



Fluid Accumulation and Deresuscitation

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IFA Commentary (SG)

Fluid accumulation of more than 10% is associated with higher morbidity and mortality. However, fluid accumulation is a continuum, and a single threshold value does not encompass everyone. It is a state of pathological overhydration with worse patient outcomes. Organ dysfunction with fluid accumulation is defined as fluid accumulation syndrome. IV fluids should be regarded as drugs, and stewardship focusing on 4D's (Drug, dose, duration, and de-escalation) is recommended to mitigate the problem of fluid accumulation. IV fluid prescription should consider four indications (resuscitation, maintenance, replacement, and nutrition) and the conceptual model of ROSE (resuscitation, optimization, stabilization, and evacuation). De-escalation and de-resuscitation are strategies to avoid fluid accumulation. Recent evidence supports the feasibility of fluid restriction during resuscitation. De-escalation means discontinuation or reducing IV fluids to prevent fluid accumulation. De-resuscitation is an active fluid removal to treat fluid accumulation causing organ dysfunction. Tools such as negative passive leg raising test, extravascular lung water and bioelectrical impedance, and venous congestion on point-of-care ultrasound are promising to guide de-resuscitation. Diuretics with or without hyperoncotic albumin are the first step in de-resuscitation. Mechanical fluid removal (ultrafiltration) can be considered in case of diuretic failure or contraindication. The end-point of de-resuscitation are either goal-based (fluid balance, physiological or clinical improvement) or safety concerns.

The goal of fluid resuscitation is to improve tissue perfusion. However, overzealous resuscitation measures may lead to fluid overload and tissue edema, further worsening tissue and organ damage. The fluid overload state is compounded further by poorly planned maintenance fluid therapy and often avoidable 'fluid creep'. Pathophysiology and clinical features of several fluid accumulation syndromes are described in this chapter in great detail. Below we will list some interventions that can be performed to prevent and treat FAS.

Avoid fluid accumulation: Key is to prevent fluid accumulation without allowing tissue hypoperfusion. We suggest the following strategies to achieve this goal.

- Avoid large fluid boluses. Fluid bolus as small as 4 ml/kg body weight has shown to be adequate for intravascular volume expansion [1].
- Further fluid boluses should be guided by patient phenotype e.g. history of large fluid loss or poor fluid intake in preceding days, obvious harm of further fluid administration e.g. pulmonary edema or B-profile in the anterior chest).
- Fluid responsiveness must be checked before additional fluid boluses and fluid should not be administered if the patient is not fluid responsiveness. However, the converse may not be true [2].

- Early initiation of vasopressors has been shown to reduce cumulative fluid balance in vasodilatory shock like septic shock [3]. Vasopressors (especially norepinephrine) should be administered along with fluid boluses in patients with diastolic blood pressure <50 mmHg or diastolic shock index >2.3 and after initial fluid volume of not more than 1–2 l of crystalloid [4–6].
- Hyperoncotic albumin boluses have shown to reduce cumulative fluid volume during fluid resuscitation [7, 8]. However, additional data and cost-benefit ratio must be considered before the widespread adoption of this strategy.
- Patients should be reassessed frequently during fluid resuscitation to look for improvement in tissue perfusion, as well as for any harmful consequences of administered fluid. In both situations, further fluid boluses must be stopped. In the ANDROMEDA-SHOCK trial, resuscitation targeting capillary refill time (CRT) as the end-point of tissue perfusion goal was shown to lower resuscitation volume compared to lactate guided resuscitation [9].
- Maintenance fluid and fluid creep contribute to over 60% of administered fluid in critically ill patients [10]. Whenever possible maintenance fluid infusion should be either avoided or limited to the minimal volume. Similarly, ‘fluid creep’ should be actively looked into and whenever feasible patient can be switched to an oral (enteral) formulation or the drug should be diluted in a smaller volume.
- Moderately hypotonic (sodium concentration 54 mmol/L) maintenance fluid infusion produces lower cumulative fluid balance compared to isotonic (sodium concentration 154 mmol/L) maintenance fluid [11]. Hence, if maintenance fluid is deemed to be necessary, the choice of fluid should be moderately hypotonic.

De-resuscitate when necessary: De-resuscitation is a strategy to remove accumulated fluid forcefully, in an otherwise hemodynamically stable patient with clinical evidence of fluid overload. The aim of de-resuscitation is to treat and/or prevent end-organ damage resulting from fluid overload without producing hypovolemia and organ ischemia. The following questions need to be raised and answered during the process of de-resuscitation [12].

- **When to start?** Patient must be hemodynamically stable on no or minimal dose of vasopressors before considering de-resuscitation. He or she should not be requiring additional boluses or fluid or there should not be any ongoing fluid loss requiring replacement. Clinical and objective evidence of fluid overload should be present with reasonable suspicion of organ damage (or impending one) directly resulting from the fluid accumulation. Evidence of fluid overload has been described in great detail in the chapter.

- **How to initiate?** Active removal of fluid can be achieved either by judicious use of diuretics or by ultrafiltration [continuous renal replacement therapy (CRRT) or slow low efficiency hemodialysis (SLED)]. Mechanisms of action and pharmacological effects of different diuretic agents have been discussed in the chapter. Discussion on CRRT and SLED techniques are beyond the scope of this book. Some relevant points on the subject are given below.
 - Berthelsen and colleagues suggested is to start de-resuscitation process with a 40 mg IV bolus of furosemide followed by an infusion titrated to a maximum dose of 40 mg/h [13]. Other loop diuretics such as torsemide may be considered in place of furosemide. Interestingly, in a large study on diuretic strategies in patients with acute decompensated heart failure, continuous infusion of furosemide was not shown to be of any additional advantage compared to bolus doses [14].
 - In a recent study, addition of intravenous acetazolamide 500 mg once daily in addition to standard loop diuretic regimen, was shown to achieve better decongestion and produce more diuresis and natriuresis compared to loop diuretic alone, in patients with acute decompensated heart failure [15]. Broader application of this combination strategy in general intensive care unit patients needs further evaluation.
 - Ultrafiltration using CRRT or SLED may be considered as alternative options in patients with inadequate response to diuretics or in anuric patients or in patients requiring renal replacement therapy for some other reason or in patients who developed serious adverse effects to furosemide or torsemide [12].
 - Adding hyperoncotic (20 or 25%) albumin to the diuretic and/or ultrafiltration regimen, in addition to maintaining intravascular volume, has been shown to produce synergistic effect [16]. In an elegant study, Greg Martin et al. randomized hemodynamically stable, hypoproteinemic patients who are on mechanical ventilator for ARDS to either furosemide with albumin (100 ml boluses of 20% albumin every 8-h) or furosemide with placebo for 72 h [16]. Addition of albumin was shown to produce larger negative fluid balance and lesser episodes of hypotension, in addition to a significant improvement in oxygenation. Alternatively, hyperoncotic albumin may be administered as a continuous infusion at 10–20 ml/h [12].
 - Addition of positive end-expiratory pressure (PEEP) matching intra-abdominal pressure (IAP), in addition to albumin plus diuretics (or ultrafiltration) (PAL strategy—PEEP, albumin and lasix or furosemide), had shown to be associated with greater negative fluid balance and greater reduction in extravascular lung water index (EVLWI) and IAP compared to control subjects [17]. PAL strategy also showed improved clinical outcomes (improved oxygenation, shorter ICU length of stay) without compromising cardiovascular or renal function.

- **How to monitor?** Patients should be monitored closely for evidence of hypovolemia and/or hypoperfusion and adequacy of fluid removal [12].
 - One suggested goal is to achieve a net negative fluid balance of at least 1 mL/kg IBW/hour [13].
 - Patients should also be monitored for serious adverse effects of diuretics e.g. thrombocytopenia, agranulocytosis, pancreatitis, Steven Johnsons syndrome, toxic epidermal necrolysis, etc.
 - Patients should also be monitored for any electrolyte abnormalities (e.g. hypokalemia, dysnatremia, hypomagnesemia or hypophosphatemia) and cardiac arrhythmias related to it.
- **When to stop?** De-resuscitation should be stopped, if the patient fulfills any of the following conditions.
 - Hemodynamic instability or obvious evidence of hypovolemia; in which case, fluid removal must be suspended and fluid may be re-administered judiciously. Fluid removal may be re-initiated at a lower rate, once hypovolemia or hypoperfusion is mitigated [12].
 - On achievement of de-resuscitation goal—negative or zero fluid balance.

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Learning Objectives

This chapter will discuss the harms of excessive IV fluids administration and overhydration. Various strategies can be employed to avoid and monitor overhydration. Fluid restriction during resuscitation and active removal of excessive fluid, also known as deresuscitation, are the strategies employed to manage overhydration. We will review the recent evidence on fluid restriction and deresuscitation. With the help of a case, we will review the judicious fluid administration, methods of monitoring overhydration, and safe deresuscitation strategy in case of overhydration.

Case Vignette

A 26-year-old man was admitted to the ICU after general seizures, syncope, non-palpable blood pressure, and a suspicion of ventricular tachycardia whilst in the Emergency Room. The emergency room physician (successfully) applied a DC shock to convert to regular sinus rhythm. Afterward the patient was alert and cooperative and he was transferred to the ICU for overnight monitoring. The next day his need for supplemental oxygen increased from 2 l via nasal cannula to 15 l administered with a non-rebreathing mask. The patient was in respiratory distress with a respiratory rate of 34 breaths/min. After the failure of non-invasive ventilation, he was intubated and mechanically ventilated within 24 h after ICU admission, illustrating the dramatic chain of events. After intubation, the patient was in profound shock and resuscitated with 3 consecutive boluses of 4 ml/kg balanced crystalloids. Despite fluids and low dose pressors, he remained hypotensive with increasing lactate and poor P/F ratio (<100). Transpulmonary thermodilution monitoring was started. The initial hemodynamic profile showed a normal cardiac index (CI) of 3.5 L/min m² (normal range 3–5), a relatively low intravascular filling status with a GEDVI of 757 ml/m² (normal range 680–800), a very low global ejection fraction GEF of 13% (normal range 25–35) in combination with severe capillary leak and high extravascular lung water index (EVLWI) of 12 ml/kg predicted body weight (normal range 3–7). At the same time; however, the patient seemed to be preload responsive with a high pulse pressure variation (PPV) of 19% (normal range <10). Heart rate was regular at 119 beats/min with a MAP of 55 mmHg. The CVP remained at 16 mmHg. His response to a passive leg raising (PLR) maneuver was positive (15% increase in CI and MAP) confirming that he was volume responsive despite the fact that he was in pulmonary edema (EVLWI 12) with a critical oxygenation status at the time (P/F ratio of 57, at IPAP of 34 cmH₂O and PEEP of 15 cmH₂O).

Questions

Q1. What does this case scenario illustrate?

The patient was given a further small volume dose of fluids in combination with an increasing dose of vasopressors. The following day, his CI increased to 5.7 L/min m², GEDVI increased to 900 ml/m² but also EVLWI had increased to 19 ml/kg PBW. The high EVLWI was suggestive of hyperpermeability edema in view of the high pulmonary vascular permeability index (PVPI) of 2.9 (normal range 1–2.5).

Q2. What is the best treatment at this stage?

Introduction

The administration of intravenous (IV) crystalloid solutions is widely regarded as the initial step in resuscitating the hypotensive critically ill ‘septic’ patient, with evidence of inadequate organ perfusion. Recent evidence suggests that overzealous administration of IV fluids, especially in the setting of sepsis with poor source control and capillary leak, may lead to fluid overload and subsequent fluid accumulation syndrome (FAS) [1].

Tissue edema is not just of cosmetic concern, it impairs oxygen and metabolite diffusion, disrupts the endothelial glycocalyx architecture, impedes capillary blood flow and lymphatic drainage and disturbs intercellular interactions. All these effects may contribute to the progression of organ dysfunction and failure. These effects are particularly pronounced in encapsulated organs, such as the liver and kidneys, which lack the capacity to accommodate additional volume without an increase in interstitial pressure, resulting in compromised organ blood flow. Furthermore, large-volume resuscitation increases intra-abdominal pressure (IAP) which further compromises end-organ (e.g. renal and hepatic) perfusion. This has led to new insights into polycompartment syndrome and more specifically, the cardio-abdominal-renal syndrome (CARS), hepato-abdominal pulmonary syndrome (HAPS) and the hepato-abdominal-renal syndrome (HARS) [2, 3].

Kelm et al. demonstrated that the majority (67%) of patients resuscitated with an early goal directed protocol, had clinical evidence of fluid accumulation after day 1, with 48% showing persistent signs of fluid overload by day 3 [4]. Multiple studies have demonstrated that a positive fluid balance is independently associated with impaired organ function and an increased risk of death [1].

This was neatly demonstrated in a retrospective study performed by Murphy and co-workers in septic patients [5]. It demonstrated that achieving just 2 consecutive negative fluid balance targets within the first week of an ICU stay (late conservative fluid management), was associated with improved organ function and survival. This has also been replicated in other reports [6, 7]. This dynamic time effect and impact of fluids was also

8. Fluid overload: poor cosmetics or bad medicine?

Edema and derailed cumulative fluid balances: are they just collateral damage or do they put the patient in additional danger? Restrictive versus liberal fluid strategies? Is there an additional effect of early removal of fluids or should we go from early adequate over late conservative fluid management towards late goal directed fluid removal? What is the Ebb and Flow phase of shock? Is anasarca edema just of cosmetic concern or is it harmful for the organs and eventually the patient? Maybe we need to rethink the 2 hit ischemia-reperfusion model and replace it by a 3 hit model, where unresolved shock will lead to the third hit, the global increased permeability syndrome? Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway that includes ischemia-reperfusion, toxic oxygen metabolite generation, cell wall and enzyme injury leading to a loss of capillary endothelial barrier function. In such a state, plasma volume expansion to correct hypoperfusion predictably results in extravascular movement of water, electrolytes and proteins. Peripheral tissue edema, visceral edema and ascites may be anticipated in proportion to the volume of prescribed resuscitation fluid. A variety of strategies are available to the clinician to reduce the volume of crystalloid resuscitation utilized while restoring macro- and microcirculatory flow. Regardless of the resuscitation strategy, the clinician must maintain a heightened awareness of the dynamic relationship between capillary leak, fluid loading, peripheral edema, intra-abdominal hypertension and the abdominal compartment syndrome and the potential need and beneficial effect of de-resuscitation.

Fig. 25.1 Screenshot taken from the 1st IFAD proceedings in 2011 coining the term de-resuscitation for the first time

illustrated by other data and has been referred to as the ebb and flow phases of shock. In 1932, Cuthbertson characterized the ebb phase as ‘ashen facies, a thready pulse and cold clammy extremities...’, while during the flow phase ‘the patient warms up, cardiac output increases and the surgical team relaxes...’ [8]. Recent data suggests that a substantial number of ICU patients will not enter the flow phase spontaneously after initial resuscitation or EGDT. In order to avoid fluid accumulation and the associated organ edema and dysfunction, these patients may require therapeutic interventions in order to trigger the transition from ebb phase to flow phase [9]. However, it remains largely unknown whether strategies that target a neutral or even negative fluid balance after the initial resuscitative phase are associated with improved clinical outcomes in humans.

The use of the correct definitions, as repeated in this chapter, may limit the deleterious effects of inappropriate fluid prescription and fluid accumulation [10]. We will focus on the deleterious effects of hyper- or overhydration (a better term for fluid overload) and fluid accumulation and will discuss restrictive and liberal fluid management strategies, as well as the different monitoring tools we can use to guide late goal-directed fluid removal, also termed deresuscitation [11]. The term deresuscitation was coined in 2011 during the first International Fluid Academy Day (IFAD) meeting in Antwerp (<https://www.fluid-academy.org/memberresources/item/extended-overview.html>, congress proceedings page A30—Fig. 25.1) and later on in 2014, defined as active fluid removal in patients with fluid overload using drugs and/or ultrafiltration (UF) [1]. Recently a concise overview has been published [12].

Definitions

The introductory chapter contains a full compendium with a list of definitions and terms. Below, we will briefly discuss those terms related to fluid overload [13–15].

Classification of fluid dynamics: With respect to the different phases of fluid resuscitation (early vs. late), one can classify the dynamics of fluid management by combining early adequate (EA) or early conservative (EC) and late conservative (LC) or late liberal (LL) fluid management. Based on this theoretical concept, four distinct strategies can be defined: EALC, EALL, ECLC, ECLL. The EALC and ECLC groups carry the best prognosis.

Cumulative fluid balance: The sum of fluid accumulated by calculating the sum of daily fluid balances over a set period of time. Usually, the first week of a patient's ICU stay is taken into account for prognostication.

Daily Fluid Balance: The difference between all fluids given to a patient during a 24-h period, and their combined output.

De-escalation: Reduction of the dose or speed of administration of fluid therapy following clinical improvement of the patient.

Deresuscitation (see also Late Goal-Directed Fluid Removal): Correction of fluid accumulation or fluid overload, by actively removing excess fluids using pharmacological and non-pharmacological methods.

Ebb phase: The initial phase of septic shock when the patient shows hyperdynamic circulatory shock, with decreased systemic vascular resistance due to vasodilation, increased capillary permeability, and severe absolute or relative intravascular hypovolemia.

Edema: Peripheral and generalized edema (anasarca) is not merely cosmetic, but harmful to the patient. *E:I ratio:* the ECW/ICW ratio is normally below 1 (0.7–0.8). An increase in ICW% will result in a decrease in E:I ratio and is seen in heart failure, liver cirrhosis, and chronic renal failure patients, especially in the early stages. A decrease in ICW% will result in a decrease in E:I ratio and is generally due to osmotic factors. Finally, an increase in ECW% will also increase the E:I ratio. This occurs due to fluid shifts from the intra to extracellular space, or from the capillary leak, which results in second (interstitial) and third-space fluid accumulation and/or edema.

Flow phase: This refers to the phase of septic shock after initial stabilization, where the patient will mobilize excess fluid spontaneously; a classic example is when a patient enters a polyuric phase during recovery from acute kidney injury (AKI).

Fluid accumulation: A pathologic state of overhydration/volume overload, associated with clinical impact which may vary by age, comorbidity, and phase of illness. It describes a continuum and may occur with concomitant intravascular hypovolemia, normovolemia, and hypervolemia. It may or may not be associated with clinical or imaging signs of edema. No specific threshold of fluid balance alone can define fluid accumulation across all individuals.

Fluid accumulation syndrome: Any degree of fluid accumulation or fluid overload with a negative impact on end-organ function, which may or may not be associated with global increased permeability syndrome.

Fluid Creep: The unintentional and unmeasured fluid volumes administered in the process of delivering medication and nutrition through enteral and parenteral routes [16]. In patients with severe burns, this includes the administration of fluids in excess of any requirements calculated by the Parkland Formula [17].

Fluid overload (see overhydration): An increase in total body fluid (both water and electrolytes) in excess of physiologic requirements. This term has sometimes been used interchangeably with volume overload [18], which generally refers to expansion of the extracellular fluid volume.

Preload responsiveness: The state in which a patient will respond to fluid administration by an increase in stroke volume of 15%. This term should replace the traditional misnomer of ‘fluid responsiveness’.

Global increased permeability syndrome (GIPS): Some patients will not enter the ‘flow’ phase spontaneously and will remain in a persistent state of increased permeability and a tendency to fluid accumulation. This is referred to as ‘the third hit of shock’. It is defined by a positive cumulative fluid balance with organ failure, in the presence of capillary leak (e.g. increased EVLWI, PVPI, CLI, E:I ratio)

Hypervolemia: The opposite of hypovolemia, defined by intravascular overfilling.

Late Conservative Fluid Management (LCFM): Two consecutive days of negative fluid balance within the first week of the ICU stay; this is a strong and independent predictor of survival [5].

Late Goal-Directed Fluid Removal (LGFR): Active fluid removal by means of diuretics or renal replacement therapy with net ultrafiltration.

Overhydration (see also fluid overload and fluid accumulation): A state of positive fluid balance or where there is excess water in the body. Overhydration may be accompanied by a normal, low or high intravascular or interstitial fluid status, with or without (peripheral or lung) edema. An increase in intravascular fluid status will eventually also lead to increased interstitial fluid by hydrostatic pressure (i.e. cardiogenic edema). Dividing the cumulative fluid balance in liters by the patient’s baseline body weight and multiplying by 100% defines the percentage of fluid accumulation. Overhydration or hyperhydration at any stage can be classified as mild (5%), moderate (5–10%) or severe (>10%) fluid accumulation. Historically, it is often defined as increase in body weight relative to admission body weight

- (Fluid intake during observation period)—(fluid losses during observation period)/pre-ICU body weight $\times 100$ or
- Actual increase in body weight (Pre-ICU admission body weight/body weight at the timepoint of fluid overload assessment $\times 100$) or
- Increase in fluid balance (cumulative fluid balance (in L)/pre-ICU body weight $\times 100$) or increase in volume excess (calculated by BIA/pre-ICU body weight $\times 100$) [19].

Positive Fluid Balance: A state in which fluid intake exceeds fluid output. An increase in net fluid balance with accumulation of excess fluids in body tissues and weight gain and in some cases, peripheral edema.

Pathophysiology

We often give too much IV fluid and in particular, too much non-physiological salt. Once within the body, such non-physiological excesses are very difficult to remove and can result in many adverse situations for our patients. There are extremes—increased fluid load can cause major electrolyte swings, whereas dehydration, left unchecked, can lead to poor organ perfusion.

Sick patients have ‘leaky capillaries’ and in this situation, even careful IV fluid administration can lead to fluid overload and resultant complications (ileus, poor mobility following peripheral edema, pressure sores, pulmonary edema, poor wound healing and anastomotic breakdown).

We have a situation whereby fluid has escaped from its beneficial site within the circulating volume, flooding the extracellular compartment, where it offers no physiological value. What these patients require, after sensible fluid challenges and identification of ‘non-response’ (better described as being ‘volume intolerant/preload un-responsive’). This is where the role of early therapy may now be prudent (i.e. noradrenaline).

Fluid administration potentially triggers a vicious cycle, where interstitial edema induces organ dysfunction, which in turn perpetuates fluid accumulation. It is now well-established that fluid overload in septic patients is associated with edema development and worse outcomes. Fluid overload affects all organ functions from head to toe. GIPS can hence be defined as fluid overload in combination with new-onset organ failure, in the setting of persistent capillary leak (Fig. 25.2).

The following list describes the potential detrimental effects of fluid overload on end-organ function:

- Central nervous system: impaired cognition, delirium, increased intracranial, intra-orbital, and intra-ocular pressure, cerebral edema and diminished cerebral perfusion pressure. A study of 35 brain injured pigs, with and without hemorrhagic shock, were randomized to Liberal (LR) vs restrictive fluid (HLS). Cerebral edema formation, as indicated by cortical water content (gravity), was studied after 24 h. The study showed that the volume of fluid infused and the fluid balance did affect the ICP, but the amount of Na infused did not [21]. In a retrospective study of 28 severe burn and trauma patients, 8 out of 28 patients required orbital decompression because of increased intra-orbital pressure, related to the amount of fluids administered [22].
- Respiratory system: pulmonary edema, pleural effusions, increased chest wall elastance, decreased dynamic and static respiratory compliance, increased extravascular lung water index, increased pulmonary vascular permeability index, hypercarbia, hypoxia, low P/F ratio, decreased lung volumes (mimicking restrictive lung disease cf. increased intra-abdominal pressure), prolonged ventilation, difficult weaning, and increased work of breathing. In the FACTT trial, 1000 patients with acute lung injury were randomized to receive either conservative vs. liberal fluid treatment. Patients in the conservative arm had a significantly less positive cumulative fluid balance after 1-week, improved lung function and shorter duration of mechanical ventilation [6].

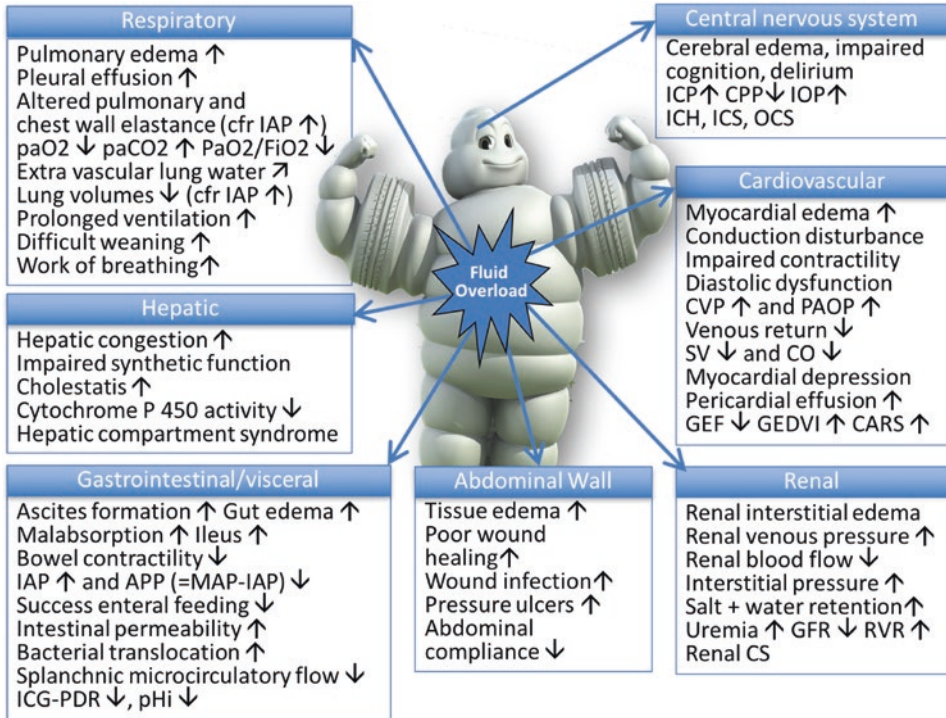


Fig. 25.2 Potential adverse consequences of fluid overload on end-organ function. Adapted from Malbrain et al. with permission [20]. *APP* abdominal perfusion pressure, *IAP* intra-abdominal pressure, *IAH* intra-abdominal hypertension, *ACS* abdominal compartment syndrome, *CARS* cardio-abdominal-renal syndrome, *CO* cardiac output, *CPP* cerebral perfusion pressure, *CS* compartment syndrome, *CVP* central venous pressure, *GEDVI* global enddiastolic volume index, *GEF* global ejection fraction, *GFR* glomerular filtration rate, *ICG-PDR* indocyaninegreen plasma disappearance rate, *ICH* intracranial hypertension, *ICP* intracranial pressure, *ICS* intracranial compartment syndrome, *IOP* intra-ocular pressure, *MAP* mean arterial pressure, *OCS* ocular compartment syndrome, *PAOP* pulmonary artery occlusion pressure, *pHi* gastric tonometry, *RVR* renal vascular resistance, *SV* stroke volume

- Cardiovascular system: myocardial edema, pericardial effusion, conduction disturbance, impaired contractility, diastolic dysfunction, increased filling pressures (central venous and pulmonary artery occlusion pressure), diminished venous return (cf. increased IAP), decreased stroke volume and cardiac output, myocardial depression, decreased stroke volume and pulse pressure variation, venous congestion, low (global) ejection fraction, increased volumetric preload indicators (e.g. global end-diastolic volume index), and cardio-abdominal-renal interactions [23]. A study in 25 dogs examining the effect of induced myocardial edema (via progressive pulmonary artery banding), showed an inversion relationship between interstitial fluid pressure and cardiac compliance [24].
- Renal system: renal interstitial edema, increased renal venous and interstitial pressure, decreased renal blood flow and glomerular filtration rate, increased renal vascular resistance, renal venous congestion, increased or decreased (hemodilution) creatinine,

increased uremia, salt and water retention, and local renal compartment syndrome. A study in 296 critically ill patients treated with RRT, showed that patients with fluid overload at RRT initiation had double the crude 90-day mortality compared to those without. Fluid overload was associated with increased risk for 90-day mortality even after adjustments [25].

- Gastrointestinal system: gut and bowel edema, diminished bowel contractility, increased ileus and malabsorption, diminished hepatosplanchnic perfusion (low ICG-PDR), ascites formation, increased intra-abdominal pressure and decreased abdominal perfusion pressure, abdominal hypertension, abdominal compartment syndrome, increased intestinal permeability and bacterial translocation [26].
- Hepatic system: diminished liver perfusion, decreased lactate clearance, hepatic venous congestion, local hepatic compartment syndrome.
- Abdominal wall and skin: tissue edema, poor wound healing, increased wound infections and pressure ulcers, decreased abdominal and chest wall compliance.

Particular attention should be paid to patients at high risk of overhydration e.g. those with cardiac, renal, hepatic failure, and nutritional disorders.

Liberal Versus Restrictive Fluid Regimens

As intravascular underfilling and hypovolaemia are the most prevalent reversible causes of shock, a 'liberal' fluid approach with repetitive administration of intravenous fluid boluses until the patient no longer responds with improvement in cardiovascular dynamics (i.e. without increase in mean arterial pressure, central venous pressure, urine output, or cardiac output), is common [27]. This approach is proposed in many international guidelines for the initial management of sepsis such as the NICE, GIFTASUP, ESICM, and SCCM [28, 29]. However, there is no strong rationale for this approach, as the physiological effects of fluid boluses given in ICU appear to be small and short-lived.

Administration of large volumes of intravenous crystalloid fluids often leads to accumulation of a positive fluid and sodium balance. Fluid accumulation and overhydration in critically ill patients, defined by a 10% increase in cumulative fluid balance from baseline body weight, is consistently associated with worse outcomes. This has been shown in broad populations of children and adults with sepsis, acute kidney injury, acute respiratory failure as well as general critical illness. However, this association may not indicate a causal relationship, since severely ill patients are more prone to receiving larger volumes of IV fluids. An interesting question is whether the deleterious effects are related to fluid or sodium accumulation, or both. It is clear that overhydration has extended effects on vascular integrity and permeability, and may trigger ongoing inflammation leading to a vicious cycle (GIPS). Hemodilution, venous congestion, decreased perfusion pressures, increased compartmental pressures (especially in the abdomen and thorax) and interstitial edema further impact on oxygen delivery and diffusion to the

tissues. Finally, this may damage the endothelial glycocalyx, a fragile barrier by which fluid is maintained within the intravascular space. Rapid fluid boluses of salt solutions have worse effects on glycocalyx integrity, compared to slow infusion of albumin, the latter having a protective effect.

The FACCT trial, studying 1000 patients with acute lung injury, showed that although there was no significant difference in the primary outcome of 60-day mortality, a conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care, without increasing non-pulmonary organ failure [6].

As stated above, Murphy and colleagues showed that early adequate fluid therapy in combination with late conservative fluid management, carried the best prognosis in a retrospective study of 212 patients with ALI complicating septic shock [5].

A recent systematic review involving a total of 19577 critically ill patients [1] found that the cumulative fluid balance after 1 week of ICU stay was 4.2 l more positive in non-survivors compared to the survivors (95% CI 2.7–5.6, $p < 0.0001$). A restrictive fluid regimen resulted in a less positive cumulative fluid balance of 5.6 l (95% CI 3.3–7.7, $p < 0.0001$) compared to controls with liberal fluid regimen, after 1 week of ICU stay. Restrictive fluid management was associated with a reduction in ICU mortality from 33.2% to 24.7% when compared to patients treated with a more liberal fluid management strategy (OR of 0.42; 95% CI 0.32–0.55, $p < 0.0001$).

Silversides et al. showed in a recent meta-analysis in adults and children with acute respiratory distress syndrome, sepsis or systemic inflammation (formerly called SIRS), that a conservative or deresuscitative fluid strategy results in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care, although the effect on mortality remained uncertain [30].

The CLASSIC pilot study examined the feasibility of a protocol restricting fluids in 151 patients after initial resuscitation for septic shock [31]. The protocol successfully reduced volumes of resuscitation fluids compared with a standard care protocol. The patient-centred outcomes pointed towards a benefit of fluid restriction, however the trial was underpowered.

In a retrospective cohort study RADAR, investigating the role of active deresuscitation after resuscitation, Silversides et al. found that a negative fluid balance achieved with deresuscitation on day 3 of ICU stay, was associated with improved outcomes [32]. The authors concluded that avoiding and / or minimizing maintenance fluid intake and drug diluents, in combination with deresuscitative measures, represent a potentially beneficial therapeutic strategy that merits investigation in randomized trials.

Although we must also advise caution against the development of hypovolemia (and hypernatremia) and the potential danger of hypoperfusion resulting from aggressive deresuscitation. Indeed, the argument in favour of restrictive fluid therapy is at present mainly based on small physiological observations and studies, and there are, on the other hand, also studies showing the potential harmful effects of restrictive fluid strategy in critically ill patients.

The use of a conservative fluid management approach has been called into question by the long-term follow-up of a subset of survivors of the Fluid and Catheter Treatment Trial (FACTT) [33]. A post-hoc analysis showed that cognitive function was markedly impaired in the conservative fluid group compared with the liberal fluid group, with an adjusted odds ratio of 3.35. Cognitive impairment was defined as impairment in memory, verbal fluency, or executive function. Although all these were more common in the conservative fluid management group, only the deterioration in executive function reached statistical significance ($p = 0.001$) [33].

The best daily target fluid balance needs a balanced view, especially in light of the results of the RELIEF study [34]. In this pragmatic trial, 3000 patients at increased risk for complications during major abdominal surgery, were randomized between a restrictive vs. more liberal fluid strategy. The authors found that whilst a restrictive regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen, it was associated with a higher rate of acute kidney injury, more RRT and more surgical site infections.

The RADAR-2 pilot study in 180 critically ill patients showed that a strategy of conservative fluid administration and active deresuscitation is feasible, reduces fluid balance compared with usual care but may cause benefit or harm [35]. Deciding when to start and stop deresuscitation is key to improving patient outcomes; research is ongoing to identify the best parameters to guide fluid removal in critically ill patients.

Results of the CLASSIC trial have been published. The study enrolled 1554 critically ill patients (770 were assigned to the restrictive-fluid group and 784 to the standard-fluid group). Primary outcome data were available for 1545 patients (99.4%) [36]. Patients received a median of 3 liters of intravenous fluid before they underwent randomization and were enrolled within 3 h after admission to the ICU. In the ICU, the restrictive-fluid group received a median of 1798 ml of intravenous fluid (interquartile range, 500 to 4366); the standard-fluid group received a median of 3811 ml (interquartile range, 1861–6762). At 90 days, mortality was the same in both groups as were the number of serious adverse events that occurred at least once. Although underpowered, this study supports a strategy of limiting any post-resuscitation fluid to patients who are either preload responsive or volume tolerant, using dynamic indices of preload responsiveness, as was recommended previously by other available data from the FEAST [37] and FACTT trials [33].

More recently the CLOVERS trial showed that among patients with sepsis-induced hypotension, the use of the restrictive fluid strategy did not result in a significant difference in mortality before discharge home by day 90 when compared to the liberal fluid strategy [38]. The CLOVERS study enrolled 1563 patients, with 782 assigned to the restrictive fluid group and 781 to the liberal fluid group. Resuscitation therapies varied between the groups, with less intravenous fluid given to the restrictive fluid group compared to the liberal fluid group (difference of medians, -2134 ml; 95% confidence interval [CI], -2318 to -1949). The restrictive fluid group also had more prevalent and longer duration of

vasopressor use. Death from any cause before discharge home by day 90 occurred in 14.0% of patients in the restrictive fluid group and 14.9% in the liberal fluid group (estimated difference, -0.9% points; 95% CI, -4.4 to 2.6 ; $P = 0.61$). The number of serious adverse events reported was similar in both groups.

While waiting for the results of the full RADAR-2 trial, prevention of fluid accumulation and de-escalation of fluid therapy remain the most effective strategies to avoid deresuscitation [12, 35, 39].

Monitoring Hypervolemia and Guiding Deresuscitation

The renewed concept of ‘fluid stewardship’ [10], analogous to antibiotic stewardship, focusses on the 4 D’s (drug, dose, duration, and de-escalation), the 4 questions (when to start and when to stop fluid therapy, and when to start and when to stop fluid removal), the 4 indications (resuscitation, maintenance, replacement, and nutrition), and the conceptual ROSE model describing 4 fluid phases (resuscitation, optimization, stabilization, and evacuation [13]). Figure 25.3 illustrates the 4 dynamic fluid phases and gives some suggestions regarding triggers and safety limits in each phase.

Clinical Signs of Hypervolemia

The absence of thirst may indicate potential overhydration, but is not very specific. Clinical signs of overhydration should be sought during physical examination, as there is a ubiquitous bias in the direction of hypovolaemia detection. These include vital signs such as increased blood pressure (mean, systolic pressure, diastolic pressure, and pulse pressure), decreased pulse rate, increased central and jugular venous pressure, and absence of orthostatic hypotension and absence of preload responsiveness. Other signs are altered mental status, increased hepatojugular reflux, orthopnea, second and third space fluid accumulation, altered capillary refill time (usually less than 2 s), increased skin turgor, altered peripheral temperature, peripheral pitting edema and anasarca, and a positive daily and cumulative fluid balance. Also, the presence of pulmonary rales or crackles are rather non-specific signs. Many of these signs are subtler, and may not be routinely looked for. Deresuscitation should not solely be based on these non-specific signs. Daily weighing of patients in the ICU is very useful, but unfortunately not routinely used. Increased urine output (regularly checked in ICU patients) can be present (e.g. in polyuric phase after acute tubular necrosis), but depends on many variables and therapeutic interventions. Some advocate the use of a furosemide stress test to identify the risk for acute kidney injury (AKI), or the readiness for deresuscitation. Figure 25.4 summarizes the clinical signs and symptoms related to hypervolemia and fluid accumulation.

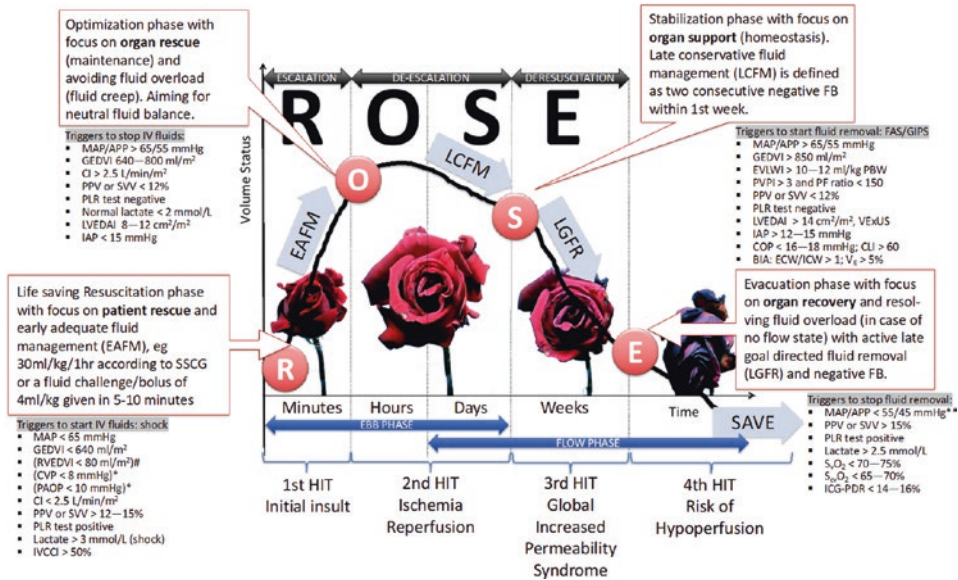


Fig. 25.3 The 4 phases conceptual model and deleterious effects of fluid accumulation syndrome. Graph showing the four-hit model of shock with evolution of patients' cumulative fluid volume status over time during the five distinct phases of resuscitation: Resuscitation (R), Optimization (O), Stabilization (S), and Evacuation (E) (ROSE), followed by a possible risk of Hypoperfusion in case of too aggressive deresuscitation. On admission patients are often hypovolemic, followed by normovolemia after fluid resuscitation (escalation or EAFM, early adequate fluid management), and possible fluid overload, again followed by a phase returning to normovolemia with de-escalation via achieving zero fluid balance or late conservative fluid management (LCFM) and followed by late goal directed fluid removal (LGFR) or deresuscitation. In case of hypovolemia, O₂ cannot get into the tissue because of convective problems, in case of hypervolemia O₂ cannot get into the tissue because of diffusion problems related to interstitial and pulmonary edema, gut edema (ileus and abdominal hypertension). Adapted from Malbrain et al. with permission, according to the Open Access CC BY Licence 4.0 [13]. * volumetric preload indicators such as GEDVI, LVEDAI, or RVEDVI are preferred over barometric ones such as CVP or PAOP. ** vasopressor can be started or increased to maintain MAP/APP above 55/45 during deresuscitation phase. # can only be measured via Swan-Ganz pulmonary artery catheter (PAC) and became obsolete. APP abdominal perfusion pressure (APP = MAP-IAP), BIA bio-electrical impedance analysis, CI cardiac index, CLI capillary leak index (serum CRP divided by serum albumin), COP colloid oncotic pressure, CVP central venous pressure, EAFM early adequate fluid management, ECW/ICW extracellular/intracellular water, EVLWI extravascular lung water index, FAS fluid accumulation syndrome, GEDVI global end-diastolic volume index, GIPS global increased permeability syndrome, IAP intra-abdominal pressure, ICG-PDR indocyanine green plasma disappearance rate, IVCCI inferior vena cava collapsibility index, LCFM late conservative fluid management, LGFR late goal-directed fluid removal, LVEDAI left ventricular end-diastolic area index, MAP mean arterial pressure, PAOP pulmonary artery occlusion pressure, PF P_aO₂ over F_iO₂ ratio, PLR passive leg raising, PPV pulse pressure variation, PVPI pulmonary vascular permeability index, RVEDVI right ventricular end-diastolic volume index, S_vO₂ central venous oxygen saturation, SSCG surviving sepsis campaign guidelines, S_vO₂ mixed venous oxygen saturation, SVV stroke volume variation, V_e volume excess (from baseline body weight), VExUS venous congestion by ultrasound

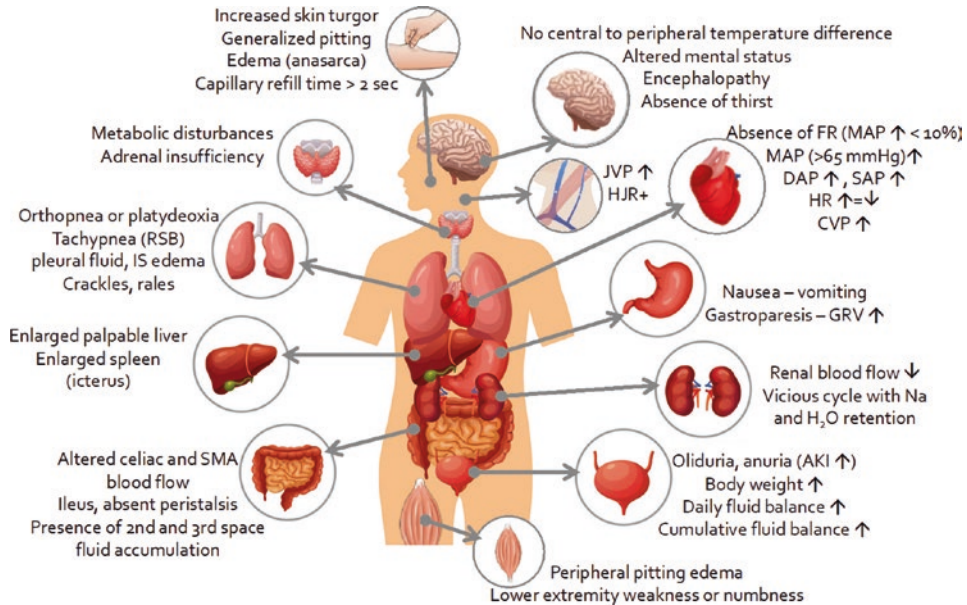


Fig. 25.4 Clinical signs and symptoms related to hypervolemia and fluid accumulation. *CVP* central venous pressure, *DAP* diastolic arterial blood pressure, *FR* preload responsiveness, *GRV* gastric residual volume, *HJR* hepato-jugular reflux, *HR* heart rate, *JVP* jugular venous pressure, *MAP* mean arterial blood pressure, *Na* sodium, *PLR* passive leg raising, *RSB* rapid shallow breathing, *SAP* systolic arterial blood pressure, *SMA* superior mesenteric artery

Laboratory Signs and Biomarkers

Laboratory parameters, although useful, cannot provide independent biomarkers of volume status (Fig. 25.5). Arterial blood gas analysis can be readily obtained and provides a quick estimation of hemoglobin and pO_2 . There are reports regarding the relationship between hypervolemia and hemoglobin or hematocrit levels, and it is widely accepted that in states of overhydration, hemoglobin levels will be lower than normal due to the effects of hemodilution [40]. In case of fluid overload, extravascular lung water may also increase. This will be discussed further (related to either hyperpermeability or hydrostatic pulmonary edema), resulting in hypoxia, which in combination with anemia may further contribute to the imbalance between oxygen delivery and consumption. This process of hemodilution is however, subject to confounders (e.g., anemia, blood loss, toxic effect of infection). Renal function can be significantly impaired in states of hypervolemia. The impact of temporary decreased renal perfusion due to venous congestion appears to rely predominantly on the pre-existing physiological condition of the kidneys. Plasma sodium is of specific interest in volume regulation. It is easily measured by point-of-care tests and is strongly associated with volume status. Many patients with hypervolemia and a net fluid gain will develop hyponatremia. However, when the different baroreceptors of the body sense hypervolemia, the secretion of antidiuretic hormone by the pituitary gland is decreased.

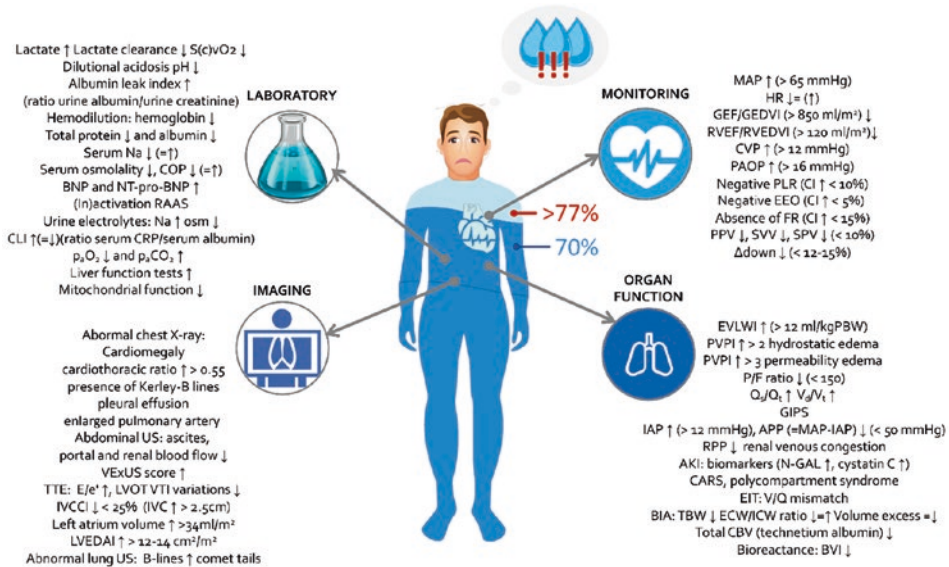


Fig. 25.5 Laboratory, imaging, hemodynamic and organ function signs and symptoms related to hypovolemia and hypoperfusion. Total body water accounts for 70% of body weight. Overt signs and symptoms of hypovolemia occur when circulating blood volume is reduced by more than 50%. *AKI* acute kidney injury, *APP* abdominal perfusion pressure, *BIA* bio-electrical impedance analysis, *BNP* brain natriuretic peptide, *BVI* blood volume index, *CARS* cardio-abdominal-renal syndrome, *CBV* circulating blood volume, *CI* cardiac index, *CLI* capillary leak index, *COP* colloid oncotic pressure, *CRP* C-reactive protein, *CVP* central venous pressure, *ECW* extracellular water, *EIT* electrical impedance tomography, *EEO* end-expiratory occlusion, *EVLWI* extravascular lung water index, *FR* preload responsiveness, *GEDVI* global end-diastolic volume index, *GEF* global ejection fraction, *GIPS* global increased permeability syndrome, *HR* heart rate, *IAP* intra-abdominal pressure, *ICW* intracellular water, *IVC* inferior vena cava, *IVCCI* inferior vena cava collapsibility index, *LVOT* left ventricular outflow tract, *MAP* mean arterial blood pressure, *Na* sodium, *P/F ratio* pO_2 over FiO_2 ratio, *PAOP* pulmonary artery occlusion pressure, *PLR* passive leg raising, *PPV* pulse pressure variation, *PVPI* pulmonary vascular permeability index, *Qs/Qt* shunt fraction, *RAAS* renin angiotensin aldosterone system, *RPP* renal perfusion pressure, *RVEDVI* right ventricular end-diastolic volume index, *RVEF* right ventricular ejection fraction, *ScvO₂* mixed central venous oxygen saturation, *SPV* systolic pressure variation, *SVV* stroke volume variation, *TBW* total body water, *TTE* transthoracic echocardiography, *US* ultrasound, *VEUS* venous excess by ultrasonography score, *V/Q* ventilation/perfusion, *VTI* velocity time integral, *Vt/Vd* dead space ventilation

As a consequence, there will be less retention of water, resulting in increase in sodium levels. Sodium values are also confounded by medication (e.g. diuretics), the type of fluids administered (e.g. saline solutions for resuscitation), the phase of fluid therapy (e.g. use of hypertonic lactated saline for deresuscitation), adrenal activity (renin angiotensin aldosterone system), and choice of replacement fluid (isotonic vs hypotonic). Hypervolemic hyponatremia in cirrhosis patients is characterized by a pronounced deficit of free water excretion and leads to inappropriate water retention in comparison with the sodium concentration.

This imbalance results in an expanded extracellular volume and dilutional hyponatremia. Plasma osmolality (normal around 287 mOsm/kg) can be decreased in cases of hypervolemia, although the body will try to regulate osmolality within normal limits. Overhydration may result in extracellular fluid accumulation and also cellular hydration depending on the type of accumulating fluids. Osmolality is mainly influenced by the non-soluble fraction of the extra-cellular fluid compartment, namely elevated concentrations of serum lipids or proteins. Many medications (e.g. diuretics, mannitol) will affect the osmolality. The plasma colloid oncotic pressure (COP) is normally around 20–25 mmHg. In overhydrated patients with sepsis, the COP value may decrease below 16 mmHg. COP values are related to left ventricular filling pressures and may help in the differential diagnosis of pulmonary edema. COP is increased in hydrostatic edema and associated with increased filling pressures, whereas in hyperpermeability edema, COP is usually decreased. As such, COP measurement can be used for the differential diagnosis of pulmonary edema (hydrostatic vs hyperpermeability). Overhydrated patients may also show lower total protein and decreased albumin levels. The measurement of BNP levels can be a useful adjunct when in doubt as to the potential cause of hypervolemia. Low BNP levels have a high negative predictive value for the exclusion of heart failure as a diagnosis. On the other hand, high BNP levels can be non-specific for volume or fluid overload. The ANP-over-BNP ratio may be indicative of chronic congestive heart failure and fluid overload.

We often look at urine output as a marker of fluid requirement, however patients who are unwell, have suffered trauma, or have undergone surgery often have a reduced urine output due to increased sodium retention (and thus water), by the kidneys. This is an evolutionary stress response geared to the preservation of intravascular volume, in order to maintain vital organ perfusion during such stress states. Stress-induced (‘inappropriate’) anti-diuretic hormone secretion, as well as intrinsic vasopressor hormone secretion, leads to a state of sodium retention and potassium loss in the urine. The patient becomes edematous, hypokalemic and hypernatremia over time, if left unchecked. If normal saline has been given as a resuscitation fluid or maintenance fluid, the potential situation of hyperchloremic metabolic acidosis can ensue, on top of these other electrolyte imbalances.

Radiological and Imaging Signs

Fluid accumulation can be characterized by an abnormal chest X-ray that shows cardiomegaly, dilated upper lobe vessels, interstitial edema, enlarged pulmonary artery, alveolar edema, prominent superior vena cava, increased cardiothoracic ratio (>0.55), presence of Kerley-B lines or pleural effusion (Fig. 25.5). The utility of lung ultrasound offers a greater diagnostic sensitivity and specificity profile over plain radiography of the chest. Moreover, portable chest X-ray, reduces the sensitivity of findings of volume overload, with pleural effusions regularly being missed if the film is performed supine or in intubated patients [41]. Abdominal ultrasound may show 2nd and 3rd space fluid accumulation with edematous abdominal wall, bowel edema, or presence of ascites [42].

Table 25.1 Grading table for assessment of Venous congestion with point-of-care ultrasound

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------------|--|--|---|---|--|
| IVC | <5 mm with respiratory variation | 5–9 mm with respiratory variation | 10–19 mm with respiratory variation | >20 mm with respiratory variation | 20 mm with minimal or no respiratory variation |
| Hepatic vein | Normal S > D | S < D with antegrade S | S flat or inverted or biphasic trace | | |
| Portal vein | < 0.3 pulsatility index | 0.3–0.49 pulsatility index | 0.5–1.0 pulsatility index | | |
| Renal doppler | Continuous monophasic/pulsatile flow | Dis-continuous biphasic flow | Dis-continuous monophasic flow (diastole only) | | |
| VEXUS score | IVC grade < 3, HD grade 0, PV grade 0 (RD grade 0) | IVC grade 4, but normal HV/PV/RV patterns. | IVC grade 4 with mild flow pattern abnormalities in two or more of the following HV/PV/RV | IVC grade 4 with severe flow pattern abnormalities in two or more of the following HV/PV/RV | |

VEXUS *venous congestion assessment with ultrasound*

Adapted with permission from Rola et al. [48]

Transthoracic cardiac ultrasound may also be highly useful demonstrating increased E/e' on tissue Doppler imaging and the absence of left ventricular outflow tract (LVOT) velocity time integral (VTI) variations. Care must be taken over reliance upon on the spot IVC measurements to ascertain volaemic status. Extremes of measurement may be more useful. If there is a complete collapse, in conjunction with an empty, hyperdynamic LV, then the patient is likely to be hypovolaemic. The converse is also true, where a plethoric IVC >2.5 cm is present, with little to no collapse at all, pointing to hypervolemia. There may be other causes of an enlarged IVC to exclude however; large PE, cardiac tamponade, severe tricuspid regurgitation, high PEEP, presence of autoPEEP, increased IAP, noninvasive ventilation, assisted spontaneous breathing, right ventricular dysfunction, right ventricular infarction, low tidal volume or respiratory tidal variation, mechanical obstruction [43]. Low IVCCI (<25%) has been quoted as a useful parameter, but only in ventilated patients and the short axis view is the preferred, more reliable measurement modality. Increased left atrium volume (LA >34 ml/m²) and lung ultrasound, may show B-lines and comet tail artifacts [44, 45]. The importance of venous congestion in the development of organ failure (and especially AKI), in fluid overload, can possibly explain the greatest improvement of renal function after medical treatment for advanced heart failure. This is particularly the case in patients with the echocardiographic signs of right ventricular dysfunction on the inferior vena cava, the portal, hepatic, and renal veins [46, 47] (Table 25.1). To analyse and objectively measure this, the VExUS score (venous excess by ultrasonography) has been suggested (Fig. 25.6) [47].

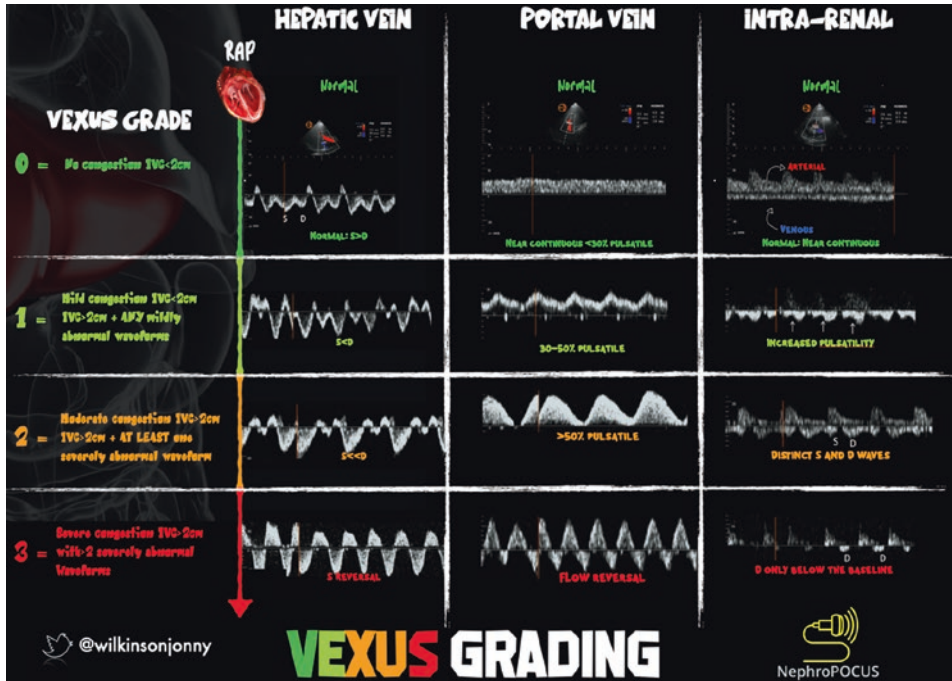


Fig. 25.6 VexUS grading in graphical format (Koratala and Wilkinson)

Advanced Hemodynamic Monitoring

These clinical, biochemical, and radiological parameters are rather non-specific. Hemodynamic assessment of fluid accumulation syndrome includes the absence of preload responsiveness, with a negative passive leg raise test (Fig. 25.7) or end-expiratory occlusion test. Also low functional hemodynamic parameters (PPV, SVV), low systolic pressure variation with normal delta up and delta down, increased MAP, SAP, and DAP, and barometric preload indicators (CVP or PCWP), increased volumetric preload parameters (like global or right ventricular end diastolic volume index; Fig. 25.5).

In critically ill patients treated with renal replacement therapy (RRT), the absence of preload dependence pre-RRT, as assessed by a negative PLR test, was found to be a predictor that fluid removal during RRT would not induce hemodynamic instability [50]. Volumetric preload parameters are superior to barometric parameters, especially if ITP, IAP or PEEP are increased, but correction of these parameters by measures of ejection fraction, can further improve their ability to assess changes in preload over time, as was shown in a heterogeneous group of critically ill patients [51]. The impact of FAS on organ function can be assessed by examining thyroid and adrenal function, looking for signs for polycompartment syndrome (increased IAP, ICP, low APP), gastric distension, gastroparesis or increased GRV, increased EVLWI, PVPI, drop in P/F ratio and ORI, decreased ICG-PDR, and presence of AKI or CARS. With a cut-off value of 3, the

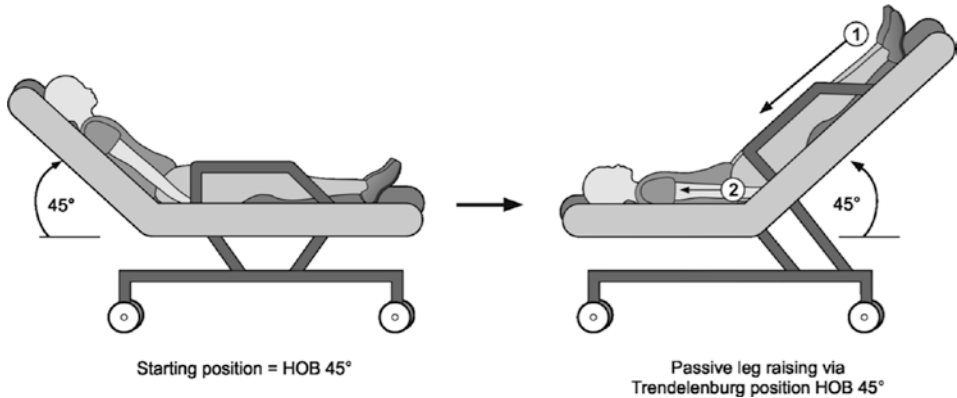


Fig. 25.7 The passive leg raising (PLR) test can also be used to assess the absence of preload responsiveness. In order to perform a correct PLR test, one should not touch the patient in order to avoid sympathetic activation. The PLR is performed by turning the bed from the starting position (head of bed elevation 30–45°) to the Trendelenburg position. The PLR test results in an autotransfusion effect via the increased venous return from the legs and the splanchnic mesenteric pool. Monitoring of stroke volume is required as a positive PLR test is defined by an increase in SV by at least 10%. See text for an explanation. Adapted from Hofer C, Cannesson M. with permission [49]

pulmonary vascular permeability index (PVPI), calculated by transpulmonary thermodilution, allows to discriminate hydrostatic from hyperpermeability pulmonary [52]. In the future, some new and less invasive technologies will become readily available at the bedside. For example bio-electrical impedance analysis with calculation of TBW, ECW/ICW ratio, EVF/IVF ratio, volume excess [19] and BIVA hyperhydration [53], calculation of blood volume index with dye densitometry [54] or total circulating BV with albumin marked isotope dilution [55], or ventilation perfusion (mis)match with EIT [56].

Use of a protocol including BV analysis resulted in a 66% reduction in mortality, a 20% reduction in LOS, 36 h earlier treatment decisions, 44% change in treatment strategy [55]. Fluid overload, defined as a 5% increase in volume excess (measured with BIA) from baseline body weight, was associated with increased mortality in a retrospective study of 101 critically ill patients [19].

How to Perform Deresuscitation?

While more restrictive use of fluid, together with earlier use of vasopressors if needed, may reduce fluid administration, it is unlikely that fluid overload can be entirely avoided using this strategy [27]. Fluid intake in ICU comes from a range of sources, many obligate such as drug diluents and nutrition. A recent study showed that this ‘fluid creep’ accounts for as much as 33% of all fluid intake compared to around 7% for resuscitation fluids [16]. As well as restriction of fluid resuscitation, avoidance of fluid overload is therefore likely to require deresuscitation, with active fluid removal using diuretics or ultrafiltration [1], an

approach that likely shortens the duration of mechanical ventilation and ICU stay [30]. Measures to remove excess fluid include drugs and UF, combined with fluid restriction.

Provided some kidney function is preserved, diuretics are usually tried first, either as monotherapy or in combination. The options include loop diuretics (furosemide, bumetanide), carbonic anhydrase inhibitor (acetazolamide), mineralocorticoid receptor antagonist (spironolactone), thiazides or thiazide-like drugs (indapamide). In case of low serum albumin levels (<30 g/L) or low serum total protein levels (<60 g/L) co-administration of hyperoncotic albumin 20% can be added for synergistic effect along with diuretics and may promote hemodynamic stability [57]. Increased EVLWI and failure to lower EVLWI resulted in poor outcomes in 123 critically ill patients with increased mortality and longer duration of ventilation. A drop in EVLWI was associated with late conservative fluid management and being preload responsive (less positive cumulative fluid balance) [58]. The combination of PEEP (in cmH₂O, set at the level of IAP in mmHg), followed by albumin 20% (up to albumin levels of 30 g/L) and furosemide (or PAL-treatment) resulted in a negative cumulative fluid balance, a reduction of EVLWI and IAP, with improved clinical outcomes in a matched cohort of 114 critically ill patients with hyperpermeability pulmonary edema [59]. In 11 critically ill patients, RRT with 1.9 l net fluid removal was able to lower IAP, EVLWI, and GEDVI significantly [60] (Table 25.2).

Table 25.2 Therapeutic options to avoid and treat fluid accumulation

| Treatment options | Description |
|--|---|
| 1. Monitoring (prevention) | <ul style="list-style-type: none"> – Basic monitoring with arterial and central venous line, pre-alerting to any shock states – Perform baseline transthoracic (or transesophageal) echocardiography – Obtain laboratory results, urea and electrolytes, arterial/venous blood gas analysis, with attention to base excess and lactate – Assess preload responsiveness with functional hemodynamics (PPV or SVV) and perform passive leg raising test or end-expiratory occlusion test – Obtain baseline body weight – Monitor for risk for fluid accumulation (FA): daily body weight, daily and cumulative fluid balance, BIA or BIVA – Assess for impact of FA on end-organ function: IAP, APP, PF ratio, EVLWI, PVPI, daily SOFA (Fig. 25.2) |
| 2. Metabolic optimization (Prevention) | <ul style="list-style-type: none"> – Limit fluid intake (e.g. de-escalation of IV fluids when oral intake is possible) – Use concentrated enteral formula's with 2 kcal/ml instead of 1 kcal/ml) – Limit sodium intake – KDIGO-derived kidney care and treatment bundle – Limit/avoid maintenance solutions – Limit/avoid fluid creep |

(continued)

Table 25.2 (continued)

| Treatment options | Description | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|--|----------------|-----------------|------------------|------------------|------------------|------------------|---------------|----|---|---|---|---|-------------------------------|---|---|---|---|---|----------|---|---|---|---|---|-------------------|---|---|---|---|---|
| 3. First line diuretics | – Loop diuretic (furosemide, bumetanide): high dose and continuous furosemide (1 mg/kg bolus and 10 mg/h) or bumetanide (0.1 mg/kg bolus and 0.1 mg/h) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4. Vasodilators (calcium antagonists, ACE-I) (care) | – Increase renal blood flow – Reduce filtration fraction – Reduce lymph flow – Improve LV function | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5. Inotropes (care) | – Dobutamine: low dose (2.5–5 ug/kg/min) – Milrinone: low dose (0.05–0.1 ug/kg/min), especially in right heart failure or when right heart pressures increased | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6. Lower IAP (care) | – Improve abdominal wall compliance – Reduce intraluminal volume (ileus) – Reduce intra-abdominal volume (ascites) – Optimize fluid administration – Optimize systemic regional perfusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7. Increase APP (care) | – APP = MAP – IAP > 60 mmHg – Vasopressors when needed, low-dose terlipressin (0.5–1 mg over 30 min), vasopressin or norepinephrine (0.05–0.1 ug/kg/min) or norepinephrine | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8. Combination therapy of diuretics (cure) | <ul style="list-style-type: none"> – Loop diuretics: increase dose – Carbonic anhydrase inhibitors (acetazolamide, 250–500 mg IV bolus): inhibition of Na reabsorption in proximal tubule in case of metabolic alkalosis – Thiazide (indapamide, 2.5–5 mg PO): inhibition of Na reabsorption in distal tubule in cases of hypernatremia – Potassium sparing (spironolactone, 25–50 mg PO): aldosterone receptor antagonist, reduction of Na reabsorption at the collector duct (ENaC channel) <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th></th> <th>Na⁺</th> <th>K⁺</th> <th>pH</th> <th>Ca²⁺</th> <th>Mg²⁺</th> </tr> </thead> <tbody> <tr> <td>Loop diuretic</td> <td>↑↓</td> <td>↓</td> <td>↑</td> <td>↓</td> <td>↓</td> </tr> <tr> <td>Carbonic anhydrase inhibitors</td> <td>–</td> <td>↓</td> <td>↓</td> <td>–</td> <td>–</td> </tr> <tr> <td>Thiazide</td> <td>↓</td> <td>↓</td> <td>↑</td> <td>↑</td> <td>↓</td> </tr> <tr> <td>Potassium sparing</td> <td>–</td> <td>↑</td> <td>↓</td> <td>–</td> <td>↑</td> </tr> </tbody> </table> | | Na ⁺ | K ⁺ | pH | Ca ²⁺ | Mg ²⁺ | Loop diuretic | ↑↓ | ↓ | ↑ | ↓ | ↓ | Carbonic anhydrase inhibitors | – | ↓ | ↓ | – | – | Thiazide | ↓ | ↓ | ↑ | ↑ | ↓ | Potassium sparing | – | ↑ | ↓ | – | ↑ |
| | Na ⁺ | K ⁺ | pH | Ca ²⁺ | Mg ²⁺ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Loop diuretic | ↑↓ | ↓ | ↑ | ↓ | ↓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carbonic anhydrase inhibitors | – | ↓ | ↓ | – | – | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thiazide | ↓ | ↓ | ↑ | ↑ | ↓ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Potassium sparing | – | ↑ | ↓ | – | ↑ | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8. Active de-resuscitation (cure) | <ul style="list-style-type: none"> – Increase dose combination therapy diuretics – Application of PEEP – Albumin 20% (where albumin <30 g/L) + diuretics – PAL treatment: PEEP (cmH₂O) = IAP (mmHg) + albumin 20% (200 ml bolus) + Lasix (furosemide 1 mg/kg bolus + drip) – SLEDD with net UF or SCUF – CVVH with net UF | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

APP abdominal perfusion pressure, CARS cardio abdominal renal syndrome, CVVH continuous venovenous hemofiltration, IAP intra-abdominal pressure, MAP mean arterial pressure, Na sodium, PEEP positive end-expiratory pressure, SLEDD slow extended daily dialysis, UF ultrafiltration

Case Vignette

Q1. Does this patient have overhydration?

A1. Yes, moderate overhydration.

Overhydration (or hyperhydration) = body weight relative to admission body weight/pre-ICU body weight \times 100

$$(4.9/67) \times 100 = 7.3\%$$

Q2. Would you consider fluid removal in this patient (deresuscitation), and how?

A2. Yes, given indicators of overhydration. An initial attempt with diuretics along with hyperoncotic albumin (if serum albumin is <30 g/L) can be attempted to induce diuresis. Using RRT for ultrafiltration can be tried in case of AKI or non-responder to diuretics.

Conclusions

No patient should suffer the effects of cellular dysfunction and ultimately multi-organ dysfunction, as a result of excessive IV fluid administration. Armed with an understanding of fluid physiology, one can see why oliguria is a poor marker of overall volaemic status. Physiological oral fluids should always be first line, unless circumstances absolutely disallow it.

The best fluid is probably the one that has not been given...(unnecessarily) [11]

Back to the case vignette; where we followed a patient, who developed shock within 18 h of ICU admission. Despite initial normal (and thus adequate) filling pressures, further fluid resuscitation was needed to overcome the ebb phase (this was guided by functional hemodynamic parameters, passive leg raising test and volumetric preload indices). However, at the very early stage of shock despite the fact that the patient was preload responsive, lung water was already increased. This is the classic example of a therapeutic dilemma which is a condition in which each therapeutic option (either fluid administration or fluid removal), may cause potential harm. Fluids are a double-edged sword. After initial further fluid resuscitation, diuretics were initiated after 24 h to help the patient transgress to the flow phase because of respiratory failure due to capillary leak, as evidenced by increased extravascular lung water. Based on barometric preload indicators, most physicians would be reluctant to start initial fluid resuscitation, therefore advanced monitoring may be indicated, especially in situations with changes in preload, afterload or contractility. This case nicely demonstrates the biphasic clinical course from ebb to flow during shock as well as the inability of traditional filling pressures, to guide us through these different phases. It also illustrates the four crucial questions that need to be solved in order not to cause harm. Therefore, it is important to know and understand:

1. When to start giving fluids (low GEF/GEDVI, high PPV and positive PLR, increased lactate)
2. When to stop giving fluids (high GEF/GEDVI, low PPV, negative PLR, normalized lactate)
3. When to start removing fluids (high EVLWI, high PVPI, raised IAP, low APP defined as MAP minus IAP, positive cumulative fluid balance, absence of preload responsiveness).
4. When to stop fluid removal (low ICG-PDR, low APP, low ScvO₂, neutral to negative cumulative fluid balance, hypovolemia with hypoperfusion).

However, one must realize that the thresholds for the above-mentioned parameters are dynamic targets with dynamic goals (from early adequate goal-directed therapy, over late conservative fluid management towards late goal-directed fluid removal). And above all, one must always bear in mind that unnecessary fluid loading may be harmful. If the patient does not need fluids, don't give them, and remember—the best fluid may be the one that has not been given to the patient!

Take Home Messages

- Tissue edema in ICU patients results from overzealous fluid administration and/or capillary leaks and may lead to worse outcomes.
- Overhydration affects multiple organs and is independently linked to organ failure and mortality.
- The clinical, laboratory, and radiological signs of overload are non-specific.
- Hemodynamic tools like the absence of fluid responsiveness by negative PLR, EEO, low functional hemodynamic variables (SVV, SPV, PPV), increased volumetric (GEDV, RVEDV) or barometric preload indicators (CVP, PAWP) can be used to diagnose and monitor overhydration.
- Evidence supports the feasibility and safety of restrictive fluid administration during resuscitation.
- Deresuscitation defined as an active removal of excessive fluid using diuretics and/or ultrafiltration, combined with fluid restriction may be considered in selected patients with overhydration.

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