactorial, its association with fluid overload has become increasingly recognized in recent years [101, 102]. Moreover, based on observations in patients with cardiorenal and cardiohepatic syndromes, it has been suggested that increased venous pressures and venous congestion, leading to edema formation, organ structure compression, and altered brain perfusion, may represent potential pathophysiologic mechanisms of neurocognitive impairment in patients with fluid overload [103]. Further complicating the issue, it could be hypothesized that the detrimental effects of hypervolemia on brain function are more pronounced in patients with blood–brain barrier (BBB) dysfunction, such as those with ABI, ARDS, and sepsis, due to increased fluid passage into the brain [104–107]. Recently, it has been suggested that the combination of increased intrathoracic pressure during controlled MV and potential meningeal lymphatic congestion, resulting from ineffective suction due to insufficient negative pleural pressure, may play a role in the pathogenesis of ICU delirium [108].

Emerging evidence points to the potential for improved outcomes with the use of restrictive fluid strategies, including diuresis, particularly among patients facing critical illness and ARDS [109–114], which are associated with a lower requirement for invasive MV, diminished organ dysfunction, and a trend toward reduced dependence on RRT [16, 112]. Unlike liberal fluid management, a conservative approach restricts resuscitation fluids and reduces fluid accumulation to mitigate pulmonary edema and enhance ventilation–perfusion balance, albeit with a potential risk of impaired cardiac perfusion and end-organ injury [86]. A historical study involving 1000 patients with LI compared liberal fluid administration with conservative administration based on hemodynamic and clinical parameters, such as shock, oliguria, and compromised circulation. The authors concluded that the restrictive fluid strategy resulted in significantly lower fluid accumulation and highlighted improvements in the oxygenation index, ventilator-free days, and lung injury scores. Moreover, the 60-day mortality, incidence of shock, vasopressor use, and dialysis rate did not differ between groups, indicating the safety of the restrictive fluid strategy [16]. These findings are further supported by previous research in mechanically ventilated ICU patients, highlighting positive fluid balance as an independent risk factor for ARDS progression [85].

Diuretics are frequently used in critically ill patients, including those with ARDS, and have demonstrated benefits in improving patient outcomes. Although the impact on mortality remains inconclusive, several studies have shown that diuretics can effectively reduce positive fluid balance, improve lung function, and shorten the duration of MV. These positive effects suggest that diuretics play a valuable role in managing ARDS, even though their direct impact on mortality has yet to be definitively established [16, 115]. In patients with ARDS and AKI, positive fluid balance may increase mortality, whereas proper use of furosemide could help resolve kidney injury and improve outcomes [116, 117]. Seitz et al.

performed a retrospective multicenter cohort study to investigate fluid management in ARDS patients, demonstrating that early diuretic use (48–72 h after ARDS onset) was associated with lower hospital mortality and lower crystalloid fluid intake during the first 48 h, which reduced hospital mortality [118]. A secondary analysis of the ARDS Network FACTT trial evaluated the effect of diuretics on 28-day mortality in ARDS patients without early RRT. Using a marginal structural Cox model, diuretics were associated with reduced mortality. Latent class analysis identified benefits in patients with worse renal function and higher CVP, while subgroup analysis showed advantages in females, sepsis-induced ARDS, $PaO_2/FiO_2 \leq$ 150 mmHg, and mean arterial pressure (MAP) $\geq$65 mmHg [119]. Moreover, an additional secondary analysis of the FACTT trial identified two ARDS subphenotypes, consistent with prior findings, with subphenotype 2 characterized by elevated inflammatory markers and hypotension. Mortality outcomes varied significantly between the subphenotypes based on fluid management strategies; while a fluid-conservative strategy reduced mortality in subphenotype 2, it increased mortality in subphenotype 1. These results underscore the existence of biologically distinct ARDS subphenotypes with distinct responses to fluid strategies, highlighting the need for personalized treatment approaches [120]; however, these results remain unconfirmed by prospective validation.

Using the GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluations), the Faculty of Intensive Care Medicine and Intensive Care Society Guideline Development Group (2019) has made recommendations for managing adult patients with ARDS. While the evidence for most outcomes is of low quality, primarily influenced by a single trial, conservative fluid management appears to provide benefits without causing harm. Based on these findings, it is advised that clinicians consider a conservative fluid strategy for ARDS patients, which involves fluid restriction, diuretics, and possibly hyperoncotic albumin, to maintain a neutral or negative fluid balance [121].

Fluid management in critical illness

Concerns persist that adopting a conservative fluid management strategy in critically ill patients could increase the risk of non-pulmonary organ failures, particularly in the form of shock and AKI [86]. Immediate fluid resuscitation is typically necessary in clinical situations such as hypovolemic shock resulting from hemorrhage due to trauma or major surgical procedures, or from extravascular fluid loss associated with systemic inflammatory responses, as observed in cases of sepsis or burns [122]. Fluid requirements for patients cannot be determined using a one-size-fits-all formula; instead, they must be tailored to the patient's needs and guided by hemodynamic monitoring. The timing of fluid administration is equally crucial and varies across the different resuscitation phases, including salvage, optimization, stabilization, and de-escalation (Fig. 2) [97, 123]. The concept of early goal-directed therapy (EGDT) has been developed with the goal of reversing sepsis-induced hypoperfusion by maintaining a CVP of 8–12 mmHg through intravenous fluid boluses, supporting MAP between 65 and 90 mmHg with vasopressors, and achieving a central venous oxygen saturation ($ScvO_2$) greater than 70%. This is done through the use of inotropes and/or red blood cell transfusions [124–128]. Moreover, the 1-h bundle guidelines for septic patients emphasize the importance of administering crystalloids quickly and early in the initial resuscitation phase. This approach is recommended for patients with either arterial hypotension or elevated blood lactate levels (above 4 mmol/L) to help restore adequate perfusion pressure [10]. Although the appropriate volume of fluid required for effective resuscitation in septic patients remains a topic of ongoing debate, most clinical studies in adults presenting to an emergency department with sepsis or septic shock adopt a fluid administration strategy of 30 mL/kg within the first 3 h of sepsis onset, which has been associated with lower in-hospital mortality, shorter ICU stays, and improved hemodynamic response, regardless of comorbidities, such as heart failure or end-stage kidney disease [127, 129, 130]. The early administration of norepinephrine should be considered, as it has been shown to positively impact cumulative fluid balance, according to a propensity-score matched analysis of 337 patients allocated to either a very early vasopressor group (< 1 h) or a delayed vasopressor group [131]. This approach is particularly important in patients with severe hypotension, as vasopressor therapy should be initiated alongside fluid administration due to the clear relationship between the magnitude and duration of hypotension and patient outcomes. In addition, in septic shock, hypotension is largely caused by vasoplegia, which cannot be corrected by fluid administration alone [132–134]. However, although existing evidence on managing patients with ARDS and circulatory failure is limited, the sub-phenotype of ARDS should be considered, as its heterogeneous nature can influence patient responses to fluid management [135]. As mentioned above, the hypo-inflammatory sub-phenotype could benefit from more liberal fluid administration, whereas the hyper-inflammatory sub-phenotype does not [120].

During the optimization phase, fluid administration should be tailored to individual needs, considering the clinical context, and guided by indices that help assess the risk of excessive fluid administration [136, 137]. To

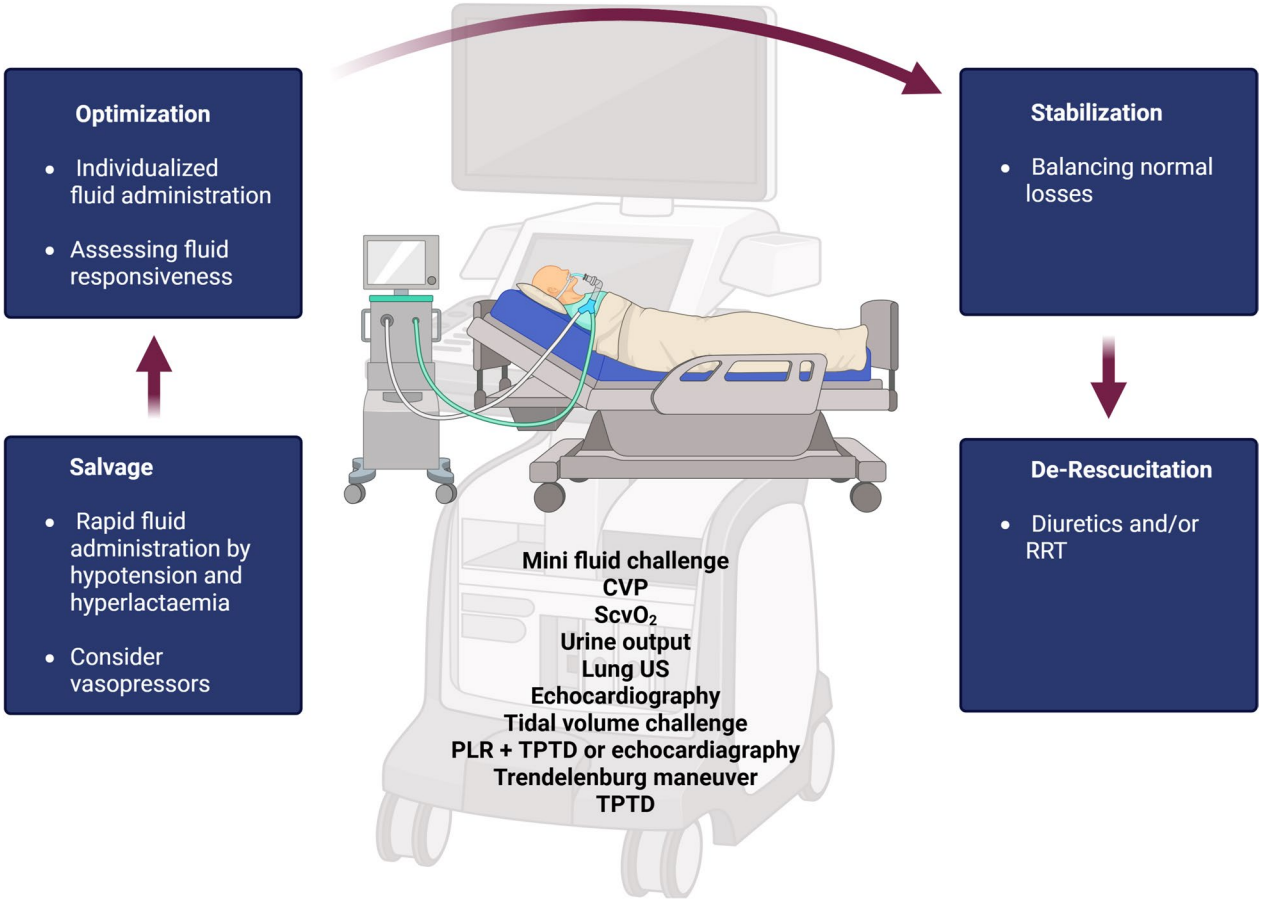

Fig. 2 Four phases of fluid resuscitation and available hemodynamic monitoring modalities in critically ill patients. *CVP* central venous pressure, *PLR* passive leg raising, *RRT* renal replacement therapy, *$ScvO_2$* central venous oxygen saturation, *TPTD* transpulmonary thermodilution, *US* ultrasound

guide adequate therapy, potential targets for personalized fluid management strategies include repeated lactate measurements, as well as clinical assessments, such as echocardiography, $ScvO_2$, invasive hemodynamic monitoring, or evaluation of capillary refill time [138]. Moreover, during this stage of fluid management, intravenous fluids are administered in carefully measured amounts, with close monitoring of the patient's response (Fig. 2). To ensure fluids are provided only to those who will benefit, it is essential to evaluate indicators of fluid responsiveness, such as pulse pressure variation (PPV), stroke volume variation (SVV), and the passive leg raising (PLR) test, before administering additional doses [97, 139]. Furthermore, fluid responsiveness can be determined using the fluid challenge test, which delivers a fixed volume of fluids to identify patients likely to increase CO and enables individualized fluid titration while minimizing hypervolemia and fluid accumulation [140]. In research on fluid challenge and fluid responsiveness, a median volume of 500 mL is commonly used, which aligns with the median volume used in the FENICE study, while smaller volumes are often employed in high-risk surgical patients receiving goal-directed therapy for optimization [141–143]. However, identifying fluid responsiveness in a patient does not necessarily indicate a need for fluid loading, as the primary objective of resuscitation is to enhance oxygen delivery and tissue perfusion to meet the body's metabolic demands, rather than simply normalizing a dynamic fluid responsiveness index [144].

In patients in the prone position, the assessment of fluid responsiveness becomes more individualized, as the hemodynamic and respiratory changes associated with it [145] can significantly influence fluid responsiveness. The determination of dynamic parameters, such as PLR, PPV, and end-expiratory occlusion (EEO), which are primarily used to assess fluid responsiveness in mechanically ventilated patients, has some limitations in patients in the prone position under MV [146]. In the prone position, the PLR test is obviously unreliable [147]. In addition, it should be used with caution in patients with ABI, as it can lead to increases in ICP and impair cerebral autoregulation [148]. However, a prospective

study including ARDS patients in the prone position with acute circulatory failure highlighted that changes in cardiac index during a Trendelenburg maneuver can be used to predict fluid responsiveness in these patients (Fig. 2) [149]. Recently, although still a topic of discussion, it has been proposed that the limitation of performing the PPV test due to low tidal volumes during protective ventilation could be minimized using the tidal volume challenge [146, 150, 151]. Importantly, this method has been shown to be acceptable for predicting fluid responsiveness during elective neurosurgical operations, in contrast to PPV and EEO [152]; nevertheless, the data are very limited and should be further validated, especially in the context of ABI.

During the stabilization phase, fluid therapy should be limited to maintaining normal fluid losses (such as renal, gastrointestinal, and insensible losses) and replacing fluids if the patient continues to experience losses due to ongoing pathological conditions [113, 153]. In this stage, neither shock (compensated or uncompensated) nor an approaching threat of shock is present, setting it apart from the previous two stages [153]. In the final stage, known as the de-escalation phase, the patient has stabilized, and fluid administration is minimized. The main objective is to eliminate excess fluids and achieve a negative fluid balance, either spontaneously or with the help of diuretics. Loop diuretics, such as furosemide, are commonly used in clinical practice but can be associated with adverse effects, including hypernatremia. As a result, careful management of fluids and electrolytes is crucial to prevent complications, making vigilant monitoring and timely adjustments essential to support the patient's recovery effectively [97, 154].

Types of resuscitation fluids

Colloids vs. crystalloids

The major types of resuscitation fluids can be divided into two main categories: crystalloids, including isotonic saline and balanced solutions, and colloids, with albumin as the principal representative [155]. Due to their larger molecular weight, colloids demonstrate prolonged intravascular persistence. Consequently, the combined use of colloids and crystalloids may reduce the total volume of fluids required, thereby lowering the risk of hypervolemia and edema [97, 156]. The CRISTAL trial, a randomized clinical trial including a mixed ICU population (sepsis, trauma, or hypovolemic shock without sepsis or trauma), investigated the effects of colloids vs. crystalloids in patients with hypovolemic shock. The study found that while 28-day mortality did not differ between groups, 90-day mortality was significantly lower in the colloid group. Moreover, patients who received colloids had more days alive without MV than those in the crystalloid group, at both 7 and 28 days. Similarly, they had more days alive without vasopressor therapy at these timepoints [157]. In the intraoperative setting, Joosten et al. demonstrated that patients receiving a combination of colloids and crystalloids required significantly less intraoperative fluid and experienced fewer postoperative complications [158]. These findings are consistent with a meta-analysis comparing colloids and crystalloids across different patient populations, which showed that larger volumes of crystalloids were required to achieve the same hemodynamic targets [159]. However, the SAFE trial, a double-blind randomized controlled trial conducted in critically ill ICU patients, compared 4% human albumin solution (HAS) to normal saline. The volume of albumin to saline varied from 1:1.2 to 1:1.6, and outcomes at 28 days were comparable between the two groups [99]. Recently, the ABC-sepsis trial, an open-label, parallel-group randomized feasibility trial, compared balanced crystalloids with 5% HAS for fluid resuscitation in septic patients during the first 6 h following randomization and found lower mortality in the balanced crystalloids group [160]. Moreover, the SAFE–TBI trial highlighted higher mortality rates in neurocritically ill patients with traumatic brain injury (TBI) who received 4% albumin compared to those who received isotonic saline [21]. Nonetheless, in contrast to the SAFE and the ABC-sepsis trial, a recent meta-analysis evaluating the efficacy of albumin vs. crystalloids for fluid resuscitation in septic patients found that treatment with 20% HAS significantly improved 90-day mortality in patients with septic shock, raising the question of whether the concentration of albumin solution should be a factor to consider [161]. Nevertheless, the mortality benefit observed in septic shock patients treated with albumin could be attributed not only to its hemodynamic effects but also to other properties, such as its antioxidant effects and drug-carrying ability [97].

Research data on the use of albumin vs. crystalloids in patients with ARDS is limited. In a subgroup analysis of the SAFE trial in patients with ARDS, the relative risk of death was slightly lower in those who received albumin compared to those who received crystalloids, although this difference did not reach statistical significance [99]. A small prospective study investigating the effects of colloids vs. crystalloids in patients with severe respiratory failure showed that in those who received albumin, the pulmonary shunt at the end of the study was significantly lower, but without influencing the outcome. Moreover, patients in the crystalloid group received greater amounts of fluids compared to the albumin group, though the difference was not statistically significant [162]. Moreover, van der Heijden et al. demonstrated in septic and non-septic mechanically ventilated patients

with clinical hypovolemia that the severity of pulmonary edema and LI score did not differ significantly between patients who received colloids, including albumin, and those who received crystalloids. Nevertheless, this study also highlighted statistically significant increases in plasma volume, cardiac index, and CVP with the use of colloids, whereas the volume administered was significantly higher in the crystalloid group [163]. Based on the populations from the three aforementioned studies, an international panel of clinical experts and methodologists conducted a pooled analysis comparing albumin with crystalloids in patients with severe acute respiratory failure and found that the use of albumin had no effect on mortality, although the evidence was very uncertain. Considering the very low certainty of the evidence and the disadvantageous factors associated with albumin use, such as higher costs, availability, limited resources, patient preferences, and rare allergic reactions, the European Society of Intensive Care Medicine (ESICM) recently recommended the use of crystalloids rather than albumin in patients with severe respiratory failure, sepsis, and ABI [164].

Balanced crystalloids vs. isotonic saline

The administration of crystalloids is a very common intervention in critical care, with isotonic saline (0.9% saline) being the most widely used resuscitation fluid worldwide [155]. However, the use of chloride-rich intravenous fluids, such as normal saline, has been associated with an increased risk of AKI [165, 166]. Indeed, the administration of large amounts of normal saline is linked to the development of hyperchloremia and hyperchloremic metabolic acidosis, which can impair renal function, disrupt coagulation, and potentially increase mortality [167–170]. Furthermore, significant elevations in chloride concentrations have been associated with hypotension, renal vasoconstriction, altered immune and inflammatory responses, and impaired microcirculation [166].

Balanced crystalloids such as Ringer's lactate and plasmalyte A (Baxter Inc.) have chloride concentrations more similar to plasma compared to normal saline, as they substitute a portion of chloride with organic anions, such as lactate and acetate, thereby reducing the risk of hyperchloremic metabolic acidosis [155, 171]. Based on the findings that the use of balanced crystalloids could lead to improved outcomes, a growing use of these fluids has been observed in recent years [172]. A secondary analysis of the SMART (Isotonic Solutions and Major Adverse Renal Events Trial), including critically ill adult septic patients, revealed that the use of balanced crystalloids was associated with a lower 30-day in-hospital mortality, a lower incidence of major adverse kidney events within 30 days, and a greater number of vasopressor-free days and RRT-free days compared with the use of saline [166]. These findings align with the results of previous studies showing that septic patients who received balanced salt solutions, compared to isotonic solutions, had decreased rates of AKI [165] and a lower risk of in-hospital mortality [173]. However, a systematic review and meta-analysis of 13 randomized controlled trials, including 35,884 critically ill patients, found no statistically significant difference in 90-day mortality between those who received balanced crystalloids and those who received isotonic saline. In addition, in studies with low risk of bias, there were also no significant differences in secondary outcomes, including the incidence of AKI, new treatment with RRT, and ventilator-free and vasopressor-free days by day 28 [174].

Fluid osmolarity is a key concern in patients with ABI, as free water may passively move through the BBB, resulting in an increase in brain water content and cerebral edema in response to an acute decrease in plasma osmolarity [175, 176]. Indeed, previous research highlights an increased mortality among patients with TBI who received balanced crystalloids compared to normal saline [177–179]. A recent additional subanalysis of the SMART trial, including neurocritically ill patients with TBI, reported a worse discharge disposition in those who received balanced salt solutions compared to saline, whereas a clinically relevant increase in mortality could not be excluded [180]. Based on current evidence, recent guidelines for fluid management in critically ill patients recommend the use of isotonic saline over balanced crystalloids for fluid resuscitation in adult patients with TBI. In addition, considering observational data that show harmful effects of Ringer's lactate administration in TBI patients, and given that most studies in neurocritical care patients used near-isotonic balanced crystalloids, experts recommend against the use of Ringer's lactate (or acetate) in those patients [164].

Hemodynamic monitoring in critical illness

The undeniable value of advanced hemodynamic monitoring in managing critically ill patients with severe shock is well-established and strongly recommended by guidelines from Intensive Care Medicine societies [181]. Despite the usefulness of CVP being questioned in various studies, CVP remains a widely used hemodynamic parameter to guide fluid management in critically ill patients (Fig. 2) [182–187]. Although there are significant limitations to the use of CVP in assessing cardiocirculatory status, CVP is suggested to potentially contribute to the management of patients with shock, provided its pathophysiological limitations are understood [188]. Indeed, extreme values of CVP can

be helpful in determining fluid responsiveness, with low values indicating a hypo- or normovolemic status that may benefit from fluid administration, and high values suggesting a normo- to hypervolemic status or RV failure, in which volume administration could have deleterious effects [182, 189]. Notably, values of 8–12 mmHg could represent useful thresholds, as most patients with CVP values below 8 mmHg are volume responders, while only a minority of patients with values above 12 mmHg will respond to fluid administration [189, 190]. However, fluid resuscitation guided by a single CVP measurement should be avoided, as baseline CVP has been shown not to differ between responders and non-responders [182].

The transpulmonary thermodilution (TPTD) method is an advanced hemodynamic monitoring technique that can be considered minimally invasive, as it requires only the insertion of a central venous catheter and an arterial thermistor catheter, allowing measurements of CO, which is a cornerstone in the management of shock as it reflects oxygen delivery to the tissues (Fig. 2) [123, 191]. Moreover, determination of CO may aid in differentiating the type of shock, as it is routinely low in hypovolemic and cardiogenic shock and high in septic shock, particularly following fluid resuscitation [123]. Beyond CO measurements, TPTD allows the holistic evaluation of hemodynamic status by estimating volumes and pressures, such as PPV and SVV to guide fluid management, ejection fraction to evaluate LV function, extravascular lung water (EVLW) to assess lung permeability and pulmonary edema, and global end-diastolic volume to reflect cardiac preload [192, 193]. Despite the questionable survival benefit of advanced hemodynamic monitoring in critically ill patients, the assessment of EVLW and pulmonary vascular permeability remains a key variable in the management of ARDS, as they predict outcomes and mirror the severity of alveolar damage, respectively, while also guiding fluid therapy [194–197]. Furthermore, clinical research highlights the prognostic accuracy of EVLW in assessing positive fluid balance and mortality after initial fluid resuscitation in septic patients [198]. In addition, studies have demonstrated that in patients with sepsis-induced LI, EVLW and permeability indexes are significantly elevated in nonsurvivors, suggesting that these parameters may serve as indicators of prognosis and severity [199]. These data are further supported by experimental research showing a strong correlation between the pulmonary vascular permeability index and the severity of septic ARDS [200].

For patients with ABI, a task force of the European Society of Intensive Care Medicine recommends the use of advanced hemodynamic monitoring to evaluate hemodynamic status and assess volume responsiveness to prevent or minimize secondary brain injury [181]. Indeed, accumulating research demonstrates that TPTD-directed fluid management in patients with subarachnoid hemorrhage results in a decreased incidence of delayed cerebral ischemia and improved systemic hemodynamics [201–203]. However, clinical approaches to hemodynamic evaluation in neurocritically ill patients vary across centers and are primarily used for those with severe damage. Nonetheless, hemodynamically stable patients may also benefit from advanced monitoring, such as TPTD [204].

Lung ultrasound has become an important tool in managing critically ill patients, including those with ARDS [205, 206]. Typical findings of ARDS on lung ultrasound include signs of aeration loss, such as bilateral B-lines and consolidations. Sonographic differentiation from cardiogenic interstitial edema can be performed by assessing heterogeneous aeration loss with spared lung regions, pleural irregularities, and subpleural consolidations [207, 208]. Moreover, combining lung ultrasound findings related to pulmonary edema with critical care echocardiography, including the evaluation of dynamic variables, such as flow velocity and velocity–time integral, can help assess fluid responsiveness through repeated bedside measurements [209–212].

The promising potential of predictive technologies with machine-learning algorithms with real-time data analysis, such as the Assisted Fluid Management (AFM) software and the Acumen Hypotension Prediction Index (HPI), to early recognize hemodynamic instability at the bedside, predict fluid responsiveness, and guide interventions, will further contribute to the optimization of hemodynamic monitoring in these complex ICU patients [213–217].

Fluid management in patients with ARDS and acute brain injury

Besides damage or dysregulation of the respiratory center, ABI is often associated with various forms of LI, including neurogenic pulmonary edema, lung inflammation, ARDS, aspiration pneumonia, and ventilator-associated pneumonia (VAP) [218–220]. LI/ARDS is commonly observed in patients with ABI, with reported incidence rates ranging from 5 to 30%, depending on the type of brain injury [106]. Although a restrictive fluid management approach and intensive diuretic therapy are frequently advised for ARDS [16], maintaining euvolemia remains essential to support adequate CPP in patients with ABI (Fig. 3) [221]. Indeed, a decrease in CPP caused by hypotension can result in cerebral vasodilation, which worsens intracranial hypertension [222], which is a crucial aspect of managing ABI [223]. Moreover, it is important to keep in mind that in patients with ABI, hemodynamic instability can arise from shock related to the brain injury, which is marked

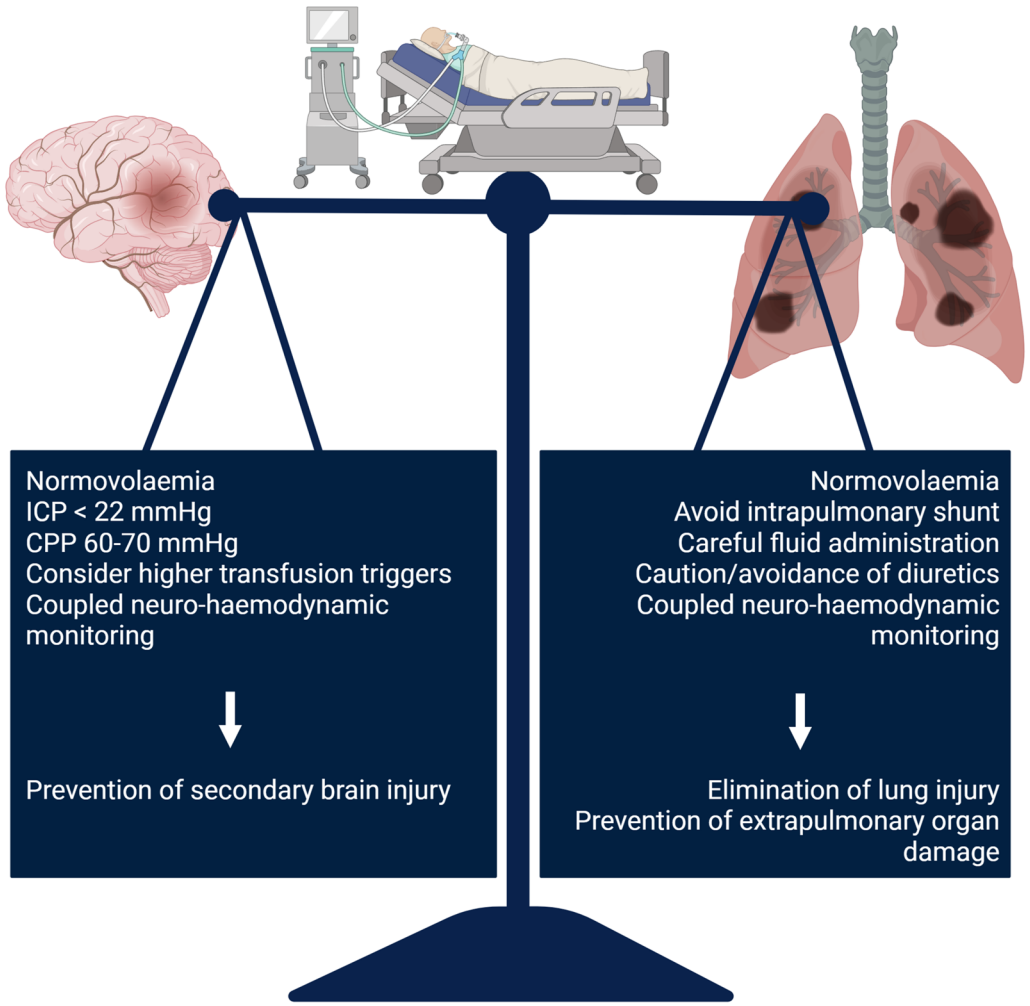

Fig. 3 Main goals of fluid resuscitation therapy in critically ill patients with concomitant ARDS and ABI. *CPP* cerebral perfusion pressure, *ICP* intracranial pressure

by a surge of catecholamines that contributes to ventricular dysfunction and vasoplegia [224]. In addition, dehydration raises the risk of acute renal failure, further complicating the management of patients with ABI [225]. In a study of 392 patients aged 16–65 with severe, non-penetrating brain injuries and Glasgow Coma Scale scores of 3–8 after resuscitation, researchers assessed the effects of moderate hypothermia. Their findings revealed that a fluid balance below − 594 mL was associated with poorer outcomes, showing a negative impact that was independent of intracranial pressure, mean arterial pressure, or CPP, underscoring the significance of optimal fluid management in improving outcomes for severely injured neurocritical ill patients [226]. Given the complex interactions between these factors, precise regulation of hemodynamics and fluid balance is essential for reducing secondary injuries and promoting optimal recovery (Fig. 3) [227].

Conversely, hypervolemia can have detrimental effects on patients with ABI. Indeed, fluid overload can exacerbate cerebral edema in patients with BBB disruption, enhance the risk of heart failure, cardiogenic shock, and pulmonary edema, and is associated with higher ICU mortality and worse outcomes in ABI [228, 229]. Robertson et al. investigated two target thresholds for CPP in patients with severe TBI, comparing 60 mmHg and 70 mmHg, and found that maintaining the higher threshold was associated with larger fluid volumes, worsening LI without improving overall patient outcomes [230]. These findings are in accordance with those of Lennihan et al., who, in a single-center study involving 82 patients, found that prophylactic hypervolemic therapy—consisting of colloids and crystalloids—had no effect on cerebral blood flow (CBF), vasospasm, or cerebral infarction compared to normovolemia [231]. In their investigation of delayed ischemic neurological deficit treatment, Ibrahim and

Macdonald observed that, among 123 patients, the use of colloids and a positive fluid balance were connected to less favorable outcomes [232]. Likewise, a separate study involving 288 patients also indicated that a positive fluid balance was associated with poorer functional outcomes [104].

Given the complexity of fluid management in patients with concomitant ARDS and ABI, a consensus reached during the ESICM LIVES2016 conference in October 2016, involving 22 international experts, emphasizes the importance of achieving normovolemia through a multimodal approach, guided by multiple hemodynamic variables. Arterial blood pressure and fluid balance should be the primary endpoints, while additional factors such as CO, $ScvO_2$, blood lactate, and urinary output may further optimize fluid therapy. The use of CVP alone is discouraged, and a restrictive fluid strategy targeting a negative fluid balance is not recommended. These approaches are essential to mitigating the risks of both hypervolemia and hypovolemia [227].

Fluid management in septic patients with ARDS

Sepsis is defined as organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is a more severe stage characterized by profound circulatory, cellular, and metabolic abnormalities, which significantly elevate the risk of mortality [233]. The diagnosis of septic shock is established when vasopressors are required to maintain a MAP of at least 65 mmHg, in conjunction with a lactate level greater than 2 mmol/L, despite adequate fluid resuscitation. As mentioned above, according to the most recent Surviving Sepsis Campaign guidelines, it is suggested that a fluid bolus of 30 mL/kg of intravenous crystalloid should be administered within the first 3 h of treatment. However, this recommendation is classified as "weak" as it is based on evidence of low quality [138]. The administration of intravenous fluids plays a crucial role in augmenting CO and blood pressure, preserving or increasing intravascular fluid volume, and facilitating the administration of therapeutic agents. However, while this follows the Frank–Starling mechanism, where increased preload enhances stroke volume in normal conditions, its effectiveness may be diminished in sepsis [124, 234].

LI is a common complication in patients with sepsis, often emerging as the earliest and most affected organ during the onset of multiple organ dysfunction. Research shows that 25–50% of individuals with sepsis develop LI, with associated mortality rates around 40% [235–237]. Although substantial research indicates that early goal-directed resuscitation improves outcomes in patients with septic shock and that conservative fluid management benefits those with LI, these two strategies may seem contradictory [22]. Indeed, inappropriate fluid resuscitation may exacerbate shock by significantly elevating filling pressures, which can exceed the compensatory capabilities of the heart as the patient approaches the plateau of the Frank–Starling curve [234]. Furthermore, although intravenous fluid boluses temporarily increase intravascular volume, they can ultimately cause pathological extravascular fluid leakage due to elevated left atrial pressure, leading to impaired cellular function in multiple organs, such as the kidneys, liver, heart, and lungs [238–242]. Moreover, administering additional volume in cases of sepsis may worsen shock in a compromised RV by exacerbating both pressure and volume overload. When volume overload becomes excessive, RV function can be impaired due to reduced contractility. This overload also causes the interventricular septum to shift leftward, which decreases LV filling. As a result, CO is further reduced, enhancing the risk of RV failure and overall hemodynamic instability [243, 244]. In addition, changes in capillary permeability and reduced oncotic pressure in septic patients can lead to edema development, even in the absence of an increase in effective circulating blood volume [97, 245]. Indeed, in conditions of severe inflammation, such as sepsis or septic shock, the release of inflammatory mediators progressively degrades the endothelial glycocalyx, disrupting capillary integrity and leading to fluid leakage [246].

Another important consideration for the management of septic patients is the development of AKI and oliguria, primarily caused by hypovolemia. However, it is noteworthy that many cases of AKI, particularly those occurring during systemic inflammation and sepsis, are not responsive to volume resuscitation [247]. Notably, in adult ICU patients with sepsis, a positive fluid balance after the first day is associated with an increased risk of AKI, with fluid overload not only increasing mortality but also serving as a negative predictor for renal function recovery [248, 249]. Fluid resuscitation, although it can restore normal renal arterial flow, may lead to disrupted microcirculatory flow in the renal cortex, creating hypoxic regions next to normoxic areas, which disrupt renal oxygen extraction and facilitate the generation of reactive oxygen species, further exacerbating kidney injury [250]. Moreover, fluids should be considered comparable to drugs, as they can have deleterious side effects, including cytokine activation, damage to the capillary glycocalyx, and reduced kidney efficiency in filtering excess fluid and nitrogenous waste [251].

Despite that liberal fluid strategy is a widely used approach during the initial resuscitation phase of septic shock management [20, 238, 252, 253], it has been increasingly questioned recently, as hemodynamic uncoupling suggests that stabilizing cardiovascular

parameters does not always enhance microcirculatory perfusion, and aggressive treatments may further aggravate glycocalyx damage and endothelial dysfunction [254]. The recommended fluid volume has been widely debated in recent years, as patients in modern early EGDT and usual care trials received a median of 27 mL/kg of fluid before randomization, leading to the conclusion that treatment should be individualized, focusing on "glycocalyx resuscitation" based on fluid tolerance and fluid responsiveness [255–257]. This approach could be meaningful, as a recent large, multicenter randomized trial (CLOVERS, NCT03434028) highlighted that in patients with sepsis-induced hypotension unresponsive to 1–3 L of intravenous fluid, a restrictive fluid strategy with earlier vasopressor use showed no significant impact on mortality before discharge home by day 90 compared to a liberal fluid strategy [258].

As previously noted, the "salvage, optimization, stabilization, de-escalation" strategy is proposed as a general framework for fluid resuscitation, emphasizing that fluid administration should be adjusted based on the disease's progression. During the initial salvage phase, generous administration of lifesaving fluids is essential. Once hemodynamic monitoring is accessible, fluid administration should be adjusted based on the patient's fluid status and the assessment of any further fluid requirements (Fig. 2) [97]. Perner et al. proposed a personalized fluid management strategy, which involves the administration of repeated 250–500 mL intravenous crystalloid boluses, continuous monitoring of fluid responsiveness, and the early use of vasopressors if circulation does not improve [259]. If hemodynamic stability is achieved or the patient no longer responds, aggressive fluid administration should be stopped [260]. Once permanent hemodynamic stability is established during the de-escalation phase, managing fluid balance may involve the use of diuresis or, in cases, where diuresis is ineffective, RRT [261]. Indeed, while diuretics may be beneficial in ICU patients with excess fluid and AKI by promoting a negative fluid balance, their effectiveness can be limited by delays in initiation, improper dosing, and concerns about side effects, such as AKI, often making RRT necessary [247, 262].

Future directions

Despite advances in fluid management for patients with ARDS, the optimal choice of fluids across the various phases of resuscitation remains unclear [136]. In addition, the role of combining different fluids, such as crystalloids and colloids, in specific clinical contexts is still unresolved [97]. Particularly for HAS, further research is needed to assess the effects of different concentrations, especially in patients with sepsis and ABI. In brain-injured patients, attention should be given to the tonicity of albumin solutions, and potential benefits of hypertonic 20–25% HAS should be explored, as existing data from the SAFE–TBI study demonstrated increased mortality in TBI patients who received 4% HAS [21, 263]. Moreover, existing data on the use of albumin or balanced crystalloids in patients with ARDS, particularly regarding patient-centered and long-term outcomes, are limited and warrant further investigation [164]. Finally, due to the uncertainty of evidence regarding fluid strategies in patients with concomitant circulatory failure and ARDS, future research considering ARDS sub-phenotypes is needed [264].

Conclusions

The destruction of endothelial and epithelial barriers and inflammatory cascades is a major contributor to the pathophysiology of ARDS. Hypervolemia is commonly present in patients with ARDS, making fluid management a cornerstone of therapeutic strategies, especially in the context of concurrent shock, as seen in septic patients and patients with ABI. The "salvage, optimization, stabilization, de-escalation" concept is the recommended strategy for fluid resuscitation, where the initial intensive fluid administration is followed by a restrictive fluid strategy, including diuretics and RRT, once hemodynamic stability has been achieved. Nonetheless, future research investigating fluid management in patients with concomitant ARDS and circulatory failure, considering ARDS sub-phenotypes, is urgently needed.

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References

1. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet. 2021;398(10300):622–37.
2. Ashbaugh DG, et al. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
3. Murray JF, et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988;138(3):720–3.
4. Bernard GR, et al. Report of the American–European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994;20(3):225–32.
5. Force ADT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33.
6. Ferguson ND, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38(10):1573–82.
7. Ziaka M, Exadaktylos A. Exploring the lung-gut direction of the gut–lung axis in patients with ARDS. Crit Care. 2024;28(1):179.
8. Matthay MA, et al. A new global definition of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2024;209(1):37–47.
9. Sakr Y, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest. 2005;128(5):3098–108.
10. Vignon P, et al. Fluid administration and monitoring in ARDS: which management? Intensive Care Med. 2020;46(12):2252–64.
11. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163(6):1376–83.
12. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122(8):2731–40.
13. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol. 2005;33(4):319–27.
14. Sibbald WJ, et al. Thermal dye measurements of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. Chest. 1985;87(5):585–92.
15. Casey JD, Semler MW, Rice TW. Fluid management in acute respiratory distress syndrome. Semin Respir Crit Care Med. 2019;40(1):57–65.
16. National Heart L, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75.
17. Grissom CK, et al. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome*. Crit Care Med. 2015;43(2):288–95.
18. Liu KD, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med. 2011;39(12):2665–71.
19. Mikkelsen ME, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12):1307–15.
20. Evans L, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–143.
21. Investigators SS, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357(9):874–84.
22. Murphy CV, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest. 2009;136(1):102–9.
23. Staub NC. Pulmonary edema: physiologic approaches to management. Chest. 1978;74(5):559–64.
24. Castillo J, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke. 2004;35(2):520–6.
25. Manley G, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. Arch Surg. 2001;136(10):1118–23.
26. Gaieski DF, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2009;80(4):418–24.
27. Wohlfahrt P, et al. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. J Hypertens. 2015;33(2):339–45.
28. Stead LG, et al. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. Neurology. 2005;65(8):1179–83.
29. LavrentiosBesmertis DCB, ClaudeHemphill J. The role of hypotension in secondary brain injury after intracerebral hemorrhage. Stroke. 2001;32:358.
30. Vemmos KN, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med. 2004;255(2):257–65.
31. Rice AD, et al. Correlation between prehospital and in-hospital hypotension and outcomes after traumatic brain injury. Am J Emerg Med. 2023;65:95–103.
32. Shibahashi K, et al. Defining hypotension in patients with severe traumatic brain injury. World Neurosurg. 2018;120:e667–74.
33. Cortes-Puentes GA, Oeckler RA, Marini JJ. Physiology-guided management of hemodynamics in acute respiratory distress syndrome. Ann Transl Med. 2018;6(18):353.
34. Cournand A, Motley HL. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol. 1948;152(1):162–74.
35. Skaburskis M, Helal R, Zidulka A. Hemodynamic effects of external continuous negative pressure ventilation compared with those of continuous positive pressure ventilation in dogs with acute lung injury. Am Rev Respir Dis. 1987;136(4):886–91.
36. Santos A, et al. Effects on pulmonary vascular mechanics of two different lung-protective ventilation strategies in an experimental model of acute respiratory distress syndrome. Crit Care Med. 2017;45(11):e1157–64.
37. Leigh JM. Pulmonary circulation and ventilation. Postgrad Med J. 1974;50(587):562–5.
38. Kleinsasser A, et al. Sildenafil modulates hemodynamics and pulmonary gas exchange. Am J Respir Crit Care Med. 2001;163(2):339–43.
39. Kaczmarczyk G, et al. Vasopressin and renin-angiotensin maintain arterial pressure during PEEP in nonexpanded, conscious dogs. Am J Physiol. 1996;271(5 Pt 2):R1396–402.
40. Annat G, et al. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology. 1983;58(2):136–41.
41. Koyner JL, Murray PT. Mechanical ventilation and the kidney. Blood Purif. 2010;29(1):52–68.
42. Wu MA, et al. Hypoalbuminemia in COVID-19: assessing the hypothesis for underlying pulmonary capillary leakage. J Intern Med. 2021;289(6):861–72.
43. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. JPEN J Parenter Enteral Nutr. 2019;43(2):181–93.
44. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. Crit Care. 2013;17(3):R98.
45. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012;81(9):819–25.
46. Lombardi R, et al. An assessment of the acute kidney injury network creatinine-based criteria in patients submitted to mechanical ventilation. Clin J Am Soc Nephrol. 2011;6(7):1547–55.
47. Yang H, Benos PV, Kitsios GD. Protecting the lungs but hurting the kidneys: causal inference study for the risk of ventilation-induced kidney injury in ARDS. Ann Transl Med. 2020;8(16):985.
48. Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med. 2016;194(4):402–14.
49. Imai Y, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA. 2003;289(16):2104–12.
50. Soni N, Williams P. Positive pressure ventilation: what is the real cost? Br J Anaesth. 2008;101(4):446–57.
51. Benites MH, et al. Ventilation-induced acute kidney injury in acute respiratory failure: do PEEP levels matter? Crit Care. 2025;29(1):130.

52. Corp A, Thomas C, Adlam M. The cardiovascular effects of positive pressure ventilation. BJA Educ. 2021;21(6):202–9.
53. Kumar A, et al. Bidirectional pressure: a mini review of ventilator–lung–kidney interactions. Front Physiol. 2024;15:1428177.
54. Jardin F, et al. Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology. 1990;72(6):966–70.
55. Verbrugge FH, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62(6):485–95.
56. Hepokoski ML, et al. Ventilator-induced kidney injury: are novel biomarkers the key to prevention? Nephron. 2018;140(2):90–3.
57. Metnitz PG, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30(9):2051–8.
58. Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. Curr Opin Nephrol Hypertens. 2007;16(3):227–36.
59. Priebe HJ, Heimann JC, Hedley-Whyte J. Mechanisms of renal dysfunction during positive end-expiratory pressure ventilation. J Appl Physiol Respir Environ Exerc Physiol. 1981;50(3):643–9.
60. Moore ES, et al. Effects of positive pressure ventilation on intrarenal blood flow in infant primates. Pediatr Res. 1974;8(9):792–6.
61. Pannu N, Mehta RL. Effect of mechanical ventilation on the kidney. Best Pract Res Clin Anaesthesiol. 2004;18(1):189–203.
62. Hemmer M, et al. Urinary antidiuretic hormone excretion during mechanical ventilation and weaning in man. Anesthesiology. 1980;52(5):395–400.
63. Farge D, et al. Interactions between hemodynamic and hormonal modifications during PEEP-induced antidiuresis and antinatriuresis. Chest. 1995;107(4):1095–100.
64. Kumar A, et al. Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. Anesthesiology. 1974;40(3):215–21.
65. Bark H, et al. Elevations in plasma ADH levels during PEEP ventilation in the dog: mechanisms involved. Am J Physiol. 1980;239(6):E474–81.
66. Andrivet P, et al. Hormonal interactions and renal function during mechanical ventilation and ANF infusion in humans. J Appl Physiol (1985). 1991;70(1):287–92.
67. Fewell JE, Bond GC. Renal denervation eliminates the renal response to continuous positive-pressure ventilation. Proc Soc Exp Biol Med. 1979;161(4):574–8.
68. Brenner BM, et al. Diverse biological actions of atrial natriuretic peptide. Physiol Rev. 1990;70(3):665–99.
69. Kurtz A, et al. Atrial natriuretic peptide inhibits renin release from juxtaglomerular cells by a cGMP-mediated process. Proc Natl Acad Sci USA. 1986;83(13):4769–73.
70. Cruz FF, et al. Ventilator-induced lung injury during controlled ventilation in patients with acute respiratory distress syndrome: less is probably better. Expert Rev Respir Med. 2018;12(5):403–14.
71. Marini JJ. Evolving concepts for safer ventilation. Crit Care. 2019;23(Suppl 1):114.
72. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med. 1998;157(6 Pt 1):1721–5.
73. Ziaka M, et al. High-tidal-volume mechanical ventilation and lung inflammation in intensive care patients with normal lungs. Am J Crit Care. 2020;29(1):15–21.
74. Ranieri VM, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1999;282(1):54–61.
75. Pinheiro de Oliveira R, et al. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Crit Care. 2010;14(2):R39.
76. Chen L, et al. Molecular mechanisms of ventilator-induced lung injury. Chin Med J (Engl). 2018;131(10):1225–31.
77. Kuiper JW, et al. Production of endothelin-1 and reduced blood flow in the rat kidney during lung-injurious mechanical ventilation. Anesth Analg. 2008;107(4):1276–83.
78. Sharkey RA, Mulloy EM, O'Neill SJ. The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. Chest. 1999;115(6):1588–92.
79. Acute Respiratory Distress Syndrome N, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med, 2000; 342(18): 1301–8.
80. Panitchote A, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome. Ann Intensive Care. 2019;9(1):74.
81. Aubert V, et al. A computer model of oxygen dynamics in the cortex of the rat kidney at the cell-tissue level. Int J Mol Sci. 2019;20(24):6246.
82. Edwards A, Palm F, Layton AT. A model of mitochondrial O(2) consumption and ATP generation in rat proximal tubule cells. Am J Physiol Renal Physiol. 2020;318(1):F248–59.
83. Marchiset A, Jamme M. When the renal (function) begins to fall: a mini-review of acute kidney injury related to acute respiratory distress syndrome in critically ill patients. Front Nephrol. 2022;2: 877529.
84. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121(11):4210–21.
85. Jia X, et al. Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. Chest. 2008;133(4):853–61.
86. Schuster DP. The case for and against fluid restriction and occlusion pressure reduction in adult respiratory distress syndrome. New Horiz. 1993;1(4):478–88.
87. Simmons RS, et al. Fluid balance and the adult respiratory distress syndrome. Am Rev Respir Dis. 1987;135(4):924–9.
88. Rosenberg AL, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med. 2009;24(1):35–46.
89. van Mourik N, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: an observational cohort study. PLoS ONE. 2019;14(10): e0224563.
90. Vincent JL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34(2):344–53.
91. Neyra JA, et al. Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. Crit Care Med. 2016;44(10):1891–900.
92. Kelm DJ, et al. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock. 2015;43(1):68–73.
93. Lee J, et al. Association between fluid balance and survival in critically ill patients. J Intern Med. 2015;277(4):468–77.
94. Legrand M, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17(6):R278.
95. Wang N, et al. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care. 2015;19:371.
96. Payen D, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74.
97. Vincent JL. Fluid management in the critically ill. Kidney Int. 2019;96(1):52–7.
98. de Carvalho EB, et al. Fluid management strategies and their interaction with mechanical ventilation: from experimental studies to clinical practice. Intensive Care Med Exp. 2023;11(1):44.
99. Finfer S, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.
100. Prowle JR, et al. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010;6(2):107–15.
101. Nguyen DN, et al. Hypotension and a positive fluid balance are associated with delirium in patients with shock. PLoS ONE. 2018;13(8): e0200495.
102. Silva JM Jr, et al. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. Crit Care. 2013;17(6):R288.
103. Mailhot T, et al. Delirium after cardiac surgery and cumulative fluid balance: a case–control cohort study. J Cardiothorac Vasc Anesth. 2019;33(1):93–101.
104. Kissoon NR, et al. Positive fluid balance is associated with poor outcomes in subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2015;24(10):2245–51.

105. Pfister D, et al. Intracranial pressure in patients with sepsis. Acta Neurochir Suppl. 2008;102:71–5.
106. Ziaka M, Exadaktylos A. Brain–lung interactions and mechanical ventilation in patients with isolated brain injury. Crit Care. 2021;25(1):358.
107. Ziaka M, Exadaktylos A. ARDS associated acute brain injury: from the lung to the brain. Eur J Med Res. 2022;27(1):150.
108. Seubert ME, Goeijenbier M. Controlled mechanical ventilation in critically ill patients and the potential role of venous bagging in acute kidney injury. J Clin Med. 2024;13(5):1504.
109. Silversides JA, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. Crit Care Med. 2018;46(10):1600–7.
110. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol. 2018;14(9):541–57.
111. Cordemans C, et al. Aiming for a negative fluid balance in patients with acute lung injury and increased intra-abdominal pressure: a pilot study looking at the effects of PAL-treatment. Ann Intensive Care. 2012;2 Suppl 1(Suppl 1):S15.
112. Silversides JA, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med. 2017;43(2):155–70.
113. Malbrain ML, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014;46(5):361–80.
114. Mekontso Dessap A, et al. Natriuretic peptide-driven fluid management during ventilator weaning: a randomized controlled trial. Am J Respir Crit Care Med. 2012;186(12):1256–63.
115. Cinotti R, et al. Diuretics decrease fluid balance in patients on invasive mechanical ventilation: the randomized-controlled single blind, IRIHS study. Crit Care. 2021;25(1):98.
116. Zinter MS, et al. Positive cumulative fluid balance is associated with mortality in pediatric acute respiratory distress syndrome in the setting of acute kidney injury. Pediatr Crit Care Med. 2019;20(4):323–31.
117. Zhao GJ, et al. Association between furosemide administration and outcomes in critically ill patients with acute kidney injury. Crit Care. 2020;24(1):75.
118. Seitz KP, Caldwell ES, Hough CL. Fluid management in ARDS: an evaluation of current practice and the association between early diuretic use and hospital mortality. J Intensive Care. 2020;8:78.
119. Zhang R, et al. The effect of loop diuretics on 28-day mortality in patients with acute respiratory distress syndrome. Front Med (Lausanne). 2021;8: 740675.
120. Famous KR, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med. 2017;195(3):331–8.
121. Griffiths MJD, et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Respir Res. 2019;6(1): e000420.
122. Mayerhofer T, et al. Fluids in the ICU: which is the right one? Nephrol Dial Transplant. 2023;38(7):1603–12.
123. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34.
124. Zampieri FG, Bagshaw SM, Semler MW. Fluid therapy for critically ill adults with sepsis: a review. JAMA. 2023;329(22):1967–80.
125. Pro CI, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93.
126. Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
127. Mouncey PR, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11.
128. Investigators A, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.
129. Kuttab HI, et al. Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. Crit Care Med. 2019;47(11):1582–90.
130. Priebe HJ. Goal-directed resuscitation in septic shock. N Engl J Med. 2015;372(2):189.
131. Ospina-Tascon GA, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. Crit Care. 2020;24(1):52.
132. Bai X, et al. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014;18(5):532.
133. Vincent JL, et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann Intensive Care. 2018;8(1):107.
134. Hamzaoui O, Scheeren TWL, Teboul JL. Norepinephrine in septic shock: when and how much? Curr Opin Crit Care. 2017;23(4):342–7.
135. Grasselli G, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023;49(7):727–59.
136. Malbrain M, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8(1):66.
137. Malbrain M, et al. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International fluid academy (IFA). Ann Intensive Care. 2020;10(1):64.
138. Evans L, et al. Executive summary: surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):1974–82.
139. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! Crit Care. 2015;19(1):18.
140. Messina A, et al. Pathophysiology of fluid administration in critically ill patients. Intensive Care Med Exp. 2022;10(1):46.
141. Messina A, et al. Fluid challenge in critically ill patients receiving haemodynamic monitoring: a systematic review and comparison of two decades. Crit Care. 2022;26(1):186.
142. Cecconi M, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. Intensive Care Med. 2015;41(9):1529–37.
143. Messina A, et al. Fluid challenge during anesthesia: a systematic review and meta-analysis. Anesth Analg. 2018;127(6):1353–64.
144. Vignon P. Evaluation of fluid responsiveness in ventilated septic patients: back to venous return. Intensive Care Med. 2004;30(9):1699–701.
145. Baka M, et al. Hemodynamic and respiratory changes following prone position in acute respiratory distress syndrome patients: a clinical study. J Clin Med. 2023;12(3):760.
146. Shi R, et al. Tidal volume challenge to predict preload responsiveness in patients with acute respiratory distress syndrome under prone position. Crit Care. 2022;26(1):219.
147. Monnet X, Shi R, Teboul JL. Prediction of fluid responsiveness. What's new? Ann Intensive Care. 2022;12(1):46.
148. Messina A, et al. The effect of passive leg raising test on intracranial pressure and cerebral autoregulation in brain injured patients: a physiological observational study. Crit Care. 2024;28(1):23.
149. Yonis H, et al. Change in cardiac output during Trendelenburg maneuver is a reliable predictor of fluid responsiveness in patients with acute respiratory distress syndrome in the prone position under protective ventilation. Crit Care. 2017;21(1):295.
150. Myatra SN, et al. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. Crit Care Med. 2017;45(3):415–21.
151. Alvarado Sanchez JI, et al. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. Ann Intensive Care. 2021;11(1):28.
152. Messina A, et al. Assessment of fluid responsiveness in prone neurosurgical patients undergoing protective ventilation: role of dynamic indices, tidal volume challenge, and end-expiratory occlusion test. Anesth Analg. 2020;130(3):752–61.
153. Hoste EA, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740–7.
154. Bellomo R. Issue and challenges of fluid removal in the critically ill. Br J Anaesth. 2014;113(5):734–5.
155. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.
156. Lewis SR, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8(8): CD000567.
157. Annane D, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.

158. Joosten A, et al. Crystalloid versus colloid for intraoperative goal-directed fluid therapy using a closed-loop system: a randomized, double-blinded, controlled trial in major abdominal surgery. Anesthesiology. 2018;128(1):55–66.
159. Orbegozo Cortes D, et al. Crystalloids versus colloids: exploring differences in fluid requirements by systematic review and meta-regression. Anesth Analg. 2015;120(2):389–402.
160. Gray AJ, et al. Albumin versus balanced crystalloid for the early resuscitation of sepsis: an open parallel-group randomized feasibility trial—the ABC-Sepsis Trial. Crit Care Med. 2024;52(10):1520–32.
161. Geng L, et al. Different concentrations of albumin versus crystalloid in patients with sepsis and septic shock: a meta-analysis of randomized clinical trials. J Intensive Care Med. 2023;38(8):679–89.
162. Metildi LA, et al. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. Surg Gynecol Obstet. 1984;158(3):207–12.
163. van der Heijden M, et al. Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. Crit Care Med. 2009;37(4):1275–81.
164. Arabi YM, et al. European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids. Intensive Care Med. 2024;50(6):813–31.
165. Yunos NM, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–72.
166. Brown RM, et al. Balanced crystalloids versus saline in sepsis. A secondary analysis of the SMART clinical trial. Am J Respir Crit Care Med. 2019;200(12):1487–95.
167. Li H, et al. 0.9% saline is neither normal nor physiological. J Zhejiang Univ Sci B. 2016;17(3):181–7.
168. Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent "pre-renal" acute kidney injury?: con. Kidney Int. 2014;86(6):1096–105.
169. Sen A, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. Crit Care Med. 2017;45(2):e146–53.
170. Soussi S, et al. Chloride toxicity in critically ill patients: what's the evidence? Anaesth Crit Care Pain Med. 2017;36(2):125–30.
171. Self WH, et al. Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis: a subgroup analysis of cluster randomized clinical trials. JAMA Netw Open. 2020;3(11): e2024596.
172. Hammond NE, et al. Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: an international cross-sectional study. PLoS ONE. 2017;12(5): e0176292.
173. Raghunathan K, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. Crit Care Med. 2014;42(7):1585–91.
174. Hammond NE, et al. Balanced crystalloids versus saline in critically ill adults—a systematic review with meta-analysis. NEJM Evid. 2022;1(2): EVIDoa2100010.
175. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine (Baltimore). 1976;55(2):121–9.
176. Ramming S, et al. The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. J Trauma. 1994;37(5):705–13.
177. Rowell SE, et al. The impact of pre-hospital administration of lactated ringer's solution versus normal saline in patients with traumatic brain injury. J Neurotrauma. 2016;33(11):1054–9.
178. Diz JC, et al. Effect of treatment with balanced crystalloids versus normal saline on the mortality of critically ill patients with and without traumatic brain injury: a systematic review and meta-analysis. Anesth Analg. 2025. https://doi.org/10.1213/ANE.0000000000007368.
179. Zampieri FG, et al. Balanced crystalloids versus saline for critically ill patients (BEST-living): a systematic review and individual patient data meta-analysis. Lancet Respir Med. 2024;12(3):237–46.
180. Lombardo S, et al. Balanced crystalloid versus saline in adults with traumatic brain injury: secondary analysis of a clinical trial. J Neurotrauma. 2022;39(17–18):1159–67.
181. Cecconi M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014;40(12):1795–815.
182. Osman D, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med. 2007;35(1):64–8.
183. Marik PE, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642–7.
184. Cook AM, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care. 2020;32(3):647–66.
185. Coudray A, et al. Fluid responsiveness in spontaneously breathing patients: a review of indexes used in intensive care. Crit Care Med. 2005;33(12):2757–62.
186. Michard F, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med. 2000;162(1):134–8.
187. Heenen S, De Backer D, Vincent JL. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? Crit Care. 2006;10(4):R102.
188. De Backer D, et al. How can assessing hemodynamics help to assess volume status? Intensive Care Med. 2022;48(10):1482–94.
189. Biais M, et al. Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: the grey zone approach. Crit Care. 2014;18(6):587.
190. Eskesen TG, Wetterslev M, Perner A. Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. Intensive Care Med. 2016;42(3):324–32.
191. Monnet X, Teboul JL. Transpulmonary thermodilution: advantages and limits. Crit Care. 2017;21(1):147.
192. Teboul JL, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med. 2016;42(9):1350–9.
193. Scheeren TWL, Ramsay MAE. New developments in hemodynamic monitoring. J Cardiothorac Vasc Anesth. 2019;33(Suppl 1):S67–72.
194. Monnet X, Lai C, De Backer D. Why do we use transpulmonary thermodilution and pulmonary artery catheter in severe shock patients? Ann Intensive Care. 2025;15(1):7.
195. Jozwiak M, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med. 2013;41(2):472–80.
196. Gavelli F, et al. Extravascular lung water levels are associated with mortality: a systematic review and meta-analysis. Crit Care. 2022;26(1):202.
197. Tagami T, et al. Quantitative diagnosis of diffuse alveolar damage using extravascular lung water. Crit Care Med. 2013;41(9):2144–50.
198. Wang H, et al. Prognostic value of extravascular lung water and its potential role in guiding fluid therapy in septic shock after initial resuscitation. J Crit Care. 2016;33:106–13.
199. Kuzkov VV, et al. Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury. Crit Care Med. 2006;34(6):1647–53.
200. Endo Y, et al. Diagnostic value of transpulmonary thermodilution measurements for acute respiratory distress syndrome in a pig model of septic shock. J Transl Med. 2022;20(1):617.
201. Tagami T, et al. Optimal range of global end-diastolic volume for fluid management after aneurysmal subarachnoid hemorrhage: a multicenter prospective cohort study. Crit Care Med. 2014;42(6):1348–56.
202. Kurtz P, et al. Fluid responsiveness and brain tissue oxygen augmentation after subarachnoid hemorrhage. Neurocrit Care. 2014;20(2):247–54.
203. Mutoh T, et al. Goal-directed fluid management by bedside transpulmonary hemodynamic monitoring after subarachnoid hemorrhage. Stroke. 2007;38(12):3218–24.
204. Messina A, et al. Hemodynamic management of acute brain injury caused by cerebrovascular diseases: a survey of the European Society of Intensive Care Medicine. Intensive Care Med Exp. 2022;10(1):42.
205. Zieleskiewicz L, et al. Point-of-care ultrasound in intensive care units: assessment of 1073 procedures in a multicentric, prospective, observational study. Intensive Care Med. 2015;41(9):1638–47.
206. Jambrik Z, et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. Am J Cardiol. 2004;93(10):1265–70.

207. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. Cardiovasc Ultrasound. 2008;6:16.
208. Heldeweg MLA, et al. Lung ultrasound signs to diagnose and discriminate interstitial syndromes in ICU patients: a diagnostic accuracy study in two cohorts. Crit Care Med. 2022;50(11):1607–17.
209. Vincent JL, et al. Clinical review: update on hemodynamic monitoring—a consensus of 16. Crit Care. 2011;15(4):229.
210. Vignon P, et al. Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated patients. Am J Respir Crit Care Med. 2017;195(8):1022–32.
211. Feissel M, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest. 2001;119(3):867–73.
212. Wetterslev M, et al. Systematic review of cardiac output measurements by echocardiography vs. thermodilution: the techniques are not interchangeable. Intensive Care Med. 2016;42(8):1223–33.
213. Coeckelenbergh S, et al. Assisted fluid management and sublingual microvascular flow during high-risk abdominal surgery: a randomized controlled trial. Anesth Analg. 2024;140:1149.
214. Rahman A, et al. Early prediction of hemodynamic interventions in the intensive care unit using machine learning. Crit Care. 2021;25(1):388.
215. Yoon JH, et al. Prediction of hypotension events with physiologic vital sign signatures in the intensive care unit. Crit Care. 2020;24(1):661.
216. Moghadam MC, et al. A machine-learning approach to predicting hypotensive events in ICU settings. Comput Biol Med. 2020;118:103626.
217. Schuurmans J, et al. Effect of a machine learning-derived early warning tool with treatment protocol on hypotension during cardiac surgery and ICU stay: the hypotension prediction 2 (HYPE-2) randomized clinical trial. Crit Care Med. 2025;53(2):e328–40.
218. Johnson NJ, Carlbom DJ, Gaieski DF. Ventilator management and respiratory care after cardiac arrest: oxygenation, ventilation, infection, and injury. Chest. 2018;153(6):1466–77.
219. Aisiku IP, et al. The incidence of ARDS and associated mortality in severe TBI using the Berlin definition. J Trauma Acute Care Surg. 2016;80(2):308–12.
220. Shih JA, et al. Acute respiratory distress syndrome after in-hospital cardiac arrest. Resuscitation. 2022;177:78–84.
221. Ergezen S, et al. Fluid therapy in the acute brain injured patient. Minerva Anestesiol. 2023;89(10):936–44.
222. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg. 1995;83(6):949–62.
223. Meyfroidt G, et al. Management of moderate to severe traumatic brain injury: an update for the intensivist. Intensive Care Med. 2022;48(6):649–66.
224. Wiedermann CJ. Albumin in normovolemic fluid management for severe traumatic brain injury: controversies and research gaps. J Clin Med. 2024;13(18):5452.
225. Carney N, et al. Guidelines for the management of severe traumatic brain injury, Fourth Edition. Neurosurgery. 2017;80(1):6–15.
226. Clifton GL, et al. Fluid thresholds and outcome from severe brain injury. Crit Care Med. 2002;30(4):739–45.
227. Oddo M, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med. 2018;44(4):449–63.
228. Wiegers EJA, et al. Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study. Lancet Neurol. 2021;20(8):627–38.
229. Fletcher JJ, et al. Fluid balance, complications, and brain tissue oxygen tension monitoring following severe traumatic brain injury. Neurocrit Care. 2010;13(1):47–56.
230. Robertson CS, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med. 1999;27(10):2086–95.
231. Lennihan L, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage : a randomized controlled trial. Stroke. 2000;31(2):383–91.
232. Ibrahim GM, Macdonald RL. The effects of fluid balance and colloid administration on outcomes in patients with aneurysmal subarachnoid hemorrhage: a propensity score-matched analysis. Neurocrit Care. 2013;19(2):140–9.
233. Singer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
234. Moschopoulos CD, et al. New insights into the fluid management in patients with septic shock. Medicina (Kaunas). 2023;59(6):1047.
235. Sadowitz B, et al. Lung injury induced by sepsis: lessons learned from large animal models and future directions for treatment. Expert Rev Anti Infect Ther. 2011;9(12):1169–78.
236. Rubenfeld GD, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–93.
237. Sevransky JE, Levy MM, Marini JJ. Mechanical ventilation in sepsis-induced acute lung injury/acute respiratory distress syndrome: an evidence-based review. Crit Care Med. 2004;32(11 Suppl):S548–53.
238. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. Ann Intensive Care. 2014;4:21.
239. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care. 2014;18(6):696.
240. Boyd JH, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259–65.
241. Maitland K, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med. 2013;11:68.
242. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med. 2001;345(8):588–95.
243. Arrigo M, et al. Diagnosis and treatment of right ventricular failure secondary to acutely increased right ventricular afterload (acute cor pulmonale): a clinical consensus statement of the Association for Acute CardioVascular Care of the European Society of Cardiology. Eur Heart J Acute Cardiovasc Care. 2024;13(3):304–12.
244. Wilcox SR, Kabrhel C, Channick RN. Pulmonary hypertension and right ventricular failure in emergency medicine. Ann Emerg Med. 2015;66(6):619–28.
245. Vincent JL, Pinsky MR. We should avoid the term "fluid overload." Crit Care. 2018;22(1):214.
246. Hippensteel JA, et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care. 2019;23(1):259.
247. Bissell BD, et al. Impact of protocolized diuresis for de-resuscitation in the intensive care unit. Crit Care. 2020;24(1):70.
248. Bellomo R, et al. Acute kidney injury in the ICU: from injury to recovery: reports from the 5th Paris International Conference. Ann Intensive Care. 2017;7(1):49.
249. Salahuddin N, et al. Fluid overload is an independent risk factor for acute kidney injury in critically Ill patients: results of a cohort study. BMC Nephrol. 2017;18(1):45.
250. Clanton TL. Hypoxia-induced reactive oxygen species formation in skeletal muscle. J Appl Physiol (1985). 2007;102(6):2379–88.
251. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit Care Med. 2018;46(6):997–1000.
252. Edwards JD. Management of septic shock. BMJ. 1993;306(6893):1661–4.
253. Tuchschmidt J, et al. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest. 1992;102(1):216–20.
254. Guarino M, et al. 2023 update on sepsis and septic shock in adult patients: Management in the Emergency Department. J Clin Med. 2023;12(9):3188.
255. Investigators P, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med. 2017;376(23):2223–34.
256. Trzeciak S, et al. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. Acad Emerg Med. 2008;15(5):399–413.
257. Bakker J, et al. Current practice and evolving concepts in septic shock resuscitation. Intensive Care Med. 2022;48(2):148–63.
258. National Heart L, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. N Engl J Med. 2023;388(6):499–510.
259. Perner A, et al. Expert statement for the management of hypovolemia in sepsis. Intensive Care Med. 2018;44(6):791–8.
260. Sakr Y, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. Crit Care Med. 2017;45(3):386–94.

261. Goldstein S, et al. Pharmacological management of fluid overload. Br J Anaesth. 2014;113(5):756–63.
262. Grams ME, et al. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011;6(5):966–73.
263. Wiedermann CJ. Use of hyperoncotic human albumin solution in severe traumatic brain injury revisited-a narrative review and meta-analysis. J Clin Med. 2022;11(9):2662.
264. Mekontso Dessap A, et al. European Society of Intensive Care Medicine (ESICM) 2025 clinical practice guideline on fluid therapy in adult critically ill patients: part 2-the volume of resuscitation fluids. Intensive Care Med. 2025;51:461.

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