Intensive Care Med (2019) 45:1469–1471
https://doi.org/10.1007/s00134-019-05703-0

EDITORIAL

Focus on fluid therapy in critically ill patients

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Decisions on fluid therapy are everyday business in critically care settings. While some of these decisions remain difficult, recent years have given us better data to support better care.

Finding the right balance between giving too little intravenous (IV) fluid and giving too much remains a major challenge with potential dire consequences for our patients [1, 2]. In the recent REFRESH pilot trial, early IV fluid restriction was feasible in patients with suspected sepsis and hypotension in the emergency department (ED) who had received 1 L of IV fluid [3]. As per protocol more patients in the fluid restrictive group received a vasopressor in the ED and did so earlier. The clinical and patient-important outcome measures did not differ between the intervention groups, but the trial was not powered for these and few events occurred in the lower risk population that ended up being recruited [3]. De-resuscitation strategies in the form of more aggressive fluid removal after stabilisation is also increasingly studied as an alternative approach to limit the potential negative consequences of fluid overload. In the forced fluid removal in acute kidney injury (FFAKI) trial [4], ICU patients with AKI and fluid accumulation of > 10% ideal bodyweight were randomized to fluid removal with furosemide and/or continuous renal replacement therapy aiming at net negative fluid balance > 1 mL/kg ideal body weight/hour. While recruitment was difficult due to low numbers of patients with > 10% fluid accumulation, the intervention resulted in markedly reduced fluid balance at day five as compared to the standard care group without obvious harm [4]. These data are support by observational data from the role of active de-resuscitation after resuscitation (RADAR) investigators [5]. In a retrospective cohort study from 10 UK and Canadian ICUs, negative fluid balance achieved in the context of de-resuscitation was associated with improved survival in adults receiving invasive mechanical ventilation for at least 24 h [5]. In contrast, a secondary adjusted analysis of the RENAL trial suggested that high net ultrafiltration rate obtain by continuous venovenous hemodiafiltration was associated with lower survival in critically ill patients with acute kidney injury [6]. As for the studies above, residual confounding may be difficult to control for in observational data of fluid therapy and removal.

Together the above data add to a recent meta-analysis of randomised trials, the results of which indicate no benefits of more liberal vs. more conservative fluid management after the initial resuscitation, but reduced time on the ventilator was observed with conservative fluid management [7]. While the Surviving Sepsis Campaign bundles still include a fixed volume of 30 mL/kg of IV crystalloid in early sepsis management [8], several large trials are currently assessing the overall benefit vs. harm of lower vs. higher fluid volumes during the resuscitation of patients with sepsis. Both the CLOVERS trial (NCT03434028) [9] and the CLASSIC trial (NCT03668236) are actively recruiting patients with septic shock who are being randomised to strategies aiming at lower vs. higher IV-fluid input during initial handling.

A part of the challenge is that we have not yet found a diagnostic marker that may predict the circulatory response to IV fluid in most critically ill patients. Single values of central venous pressure have repeated been shown to be of little use, latest using data from the ARISE trial on goal-directed therapy in sepsis resuscitation in the ED [10]. Echocardiographic parameters are increasingly used, but they are not fully validated and often difficult to use in complex ICU patients [11]. In any case, the fluid volumes used for resuscitation is only a small proportion (6.5%) of the total fluid input, at least in those patients who stay in ICU for some days as observed in a retrospective single-centre study [12]. The

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largest proportion of fluid was given as maintenance and replacement fluids adding up to 25% of all inputs during an average ICU stay of 6 days. Another way to facilitate lower fluid volume resuscitation is to use concentrated human albumin solutions [13]. In the recent randomised small volume resuscitation with 20% albumin in intensive care: physiological effects (SWIPE) trial of adult ICU patients requiring fluid resuscitation, the use of 20% albumin resulted in lower cumulative resuscitation fluid volume and lower cumulative fluid balance at 48 h as compared with the use of 4–5% albumin [14]. There were no or minor differences between the two interventions groups in urinary output, blood pressures or blood values; the maximum albumin level was higher in the 20% vs. the 4–5% albumin group. Among the more patient-important outcomes, there were no marked differences between the group, but the number of patients discharged alive from the ICU may have been higher in the albumin group. In patients treated with extracorporeal membrane oxygenation (ECMO), the use of albumin was associated with improved survival in a retrospective, single-centre, registry study [15]. Clearly, such observations come at high risk of bias, and the results should be confirmed in an RCT with lowest possible risk of bias. If albumin is beneficial, the effects may be beyond the macrocirculation; albumin use may be associated with improve endothelial dysfunction as compared to saline in a small controlled study of patients with septic shock [16].

The choice between the crystalloid solutions, i.e. isotonic saline vs. buffered solutions, also remains a challenge. Recent data from the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) suggested that the acetate–gluconate–buffered solution Plasmalyte™ resulted in a lower incidence of major adverse kidney events as compared to isotonic saline in adult ICU patients [17]. The interpretation of the SMART trial is hampered by the single-centre, open-label cluster cross-over design. At least two large trials using individual patient randomisation to Plasmalyte™ vs. saline in ICU is on the way (BASICS (NCT02875873) from Brazil and PLUS from Australasia (NCT02721654)). Added together, these three large trials will inform us on the overall balance between benefit vs. harm of the use of saline vs. buffered solutions. They will not inform us on the benefits and harms of the use of acetate-buffered vs. lactate-buffered crystalloid solutions in critically ill patients—a question that now should receive focus to improve the use of IV-fluids in critically ill patients [18].

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Compliance with ethical standards

Conflicts of interest
The Department of Intensive Care, Rigshospitalet receives support for research from Ferring Pharmaceuticals and the Novo Nordisk Foundation.

Publisher's Note

Received: 3 May 2019 Accepted: 17 July 2019
Published online: 25 July 2019

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