Fluid Management in Sepsis

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Abstract

Adequate fluid management in sepsis requires a thoughtful approach. While early aggressive fluid therapy is generally required, one should also be aware of the risks of blind continued administration of large fluid volumes. In the first part of this chapter, we offer an in-depth literature overview on the available fluids in sepsis. In the second part, we stress the importance and prove the relevance of viewing fluids as drugs. Finally, we explain that sepsis can be divided into four temporally distinct phases each requiring a different fluid strategy: resuscitation, optimization, stabilization, and evacuation. We offer a phase-by-phase guidance using this ROSE conceptual model.

Keywords

Fluid management · Sepsis · Septic shock · Intensive care medicine · ICU

Introduction

The third international consensus definition for sepsis and septic shock stated the following: "Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality [1]. In order to address the circulatory dysfunction, early aggressive fluid therapy has been one of the cornerstones in the treatment of septic shock using an early goal-directed therapy [2]. The revised surviving sepsis campaign guidelines advocate the start of 30 ml/kg of IV fluid within the first hour [3]. On the other hand, the body of evidence and awareness has grown that positive daily and cumulative fluid balances during ICU stay could increase mortality [4]. Furthermore, studies have shown that the type of IV fluid given during resuscitation also has an impact on the patients' outcome [5–7].

This led to two important concepts. The *first concept* is the fact that fluids should be considered as drugs. They come with indications, contraindications, and potential adverse effects.

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Similar to antibiotic stewardship, a more thoughtful administration of fluids is necessary, hence giving birth to the concept fluid stewardship. This addresses the importance of choosing the right drug, applying the right dose, using it for the correct duration, and thinking timely about de-escalation. This concept is named the 4 Ds of fluid therapy referring to drug, dose, duration, and de-escalation [8].

Even more important, the *second concept* states that adequate fluid therapy during sepsis requires a different strategy depending on the phase of illness. The first phase is one of a more aggressive resuscitation to *rescue* the patient's life; second, we need to *optimize* organ perfusion by more diligently titrating fluids; in the third phase, we aim at *stabilizing* the fluid balance to a neutral daily fluid balance; and in the final phase, we try to *evacuate* the potentially accumulated fluids. Hence, the ROSE acronym has been proposed as a mnemonic for this conceptual model [8].

In this chapter, we will summarize the available literature on fluid therapy in sepsis using the abovementioned concepts of 4 Ds and ROSE as illustrated in Fig. 1 [8].

Key points that will be discussed:

- Fluids are drugs and should be treated accordingly with indications, contraindications, and adverse effects.
- One should consider the 4 Ds of fluid therapy: drug, dose, duration, and de-escalation.
- We need to consider the four dynamic phases of fluid therapy in sepsis applying the ROSE conceptual model: resuscitation, optimization, stabilization, and evacuation.

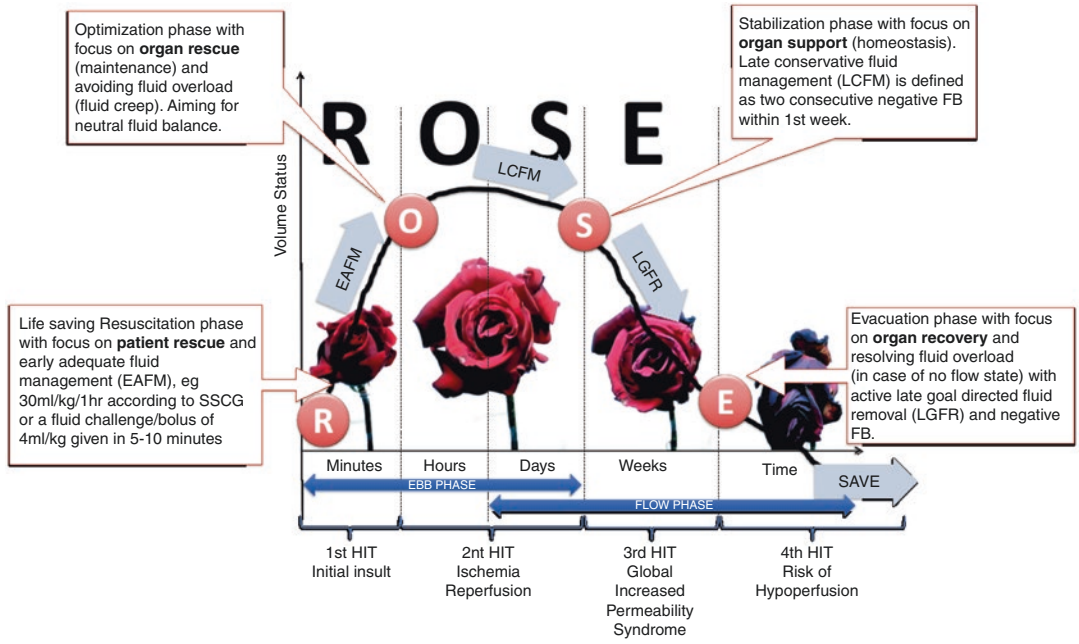

Fig. 1 Visualization of the ROSE conceptual model. Graph showing the four-hit model of shock with evolution of patients' cumulative fluid volume status over time during the five distinct phases of resuscitation: resuscitation (R), optimization (O), stabilization (S), and evacuation (E) (ROSE), followed by a possible risk of hypoperfusion in case of too aggressive deresuscitation. On admission patients are hypovolemic, followed by normovolemia after fluid resuscitation (EAFM, early adequate fluid management), and possible fluid overload, again followed by a phase going to normovolemia with late conservative fluid management (LCFM) and late goal-directed fluid removal (LGFR) or deresuscitation. In case of hypovolemia, O_2 cannot get into the tissue because of convective problems; in case of hypervolemia, O_2 cannot get into the tissue because of diffusion problems related to interstitial and pulmonary edema and gut edema (ileus and abdominal hypertension). Adapted according to the Open Access CC BY License 4.0 with permission from Malbrain et al. [8]

Drug

The available types of fluids have been extensively described in earlier chapters. In this section, we will take you through the available literature on the use of different types of fluid in sepsis.

Colloids

Background

Historically, synthetic colloids have been used in abundance in septic shock mainly because it was assumed that when using colloids less volume would be needed to expand the circulating blood volume in order to obtain hemodynamic stabilization. Traditionally, it was suggested that one would need to double the volume of crystalloids as compared to colloids to achieve the same increase in intravascular volume. However, recent data show that in reality this ratio may be closer to 1.3:1 or even 1:1 in cases of acute shock, after induction of anesthesia and during surgery where fluid distribution, elimination, and excretion are altered [9, 10].

Hydroxyethyl Starches (HES)

Over time, strong evidence grew regarding the negative effects of synthetic colloids. In the VISEP study, a two-by-two factorial randomized controlled clinical trial (RCCT) including 537 patients, administration of hydroxyethyl starch (HES, $n = 262$) was compared to using crystalloids, mainly Ringer's lactate ($n = 275$) [6]. A central venous pressure (CVP) of 8 mmHg was targeted. Administration of HES as opposed to crystalloids was associated with higher rates of acute renal failure and/or renal replacement therapy (RRT): 34.9% vs. 22.8% ($p = 0.002$) [6]. Acute kidney injury (AKI) was defined as a doubling of baseline creatinine values or requirement for renal replacement therapy. This complex study also compared intensive insulin therapy ($n = 247$) to conventional insulin therapy ($n = 290$). HES 10% was given at a maximum limit of 20 mL/kg/day; however, more than 10% of the patients exceeded this limit. More patients in the HES group had heart failure or received emergency surgery, and the study was stopped prematurely because of a higher incidence of hypoglycemia in the intensive insulin group.

The increased need for RRT in patients treated with synthetic colloids was later confirmed, albeit discussable, by the CHEST trial including 7000 patients, comparing administration of HES with saline [7]. In this pragmatic study, there was no difference in 90-day mortality nor in the incidence of AKI (according to RIFLE scoring). There was even a reduction in patients with RIFLE-R and RIFLE-I and similar RIFLE-F in patients administered 6% HES. The use of 6% HES did result in an increased urinary output and slight increase in serum creatinine. Only the (subjective) need for RRT was significantly different: 7.0% in the HES group vs 5.8% in the crystalloid group (RR 1.21; 95%CI 1–1.45; $p = 0.04$). Patients were randomized after an average of 11 ± 156 h pointing toward large differences between patients and non-Gaussian distribution. There has been a lot of criticism on the CHEST trial especially since the authors did not want to share the raw data [11, 12].

In a 2012 RCCT, the 6S study in 798 patients showed that administration of HES not only increased the need for RRT when compared to Ringer's acetate but also significantly increased mortality in patients treated with HES [5].

The defenders of the popular HES solutions were at first relieved when the results of the CRYSTMAS study were published. In this study, 196 patients were randomly resuscitated using either 6% HES 130/0.4 or NaCl 0.9%. The authors stated there was no difference in adverse events between both groups, while a lower volume of fluids was needed when using HES [13]. However, soon after, publication concerns arose about potential publication bias. When the full data set was reassessed, there appeared to be no volume-saving effect when using HES. The study was also proven to be underpowered to identify differences in the need for RRT. However, there was a trend against the use of HES regarding mortality and time to RRT with a doubling in the need for RRT in the patients treated with HES [14].

The CRISTAL study is another trial at first seemingly stating similar outcomes when administering crystalloids or colloids, this time in patients with hypovolemia. Over 9 years, 2847 patients were included. However, it was an open-label trial where mainly HES was used as a colloid besides gelatins and dextran, but also human albumin was administered. All these colloids were analyzed as one group. Although subgroup analyses were performed, these were underpowered to show significant differences in renal failure or mortality. It should also be noted that NaCl 0.9% was the main crystalloid used. As explained later, NaCl 0.9% is also associated with detrimental effects on renal function and an increased need for RRT [15].

Based on this evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA stated that starches mustn't be used anymore in patients with burn injuries, renal failure, sepsis, and septic shock [16].

Gelatins

Gelatins have always been less popular as a colloid. A recent systematic review stated that gelatins increase the risk of anaphylaxis and may increase mortality, renal failure, and bleeding due to extravascular uptake and coagulation impairment. The prospective GENIUS trial aiming at confirming or refuting this statement should be finalized in 2021. Given the cheaper and safer alternative fluids, we advise against the use of gelatins for the time being [17].

Dextran

Data on effectiveness and complications of dextran are scarce. A retrospective analysis of 332 patients stated that dextran 70 increased bleeding risk and need for blood products [18]. A more recent study propensity score matching 778 patients could not confirm these findings [19]. However, older data also showed tissue deposition of dextran after administrating this fluid in hemodialysis patients [20]. Given the absence of evidence favoring dextran and given the cheaper and proven safe alternatives, we do not recommend the use of dextran.

Human Albumin

Following the evidence on synthetic colloids, concerns arose about the use of albumin in ICU patients. The SAFE study was an RCCT comparing administration of fluid boluses of either albumin 4% or saline 0.9% in patients with sepsis. In this study, albumin appeared to be safe to administer [21]. A post hoc analysis in a subset of patients with severe sepsis showed that the use of albumin had an adjusted odds ratio for death of 0.71 (95% CI: 0.52–0.97; $p = 0.03$), suggesting a mortality benefit [22]. However, it should be noted that all patients already received initial fluid resuscitation before inclusion resulting in less administered fluid volumes during the intervention in both groups. As later explained, this implies that this trial is performed during the optimization phase rather than during the resuscitation phase.

In the ALBIOS trial, including patients with sepsis, simultaneous administration of crystalloids and albumin 20% ($n = 903$) to achieve and maintain a serum albumin of 30 g/L (with a normal range being 34 to 54 g/L) also appeared to be safe when compared to using only crystalloids ($n = 907$). Again, a post hoc analysis suggested a potential outcome benefit when using albumin in septic shock [23]. Given the broad use of NaCl 0.9% in both studies, the post hoc analysis should be critically appraised keeping in mind the available literature on balanced and unbalanced crystalloids that will be discussed later, disfavoring the use of NaCl 0.9%.

A third trial on albumin, the EARSS study by Charpentier and Mira in 2011, has only been published in abstract. In this multicenter prospective trial, early administration of 100-mL albumin 20% every 8 h was compared to sole application of saline 0.9%. The mortality, 24.1% in the albumin group and 26.3% in the saline group, was not significantly different [24].

While all individual trials merely show a trend toward mortality reduction, Wiedermann combined the data and showed that the pooled relative risk is 0.92 (CI: 0.84–1.00; $p = 0.046$) [24]. In our opinion, this implies that albumin 4% or 20% could be a viable option in a subset of

patients with severe sepsis or septic shock, respectively, in case of low serum albumin levels (<30 g/L).

A final large trial worth mentioning is the FEAST trial. This RCCT in African children with febrile illness and impaired perfusion compared administration of either albumin boluses, NaCl 0.9% boluses, or no boluses. The fluid administrated in the intervention groups was 20 mL/kg or 40 mL/kg over 1 h potentially followed by another 20 ml/kg or 40 ml/kg over 1 h. After inclusion of 3141 patients, this study was prematurely ended due to increased mortality in both groups treated with fluid boluses. While technically this is a study including albumin resuscitation, it should mainly warn against uncontrolled fixed administration of large fluid boluses [25].

Take-home messages on the use of colloids for resuscitation in sepsis:

- Based on the literature, synthetic colloids (especially HES solutions) mustn't be used in sepsis, burns, or patients with renal failure.
- Albumin 4% or 20% could be a viable option in a subset of patients with severe sepsis or septic shock, respectively, in case of low serum albumin levels (<3 g/dL).

Crystalloids

Crystalloids are less expensive than colloids. As they appear to be as effective as human albumin, they are more generally used in septic shock. However, the term crystalloid covers a lot of different fluid types with different properties. The tonicity of the fluid will determine its initial distribution volume. As such, *hypotonic* crystalloids have no place in fluid resuscitation during septic shock. However, in the absence of contraindications such as craniocerebral trauma or ischemic stroke, these are the maintenance fluids of choice. Maintenance fluids are given when daily fluid needs cannot be covered orally or in case of cellular dehydration [26–28]. Regarding resuscitation fluids, we will now first cover the hypertonic crystalloids followed by the unbalanced and balanced isotonic crystalloids.

Theoretically, administering a *hypertonic* fluid should increase the intravascular volume more than isotonic infusions due to the higher tonicity favoring a fluid flux toward the intravascular space. However, the recent HYPERS2S trial using hypertonic saline as a resuscitation fluid did not show reduced cumulative fluid administration nor positive outcome effects. Although there was an initial trend toward less fluid administration during resuscitation, this effect was nullified by supplementary fluid administration due to hypernatremia [29]. Similar results were found in the HERACLES trial examining the use of hypertonic saline for resuscitation in patients admitted to the ICU after cardiac surgery [30].

The detrimental effects of *isotonic* hyperchloremic fluids when compared to balanced solutions have been well established in preclinical studies. The use of (ab)normal saline 0.9% was consistently associated with metabolic acidosis, decreased renal perfusion, and increased AKI [31–38]. Two pilot studies SPLIT and SALT, while underpowered to show a significant difference, confirmed the feasibility of comparing balanced and unbalanced crystalloid solutions in the ICU [39, 40]. Two large randomized trials, SMART [40] in the ICU and SALT-ED [41] in the emergency department, showed that patients treated with balanced crystalloids had a significant reduction in MAKE 30 (*m*ajor *a*dverse *k*idney *e*vents within *30* days), a composite outcome for death, need for RRT, and persisting renal dysfunction. In these trials, the benefit of balanced crystalloids was greatest in the subgroup of patients admitted to the ICU with sepsis or septic shock. The number needed to treat to prevent one death, new RRT, or persisting renal dysfunction was around 20.

Take-home messages on crystalloids for resuscitation in sepsis:

- Based on the available data, isotonic balanced crystalloids (and not saline) should be the

resuscitation fluid of choice in patients with sepsis and septic shock.
- Overzealous administration of (ab)normal saline may contribute to hyperchloremic metabolic acidosis.

Blood Products

Blood products are not commonly administered as a resuscitation fluid in patients with septic shock. However, the concern of an adequate hemoglobin level as a means for oxygen transport has led Rivers and coworkers to implement transfusion triggers in their bundle of early goal-directed therapy [2]. During the last decade, evidence grew that a more restrictive transfusion strategy might be as good or even better than aiming for a higher hemoglobin level [42–44].

The first large RCCT suggesting the benefit of a lower transfusion threshold in ICU was the TRICC trial by Hébert et al. Contrary to previous beliefs and retrospective studies, they showed that maintaining a hemoglobin level between 7 g/dL and 9 g/dL resulted in a similar to better outcome than aiming for a hemoglobin level between 10 g/dL and 12 g/dL. There was a trend favoring overall survival and a significant lower in hospital mortality in the group treated with a restrictive transfusion strategy [43].

The TRISS trial, including nearly 1000 anemic patients with septic shock, proved that also in septic patients a hemoglobin transfusion threshold of 7 g/dL led to similar outcomes than aiming for a hemoglobin level above 9 g/dL. This was true for all age groups, for patients with cardiovascular comorbidities and who were independent of SAPS II score. Patients with an acute coronary syndrome, active bleed, or burns were excluded from this study [44]. On the other hand, a more recent RCT targeting 300 oncological septic patients reported a lower 90-day mortality in the group with the more liberal transfusion strategy [45].

It remains unclear whether blood product shelf life or the nonapplication of leucocyte depletion could be an explanation as to why adhering to a higher transfusion threshold leads to more unfavorable outcomes. While leucocyte reduction is common practice nowadays in Europe and Australia, its application in the beforementioned studies is unclear. In 2008, leucocyte depletion was proven to be associated with reduced frequency of non-hemolytic febrile transfusion reactions, reduced risk of CMV transmission, reduced risk of HLA alloimmunization and platelet refractoriness, as well as reduced mortality and organ dysfunction in cardiovascular surgery patients [46]. The impact of red blood cell shelf life remains unclear. The first concerns arose in 2008, after the publication of a retrospective study stating that transfusion of red blood cells after 14 days of storage was associated with a higher rate of postoperative complications and a reduction in short- and long-term survival. However, post hoc analysis showed that patients receiving these “older” red blood cells also received more units of red blood cells, possibly suggesting a selection bias toward more severely ill patients in the group treated with older blood products [47].

Take-home message on blood products in sepsis:

- Given the current evidence, we propose to adhere to a lower transfusion threshold of 7 g/dL, transfusion practice that can however be further tailored to the individual patient’s needs.

Duration

Murphy et al. showed that the more microcirculatory hypoperfusion and subsequent organ damage related to ischemia reperfusion occurs, the longer the delay in fluid administration in patients with septic shock [48]. They compared outcomes in sepsis when using a strategy of either early adequate or early conservative fluid therapy combined with either late conservative or late liberal fluid administration. They found that patients treated with a combination of early adequate and late conservative fluid management had the best outcomes [48]. Other studies suggest that especially the late conservative approach might have

the biggest impact on outcome [49–52]. One should not continue fluids to treat the numbers (e.g., to normalize a low urine output, central venous pressure, cardiac output, or blood pressure), but one should give fluids to treat shock and DO_2/VO_2 imbalance. Fluid therapy should be stopped when shock has resolved, or fluids are no longer needed.

Take-home messages on duration:

- Treating patients with a combination of early adequate and late conservative fluid management has the best outcome.
- Don't give fluids to treat the numbers but to treat shock and stop them when they are no longer needed.

Dose

As stated by Paracelsus, "all things are poison, and nothing is without poison; only the dose permits something not to be poisonous," and as described earlier, the detrimental effects of fluid overload are well established. Dosing should be adjusted to both pharmacokinetics and pharmacodynamics.

Pharmacokinetics describes how the body interacts with a drug. In fluid therapy, different types of fluids remain intravascular for a different percentage and for a different time period, favoring fluids with higher tonicity. It is well established that during vasoplegic shock these characteristics can be altered [9, 10].

Pharmacodynamics describes the interaction of a drug to its specific effect. Here, the Frank-Starling relationship between cardiac preload and cardiac output correlates to the dose effect curve as can be seen for other drugs. Due to the shape of the Frank-Starling curve, the effect of fluids on cardiac output is not constant. Determining an individual patient's position on the Frank-Starling curve and subsequently predicting the effect of fluid administration are the arts of prescribing adequate fluid therapy [53].

Given the evolving pharmacokinetic and pharmacodynamic properties of fluid therapy, the adequate dose of fluid therapy is dependent on individual factors as well as the timing of fluid administration. We will dig deeper into these characteristics when describing the four dynamic phases of fluid therapy.

Dynamic tests for assessing fluid responsiveness and tailoring fluid therapy according to patient needs, such as the passive leg raising test, are described elsewhere [8]. We would however like to point out that it is a misconception that all fluid-responsive critically ill patients should receive fluids. Resuscitation fluids can be stopped safely once the initial signs and symptoms of hypovolemia and shock have resolved and should not be continued to treat numbers.

Administration of a fluid bolus or even better a (mini-)fluid challenge is the preferred way of fluid administration during resuscitation. It is a quick infusion of a small amount of fluids within a short period of time (5–10 min). The volume administered with a fluid bolus is highly clinician-dependent varying between 500 mL (over 10 min) and 1000 mL (over 15–20 min) [54]. However, the smaller, the better, and the minimal fluid volume required to increase venous return is around 4 mL/kg/5 min [55]. We would advocate using smaller volumes when appropriate in combination with clinical evaluation of the hemodynamic effect after administration.

Take-home messages on dose:

- Given the evolving pharmacokinetic and pharmacodynamic properties of fluid therapy, the adequate dose of fluid therapy is dependent on both individual factors and the timing of fluid administration.
- We propose using fluid challenges of 4 mL/kg/5 min combined with clinical evaluation of the effect after administration.

De-escalation

As stated in the ROSE conceptual model, which will be discussed later, we must be aware when to stop administering resuscitation fluids and when to start fluid evacuation in case of accumulation. This is essential to prevent fluid overloading and the herewith associated increase in adverse

events. Fluid overload is defined as a 10% increase in fluid accumulation from baseline body weight.

The approach of restricted fluid therapy after initial resuscitation as well as application of diuretic therapy after stabilization is supported by the FACTT trial. In this trial, patients treated with a restrictive fluid management after initial resuscitation and diuretic therapy after stabilization had a reduced number of ventilator-dependent days [56].

The retrospective RADAR-trial including 400 patients also identified that a negative fluid balance on day three, achieved by active evacuation of accumulated fluid, is associated with an improved outcome. Limiting the intake of maintenance fluids and drug diluents and active fluid evacuation are essential steps toward achieving this goal [57].

The CLASSIC trial tries to evaluate the impact of early de-escalation: a fluid restrictive fluid resuscitation. While the CLASSIC trial was only a feasibility trial, it did show a trend toward benefit with a fluid restriction strategy. The results of the larger CLASSIC-2 trial are eagerly awaited [51].

In contrast to these results, the RELIEF trial, conducted in patients undergoing major abdominal surgery, showed that a restrictive fluid regimen was associated with increased AKI. There was no difference in mortality or disability between the two strategies. In our opinion, this study warns against blind fluid removal potentially leading to hypovolemia, while it should not necessarily refute controlled active fluid removal [58].

Take-home messages on de-escalation:

- Restrictive fluid management and diuretic therapy after stabilization can reduce the number of ventilatory-dependent days.
- During de-escalation, one should avoid hypovolemia.

The Four Phases of Fluid Resuscitation: The ROSE Principle

When managing fluid therapy during sepsis, one should mind not only the fluid but also the fluid-patient interaction as well as the phase of illness. Malbrain et al. proposed the mnemonic ROSE in 2014 after an initial publication describing four distinct phases in septic patients by Vincent in 2013 [8, 59]. This concept is summarized in Table 1.

During the initial phase, aggressive yet adequate fluid administration should be applied to rescue the patient. Following initial *resuscitation*, a more careful titration of fluids ought to be applied to *optimize* the circulation. This aims at counteracting organ damage while avoiding fluid overload. Neutral fluid balances should be targeted a few days after the initial septic shock to avoid the detrimental effects of positive fluid balances as described by the SOAP trial [4]. This phase is called the *stabilization* phase. The fourth and more heavily debated phase is the active *evacuation* phase to remove accumulated fluids. The recently published FACTT trial supports this active approach of fluid elimination [56].

Resuscitation Phase

When administering fluids during the resuscitation phase, we aim at restoring the intravascular volume to increase and maintain cardiac output. In this way, we try to increase oxygen delivery and restore tissue oxygenation.

As suggested by Rivers et al., the sepsis guidelines still favor the liberal use of resuscitation fluids, proposing 30 mL/kg of fluid therapy started in the first hour after presentation with septic shock [2, 3]. The blind adherence to these protocols does however not improve the outcome of patients with sepsis as was clearly shown by the PROCESS, PROMISE, ARISE, and SEPSISPAM studies [61–64] that have been discussed in previous chapters. Growing evidence from cohort studies and smaller trials support a more restrictive resuscitation strategy in septic shock [51, 58, 65]. In children and adults from low-income countries, early aggressive fluid therapy was even associated with increased mortality [25, 66]. Although these results might be related to the lack of access to mechanical ventilation or patient- and disease-specific parameters, other studies in high-income countries such as the SOAP and VASST trials also identified a

Table 1 The ROSE conceptual model avoiding fluid overload (adapted from Malbrain et al. with permission) [60]

	Resuscitation	**O**ptimization	**S**tabilization	**E**vacuation
Hit sequence	First hit	Second hit	Second hit	Third hit
Time frame	Minutes	Hours	Days	Days to weeks
Underlying mechanism	Inflammatory insult	Ischemia and reperfusion	Ischemia and reperfusion	Global increased permeability syndrome
Clinical presentation	Severe shock	Unstable shock	Absence of shock or threat of shock	Recovery from shock, possible global increased permeability syndrome
Goal	Early adequate goal-directed fluid management	Focus on organ support and maintaining tissue perfusion	Late conservative fluid management	Late goal-directed fluid removal (deresuscitation)
Fluid therapy	Early administration with fluid boluses, guided by indices of fluid responsiveness	Fluid boluses guided by fluid responsiveness indices and indices of the risk of fluid administration	Only for normal maintenance and replacement	Reversal of the positive fluid balance, either spontaneous or active
Fluid balance	Positive	Neutral	Neutral to negative	Negative
Primary result of treatment	Salvage or patient rescue	Organ rescue	Organ support (homeostasis)	Organ recovery
Main risk	Insufficient resuscitation	Insufficient resuscitation and fluid overload (e.g., pulmonary edema, intra-abdominal hypertension)	Fluid overload (e.g., pulmonary edema, intra-abdominal hypertension)	Excessive fluid removal, possibly inducing hypotension, hypoperfusion, and a "fourth hit"

relationship between positive fluid balances and increased mortality rates [4, 67].

Septic shock is a state of imbalance between oxygen supply (DO_2) and demand (VO_2) due to an effective or functional state of hypovolemia. Interest for the early introduction of vasopressors to reduce the functional hypovolemia and increase venous return by recruiting fluids from the splanchnic bed was sparked by the vasoplegic nature of septic shock [68]. Up to this day, no hard evidence supports this physiological plausible strategy. We are eagerly awaiting the results of the CLOVER trial, aimed at providing evidence on this topic. Inclusions should finish in the summer of 2021.

Summarizing the results from the literature, rapid fluid administration to achieve hemodynamic goals remains important. Rather than administering a fixed dose of fluids (one size fits all), an individualized approach, keeping the patient's premorbid conditions in mind, seems more appropriate [69–71]. The lower autoregulation threshold of the most vulnerable organs (brain and kidneys) should be reached [72]. To achieve this, it is key to obtain a correct assessment of fluid status as well as fluid responsiveness. The most adequate method is assessing functional hemodynamic parameters such as stroke volume and pulse pressure variation and tests such as end-expiratory occlusion or passive leg raising. The passive leg raising test is particularly interesting since it perfectly mimics fluid administration without giving a single drop of fluid. It is well studied and is recommended by the surviving sepsis campaign [73, 74]. Even more important than predicting fluid responsiveness is the repeated evaluation of the patient both before and after fluid administration in order to guide further fluid therapy.

Take-home messages on resuscitation phase:

- Rapid fluid administration to achieve hemodynamic goals remains important while keeping in mind the patient's premorbid conditions.
- The passive leg raising test is the preferred test to assess fluid responsiveness.
- Assessment of changes in functional hemodynamic parameters before and after fluid administration should be used to guide further individualized fluid therapy.

Optimization Phase

Within hours of initial resuscitation, a second hit occurs due to the reperfusion of previously ischemic cells. While fluid administration is evident during the initial resuscitation phase, a more cautious approach is warranted during optimization using the previously described dynamic tests for fluid responsiveness. In this phase, the risks of fluid overload should be monitored closely when deciding to administer extra fluids. Especially the evolution of lung impairment should warn against overaggressive fluid therapy at this stage. When in doubt, advanced hemodynamic monitoring can be of additional value. These techniques are described in previous chapters as well as in dedicated articles [75, 76].

Take-home messages on optimization phase:

- During optimization, a more diligent application of fluids is warranted.
- Invasive hemodynamic monitoring can help to optimize fluid therapy during this phase.

Stabilization Phase

A stabilization phase is usually obtained within a few days. This phase is characterized by the absence of shock or impending deterioration. During this phase, there should be no need for additional fluid boluses. In case the patients cannot have oral intake, hypotonic maintenance fluids should be given to cover the daily fluid needs (1 mL/kg/h), sodium (1–1.5 mmol/kg/day), potassium (0.5–1 mmol/kg/day), and glucose (1–1.5 g/kg/day) [28].

The focus should be on awareness of the total volume of fluids administered, including maintenance fluids, replacement fluids for ongoing losses, feeding fluids, as well as fluids administered along with medication. The recent retrospective RADAR study showed that these fluids contribute more to fluid input than resuscitation fluids [57]. The quantitative relevance of fluids administered as drug diluents and fluids to guarantee catheter patency, the so-called fluid creep, has been stressed by Van Regenmortel et al. [77]. It is important to take all these administered fluids into account when assessing the needs of a patient in order to prevent the detrimental effects of fluid overload [4, 57]. More often than not, this implies cessation of maintenance fluids due to an already sufficient administration.

Take-home messages on stabilization phase:

- During stabilization phase, one should aim for a neutral to negative fluid balance.
- All fluids, including drug diluents, should be taken into account when assessing the daily fluid needs of a patient.

Evacuation Phase

After the second hit due to ischemia reperfusion, patients can either start spontaneous evacuation of the accumulated fluids in the second and third space or remain in a "no flow state" retaining all administered fluids. This last scenario (or the global increased permeability syndrome) can result in a third hit due to impaired oxygen diffusion and nutrient absorption [78]. Conservative fluid administration or even active goal-directed fluid removal is advised during this late phase of illness. Late conservative fluid administration is defined by Murphy et al. as 2 consecutive days with a negative fluid balance during the first week of ICU stay [48]. Late goal-directed fluid removal implies the aggressive use of diuretics or renal replacement therapy with net ultrafiltration to actively remove the accumulated fluids. In order to achieve negative fluid balances with this strat-

egy, it is mandatory to minimize fluid administration to basic needs [50].

Recent literature supports this strategy by showing an independent survival benefit when obtaining 2 consecutive days with a negative fluid balance within the first week of admission or by attaining negative fluid balances by day three [48, 57]. Further confirmation from prospective randomized controlled trials such as the RADAR-2 and CLASSIC-2 studies is eagerly awaited since the current retrospective literature may only indicate that positive fluid balances are merely a biomarker for severity of illness [79]. The main risk to consider is being too aggressive while removing fluids, causing hypovolemia and hypoperfusion. Close monitoring is of paramount importance to avoid this fourth hit. Given its restoring effect on permeability of the glycocalyx, albumin might be the fluid of choice at this stage to facilitate fluid migration and removal from the second and third space.

Take-home messages on evacuation phase:

- While awaiting further studies, we would suggest aiming for 2 consecutive days with a negative fluid balance within the first week of admission and attaining negative fluid balances by day three.
- When evacuating accumulated fluids, one must avoid inducing hypovolemia.

Conclusion

Fluids administered during sepsis should be as meticulously selected as antibiotic therapy, and clinicians are to consider the drug choice, dose, preferred duration, and timely de-escalation. Balanced crystalloids are a good first choice and synthetic colloids should be avoided. Whenever prescribing fluid therapy for septic patients, one should be aware of the different dynamic phases during the course of illness. While early aggressive therapy is generally required during the initial resuscitation phase, continuous reassessment of fluid status and fluid responsiveness is mandatory. During the optimization phase following resuscitation, this becomes even more important, and advanced hemodynamic monitoring can be a useful aid for tailoring fluid therapy. Once the initial shock phase has resolved during stabilization, a restrictive fluid approach is warranted, aiming for neutral to negative fluid balances by taking into account all administered fluids and avoiding fluid creep. Finally, the accumulated fluids should be evacuated with diuretics or renal replacement therapy with net ultrafiltration Avoiding a third hit caused by decreased diffusion of oxygen and absorption of nutrients due to second and third space fluid accumulation as well as a fourth hit caused by hypovolemia and tissue hypoperfusion is quintessential.

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