Journal of Critical Care 52 (2019) 254–257

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

The search for the holy grail continues: The difficult journey towards the ideal fluid!

1. Background

Since the early days of the blue stage of spasmodic cholera, fluid therapy always played a vital role in daily critical care practice. Recently a paradigm shift occurred looking at IV fluids in a similar fashion as any other drug [1]. In analogy to antibiotic stewardship it is time for fluid stewardship [2]. The main goal for administration of intravenous fluids in patients with septic shock is to maintain organ perfusion [3]. However, the ideal fluid does not exist, and both, crystalloids as well as colloids may cause deleterious metabolic or systemic effects [4]. It is a common belief that colloids may provide a quicker expansion of the intravascular space; nevertheless, they carry the risk for renal failure, coagulopathy and anaphylactic reactions. In contrast, crystalloids don't have these side effects, although larger amounts of fluids may be necessary, leading to edema [4,5].

2. Heterogeneity and risk of bias in fluid trials

Despite the interesting results of the present review by Martin et al. on crystalloids vs. colloids for fluid resuscitation [6], some limitations must be considered. There was a significant clinical heterogeneity in the study population between included studies. Resuscitative interventions cannot be extrapolated from critically ill patients to trauma patients. Already for trauma patients there are three different groups, penetrating vs. blunt injury vs. head injuries who require distinct types of fluids and specific volumes of infusion [7,8].

Also, most of the trials included in the review had high risk of bias, but neither the results nor the conclusions were adjusted accordingly. Importantly, risk of bias overestimates intervention effects in trials in general [9]. Along this line, the 3 large blinded RCTs comparing crystalloid vs. colloid solutions in critically ill patients observed only minor differences, if any, in macrocirculatory markers and in fluid volumes between groups [10-12].

3. Resuscitation endpoints

There is a lot of controversy regarding the recent adaptation of the 1 h surviving sepsis guideline bundle where it is mandated that 30 ml/kg of crystalloids should be given in 1 h to ALL patients with sepsis/septic shock. One size simply does not fit all [13,14]. According to the Surviving Sepsis Campaign guidelines crystalloids are advocated for initial resuscitation, followed by albumin for additional volume replacement [15]. But evidence to support that recommendation is low. Within this perspective, the recent publication by Martin et al. describes the effects of crystalloids vs. colloids for fluid resuscitation based on traditional macrohemodynamic resuscitation endpoints [6]. The authors conclude that crystalloids were less efficient than colloids at stabilizing resuscitation endpoints such as central venous pressure (CVP), mean arterial pressure (MAP) and cardiac index (CI). Another point was that saline seemed to be more effective than balanced crystalloids for reaching resuscitation endpoints. And that hydroxyethyl starch (HES) solutions was the only colloid increasing mortality as compared to crystalloids.

It must be noted that hemodynamic parameters such as CVP, MAP and CI as measures for fluid resuscitation are poor predictors of fluid responsiveness in septic patients [16]. Marik et al. already suggested to abandon CVP as guide for fluid management. The likelihood that CVP can accurately predict fluid responsiveness is only 56% [17]. So, it should be better to perform a review on crystalloids vs. colloids for fluid resuscitation, where dynamic tests of cardiac preload are used to evaluate fluid responsiveness.

4. Assessment of hypovolemia

The assessment of hypovolemia is one of the most difficult tasks to handle in critically ill patients. More than 70% of total blood volume is in the venous part. Venous capacitance is the total volume that can be contained within the venous vascular beds at a given pressure and consists of stressed (30%) and unstressed (70%) volume. Stressed volume can be increased by decreasing vascular capacitance, which means recruiting unstressed volume into stressed volume. This is the equivalent of an auto-transfusion [18-20]. This compensatory mechanism impedes that hypovolemia becomes present before clinical signs and symptoms occur [21]. A variety of non-invasive and invasive monitoring tools exist to assess fluid status, yet each tool has his limitations (Table 1). The big challenge for the future will be to correctly assess hypovolemia vs. hypervolemia (intravascularly) but also dehydration vs hyperhydration and the impact of capillary leak on body fluid composition. Assessment consist of clinical parameters, imaging techniques, POCUS (point-of-care ultrasound), biomarkers, hemodilution parameters (hemoglobin, albumin), blood volume assessment, transpulmonary thermodilution with volumetric preload indices, etc… [21-23]. Moreover, fluid DE-resuscitation may even be of more importance than the initial resuscitation [24-27] (Fig. 1).

https://doi.org/10.1016/j.jcrc.2019.04.015

5. Variable volume effect

The amount of fluid administered was significantly higher with crystalloids than with albumin and hemodynamic endpoints were significantly lower in the crystalloid group [6]. Still, included studies did not address the type of albumin administered, 20% vs 4%. Bannard-Smith et al. showed in a retrospective analysis that the hemodynamic and biochemical effects of 20% vs.4% of albumin were similar for fluid bolus therapy. However, 20% albumin provided 80% less volume, seven times less sodium and about 30 times less chloride [28]. Although in the ALBIOS trial net fluid balance was marginally lower and MAP higher in the albumin group compared to the crystalloid group during the first seven days of treatment, this effect could not be translated to an improvement in rate of survival in the albumin replacement in addition to crystalloids, as compared with crystalloids alone [29].

The FEAST trial indicated that the method of fluid resuscitation must be considered. In children with shock and life-threatening infections in resource-limited settings fluid boluses until no longer fluid responsive significantly increased 48-h mortality [30,31].

Hahn suggested that the efficacy of crystalloid fluids is time-dependent and enhanced by distribution, hypotension and surgery-induced prolongation of the half-life [32]. Distribution of crystalloids requires a half-life of about 8 min, meaning that equilibration requires 30 min to be accomplished. While a decrease in MAP by 20 to 30% postpones the distribution of infused fluid for 20 to 30 min.

6. Time course

In a post-hoc analysis of the CLASSIC trial the effect of a fluid bolus on the surrogate markers of hypoperfusion: hypotension, low urinary output and high plasma lactate levels were investigated [33]. The analysis failed to demonstrate any effect on these markers of hypoperfusion, however data did suggest that time from randomization altered the effect where fluid may have increased urinary output when given early and increased noradrenalin dose when given later.

However, using oliguria as a trigger for the administration of fluid in critically ill patients should be handled with care. Higher fluid volumes appear to be associated with harm and may precipitate rather than alleviate AKI [34].

7. Glycocalyx

The glycocalyx coats the vascular endothelium and performs a fundamental role in preserving fluid homeostasis of the body. The type and amount of fluids as well as the rate of administration can cause damage to the endothelial glycocalyx. Ideally, fluid therapy should be guided towards preserving the integrity of the endothelial glycocalyx [35,36], but it is still unknow how this can be done and if it translates into improved outcomes. There is some evidence (at least in vitro) of endothelial glycocalix restoring properties of albumin, fresh frozen plasma and even some artificial colloids (like HES solutions). Crystalloids on the other hand do not have the ability to repair the glycocalix.

8. Fluid stewardship

Fluids should be treated as drugs [37] and the risks of fluid overload [38] cannot be ignored [1]. There are only four major **indications** for fluid administration in the critically ill: resuscitation, maintenance, replacement and nutrition. Fluids should be treated as drugs taking into account the four **D's** (drug selection, dose, duration and de-escalation) and the four **phases** of fluid therapy (ROSE concept) [1,38,39] with resuscitation, optimization, stabilization, and evacuation. The four **hits** model represents the first hit (sepsis, trauma, pancreatitis, burns, surgery), the second hit (ischemia-reperfusion with fluid accumulation), third hit or GIPS (global increased permeability syndrome with persistent fluid overload) and a possible fourth hit when fluid is removed

Table 1
Signs and symptoms of hypovolemia.

CLINICAL SIGNS
Body weight ↓
Fluid balance ↓=
Cumulative FB ↓=
Absence of pitting edema
Decreased skin turgor
Absence of 2nd and 3rd space fluid accumulation
JVP normal and HJR absent
Capillary refill time (>2 s) ↑
No orthopnea or platydeoxia
Dry mucosa, thirst
Mottled skin (livedo), peripheral cyanosis
Central to peripheral temperature difference ↑
Drop in urine output ↓ < 0.5 ml/kg/h
LABORATORY SIGNS
Lactate ↑ S(c)vO2 ↓
Albumin leak index ↑ (ratio urine albumin/urine creatinine)
Hemoconcentration: hemoglobin↑
Total protein ↑ and albumin ↑
Serum Na ↑
CLI ↑ = ↓(ratio serum CRP/serum albumin)
Serum osmolality ↑, COP ↑
BNP and NT-pro-BNP ↓
(In)activation RAAS
Urine electrolytes: Na↓ osm↑
IMAGING SIGNS
Normal chest X-ray, absence of Kerley-B lines, no pleural effusion
Abdominal US: no ascites
TTE: low E/e', LVOT VTI variations ↑
IVCCI ↑ > 50% (IVC ↑ < 1.5 cm)
Left atrium volume ↓
Normal lung US: no B-lines
HEMODYNAMIC SIGNS
MAP (< 55 mmHg)↓, HR ↑ = ↓
CVP ↓, PAOP ↓
GEF/GEDVI (<680) ↓
RVEF/RVEDVI (<80)↓
Presence of FR (CI increase >15%)
PPV ↑, SVV ↑, SPV ↑, Δdown ↑ (> 12–15%)
Positive PLR (CI increase >10%)
Positive EOT (CI increase >5%)
ORGAN DYSFUNCTION
EVLWI ↓ = ↑, PVPI ↓ = ↑
P/F ratio ↓
GIPS
IAP ↑, APP ↓ (=MAP-IAP)
RPP ↓ renal venous congestion
AKI: biomarkers (N-GAL ↑, cystatin C ↑)
CARS, polycompartment syndrome
EIT: V/Q mismatch
BIA: TBW ↓ ECW/ICW ratio ↓ = ↑ Volume excess = ↓
Total CBV (technetium albumin) ↓
Bioreactance: BVI ↓

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,
EOT: end-expiratory occlusion,
EVLWI: extravascular lung water index,
FB: fluid balance,
FR: fluid responsiveness,
GEDVI: global end-diastolic volume index,

GEF: global ejection fraction,
GIPS: global increased permeability syndrome,
HJR: hepatojugular reflex,
HR: heart rate,
IAP: intra-abdominal pressure,
ICW: intracellular water,
IVC: inferior vena cava,
IVCCI: inferior vena cava collapsibility index,
JVP: jugular venous pressure.
LVOT: left ventricular outflow tract,
MAP: mean arterial blood pressure,
Na: sodium,
P/F ratio: pO2 over FiO2 ratio,
PAOP: pulmonary artery occlusion pressure,
PLR: passive leg raising,
PPV: pulse pressure variation,
PVPI: pulmonary vascular permeability index,
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,
V/Q: ventilation/perfusion.
VTI: velocity time integral.

too aggressively resulting in hypoperfusion. Understanding these concepts will provide the bedside clinician with answers to the four basic **questions** of fluid therapy: When to start IV fluids? When to stop fluid administration? When to start fluid removal and finally when to stop fluid removal? In fact, recent studies have paid attention to this paradigm shift [40] and some studies showed an effect on outcome with restrictive fluid use [41].

Considering the issues raised above it is time for improved stewardship. Similar to antibiotic stewardship, the purpose is threefold. First, the most appropriate, personalized fluid therapy has to be chosen based on the actual micro- and macro-hemodynamics, the presence of shock and/or fluid responsiveness. It is crucial that the right fluid is prescribed in the right dose, speed of administration and duration and that there is a timely evaluation to start de-escalating fluid therapy. Second, an early detection and prevention of inappropriate fluid prescription and administration is necessary to avoid possible adverse events and complications (e.g. renal failure or fluid overload). Finally, although more relevant when it comes to avoidance of unnecessary expensive antibiotic use, cost effectiveness and savings should be achieved by implementing preventive quality improvement measures and follow up of KPI's like the amount of fluids used per patient, the avoidance of inappropriate fluid administration, the ratio between buffered and unbuffered crystalloids, the ratio between colloids and crystalloids, etc.

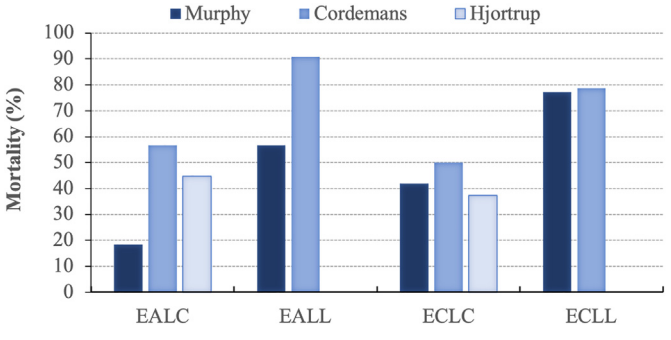

Fig. 1. Impact of different fluid management strategies on patient outcome. Data adapted from Murphy et al. [42], Cordemans et al. [26,27] and Hjortrup et al. [41] EALC: early adequate followed by late conservative fluid management. EALL: early adequate followed by late liberal fluid management. ECLC: early conservative followed by late conservative fluid management. ECLL: early conservative followed by late liberal fluid management.

9. Take home message

In conclusion, the study performed by Martin et al. on hemodynamic response to crystalloids vs. colloids for fluid resuscitation in critically ill adults is noteworthy. However, future high-quality research, i.e. low risk of bias, is required where timing and rate of fluid administration should be investigated and dynamic tests are used to make correct decisions at the bed-side. Fluids are drugs - a tailored approach is mandatory to avoid the detrimental effects of fluid overload. Importantly, potential adverse effects of fluids and patient important outcome measure should always be assessed in fluid trials. The ideal IV fluid has yet to be invented (and hemofiltration substitution fluids may come closest). The difficult journey continues.

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 Serenno Medical, and consults for ConvaTec, Acelity, Spiegelberg, and Holtech Medical. He is 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).

AP is the sponsor of the CLASSIC trial (www.cric.nu/classic), which is funded by the Novo Nordisk Foundation. His ICU receives support for research from Ferring Pharmaceuticals.

RJ has no potential conflicts of interest in relation to the contents of this paper.

Financial disclosure

None.

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26 March 2019