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Fluid overload FADEs away! Time for fluid stewardship

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Fluids save lives but also cause harm

Administration of fluids is a mainstay during the resuscitation phase of critically ill patients, in order to increase cardiac output and to enhance oxygen delivery. Furthermore, maintenance fluids are often prescribed to preserve total body water and electrolyte balance [1]. Capillary leak represents the maladaptive, often excessive, and undesirable loss of fluid into the interstitium that generates oedema [2]. There are several discrete compartments into which fluids are partitioned, including the intravascular, extravascular, and intracellular, extracellular space. The interstitium consists of a collagen matrix that is laced with proteoglycan filaments and a variety of enzymes including matrix metalloproteinases [2]. This is called the glycocalyx. This space functionally behaves as gel that allows transit of molecules by diffusion, but tends to inhibit the free flow of fluids based on maintenance of colloid oncotic pressure equilibrium between the intra-and extravascular compartments [2]. Systemic inflammation quickly increases vascular permeability, mainly due to glycocalyx damage and disturbances of lymphatic flow [3]. Due to the destruction of the glycocalyx, fluids are leaving vascular beds resulting in interstitial fluid accumulation in vital organs, leading to organ dysfunction with adverse outcomes [3-5]. Glycocalyx damage can be reduced by avoiding hypervolemia and hyperglycemia and by maintaining a physiological concentration of plasma proteins, mainly albumin [3]. Critically ill patients often suffer from hypoproteinemia and hypoalbuminemia, leading to decreased capillary oncotic pressure, promoting capillary leakage, finally resulting in interstitial edema. Achieving a negative fluid balance is associated with decreased morbidity and mortality [7-9].

What the present study tells and does not tell

Within this perspective, the recent publication of the FADE study [10] in the Journal of Critical Care is hypothesis generating. Hyperoncotic albumin in addition to moderate doses of furosemide was used to improve diuresis and thereby facilitate liberation from mechanical ventilation in critically ill adults. This randomized controlled clinical trial compares intravenous 25% albumin with 0.9% saline. Feasibility, assessed by the ability to recruit patients as well as administration of study treatment and clinical effect on fluid balance, ventilator-free days and mortality were defined as endpoints.

The study could not demonstrate adequate feasibility. Patients assigned to albumin had a more significant increase in colloid osmotic pressure and serum albumin levels. However, this increase was not translated to a benefit in clinical outcomes.

The study adds to the current understanding that severe hypoalbuminemia impairs furosemide secretion in the tubular lumen, leading to diuretic resistance [11-12]. The extent of diuretic resistance may depend upon the degree of hypoalbuminemia, which in itself may act as an essential effect modifier on furosemide-albumin interactions [13]. A possible approach for future research could be to identify patients with diuretic resistance through a furosemide stress test [14].

The relatively low albumin levels in the treatment group ($< 30\text{g/L}$) as well as the timing of diuretic administration (given within a 2 hour time-frame after or even before albumin administration) observed in this study also helps to understand why some patients exhibited an absence of significant difference in urine output. The timing of diuretic administration could be a topic for future research as furosemide may be better given immediately, or at least within 30 minutes of albumin administration [7].

Therefore, it is of interest that the authors “tried” to obtain serum albumin levels of 35 g/L, in line with the ALBIOS trial suggesting a benefit for 20% albumin given later during the course in patients with septic shock to achieve at least an albumin level of 30 g/L [15]. It is hypothesized that the higher the albumin level, the higher the colloid oncotic pressure and the higher the shift of fluids from the interstitium. Although this may only be partially true in view of the revised Starling equation as the lymphatics probably play a more prominent role in fluid clearance [3].

Future studies should address the above mentioned issues and could focus on other interesting parameters for capillary leak such as CRP divided by albumin, or evolution of protein, hemoglobin or hematocrit (hemodilution vs. hemoconcentration) [7]. This in combination with serum osmolality and chloride levels as well as urinary electrolytes. In burn patients for instance, urine albumin over creatinine ratio has been used to quantify capillary leak [9,16].

When and how to start de-resuscitation?

Several studies have addressed different strategies to achieve a negative fluid balance by using furosemide along with albumin [17]. According to the ROSE concept, fluid management during critical illness has four distinct phases: Resuscitation (ebb), Optimization, Stabilization, and Evacuation (flow)[9,16](Figure 1). The ROSE concept is summarized in Table 1. Fluid Resuscitation can be life-saving during the initial shock state. Increased capillary permeability and albumin leak characterize this ebb phase. Mobilization and evacuation of excess fluids during the flow phase should induce a negative fluid balance, putting the cumulative fluid balance back in “balance” [16]. PEEP (positive end-expiratory pressure) has been shown to increase alveolar fluid mobilization clearance [18-22]. Active late goal-directed fluid removal using PAL-treatment (PEEP, albumin, and Lasix®) is feasible in patients with acute lung injury who do not transgress spontaneously from the ebb to the flow phase of shock [7]. A neutral cumulative fluid balance without deleterious effects on organ function, as well as a reduction of extravascular lung water and intra-abdominal pressure and improved clinical outcomes were attained [7].

As mentioned by the authors, the research team and the clinical team had different opinions on the requirement of diuretic treatment. However, initiation of de-resuscitation should not be based just on clinical judgement or the presence of (peripheral) edema or a diuresis of at least 3 liters within the following 72 hours. The best timing of de-resuscitation after initial resuscitation is assessed by ruling out fluid responsiveness in addition to evaluating effective volume status, especially in patients not transgressing spontaneously to flow phase. Several strategies to predict preload responsiveness can be used: passive leg raising test, pulse pressure or stroke volume variation, respiratory variation of the inferior vena cava, and end-expiratory occlusion test [5,16,23]. A standardized approach defining fluid overload as a cumulative fluid balance of > 10 % of the patient's baseline body weight is more appropriate for clinical assessment of fluid overload [16,24,25]. Besides the combination of clinical, laboratory and hemodynamic variables (eg global end-diastolic volume and extravascular lung water obtained via transpulmonary thermodilution), another non-invasive method to guide de-resuscitation seems promising by using bioelectrical impedance analysis (BIA). BIA is a tool that allows calculation of body composition and assessment of volumes, such as total body

water, intracellular water (ICW), extracellular water (ECW), ECW/ICW ratio and volume excess [26].

Is less always more and should fluid overload be avoided?

The impact of de-resuscitation and achieving neutral or negative cumulative fluid balance in terms of long-term cognitive impairment is still unclear. A secondary analysis of a cohort of 75 survivors from the FACTT trial with a follow-up of the cognitive function showed evidence of harm due to a conservative fluid approach [27]. It remains uncertain what is the chicken and what is the egg. Guiding fluid therapy to more restrictive measures will lead to less fluid overload, therefore not necessitating diuretic treatment [9].

The CLASSIC trial assessed the effect of a conservative versus liberal approach of fluid therapy in patients with septic shock. Although lower volumes of resuscitation fluid administration was possible (at the expense of higher doses of vasopressors), this difference did not affect fluid balances or rates of serious adverse reactions or clinical outcomes [28].

The multicenter randomized RELIEF trial compared a restrictive versus a liberal fluid therapy in 2578 patients at increased risk for complications while undergoing elective major abdominal surgery. The restrictive fluid regimen was not associated with a higher rate of disability-free survival one year after surgery, but was associated with a higher rate of acute kidney injury [29]. However, this did not shed more light on the penumbra as it was a pragmatic study without individualized fluid administration.

We therefore look forward to the upcoming results from the RADAR-2 trial, a pilot randomized trial in mechanically ventilated patients, comparing conservative fluid administration and active de-resuscitation with usual care. This study aims to reduce net fluid balance to improve clinical outcomes [30]. Awaiting those results, a modestly liberal fluid regimen is perhaps preferred and the Goldilocks principle is reinforced – not too much, not too little, but an amount that's just right [31].

Take home message

In conclusion, the study performed by Ockzkowski et al. on furosemide and albumin to enhance diuresis in critically ill patients with edema (anasarca) is a promising intervention to treat fluid overload. Future studies should focus on the timing and dosing of the administration of both, hyperoncotic albumin as well as diuretics. Correct identification of the patient that needs an individualized DE-resuscitative approach will be the main challenge to allow the clinician to make the correct decisions at the bed-side in critically ill patients with fluid overload. It may be the right time to pay attention to the four phases of fluid therapy and to implement fluid stewardship in your ICU.

Conflict of interest

MLNGM is Professor of Medicine at the Vrije Universiteit Brussel (VUB) and ICU Director at the University Hospital in Brussels (UZB), Belgium. He is founding President of WSACS (The Abdominal Compartment Society, <http://www.wsacs.org>) and current Treasurer, he is also member of the medical advisory Board of Pulsion Medical Systems (part of Getinge group) and consults for ConvaTec, Acelyt, Spiegelberg, Serenno and Holtech Medical. He is also co-founder of the International Fluid Academy (IFA). The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The IFA website (<http://www.fluidacademy.org>) is now an official SMACC affiliated site (Social Media and Critical Care) and its content is based on the philosophy of FOAM (Free Open Access Medical education – #FOAMed). The site recently received the HONcode quality label for medical education (<https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739>). The other authors have no potential conflicts of interest in relation to the contents of this paper.

Financial disclosure

None

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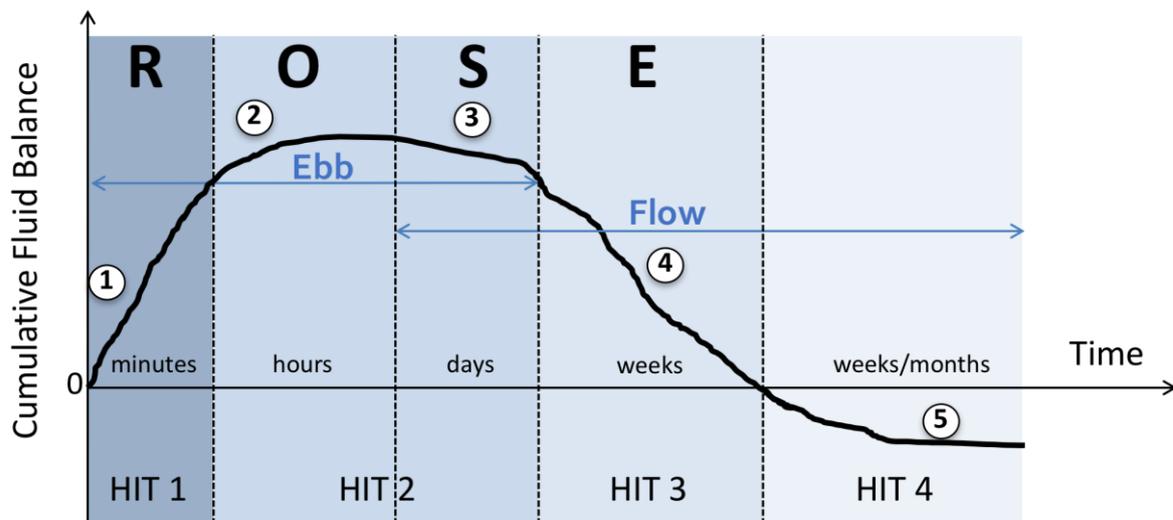
Table 1. The ROSE concept avoiding fluid overload (adapted from Malbrain et al. with permission [9,16])

	<i>Resuscitation</i>	<i>Optimization</i>	<i>Stabilization</i>	<i>Evacuation</i>
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 (de-resuscitation)
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"

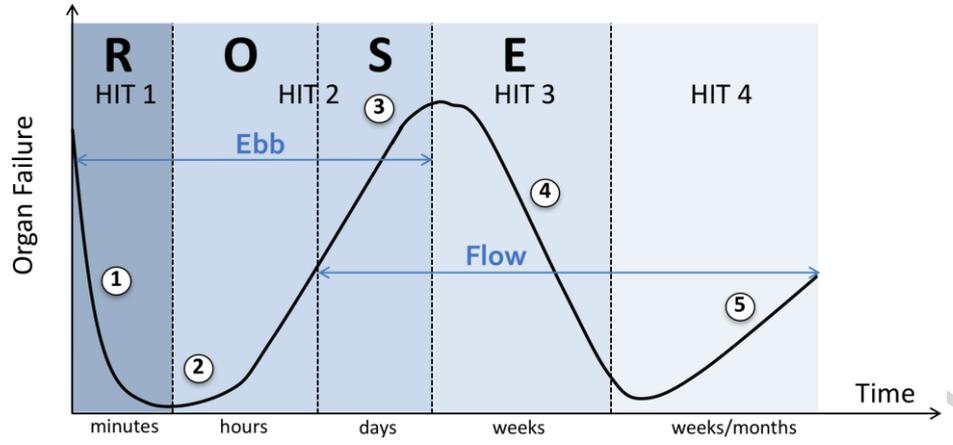
Figure 1. The different fluid phases during shock.

Adapted from Malbrain et al. with permission [9,16].

Panel A. Graph showing the four-hit model of shock with ebb and flow phases and evolution of patients' cumulative fluid volume status over time during the five distinct phases of resuscitation: **R**esuscitation (1), **O**ptimization (2), **S**tabilization (3), and **E**vacuation (4) (ROSE), followed by a possible risk of **H**ypoperfusion (5) in case of too aggressive deresuscitation. See text for explanation.



Panel B. Graph illustrating the four-hit model of shock corresponding to the impact on end-organ function in relation to the fluid status. On admission patients are hypovolemic (1), followed by normovolemia (2) after fluid resuscitation, and fluid overload (3), again followed by a phase going to normovolemia with deresuscitation (4) and hypovolemia with risk of hypoperfusion (5). In case of hypovolemia (phase 1 and 5) O_2 cannot get into the tissues because of convective problems, in case of hypervolemia (phase 3) O_2 cannot get into the tissue because of diffusion problems related to interstitial and pulmonary edema, gut edema (ileus and abdominal hypertension). See text for explanation.



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