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EDITORIAL

Liberal or restricted fluid resuscitation in critical illness: Shifting the needle back towards equipoise

Intravenous fluids are one of the most frequently administered interventions in the ED. For patients with critical illness and shock, infusion of a bolus of isotonic crystalloid is a universal first-line treatment. Sepsis, for example, is frequently associated with hypovolaemia because of exogenous fluid losses and volume redistribution from capillary leak and vasodilatation.[1] This can lead to systemic hypotension and, combined with alterations of the microcirculation and cellular function, result in tissue hypoperfusion or septic shock.[2] International consensus guidelines recommend initial volume resuscitation with at least 30 mL/kg of isotonic fluid within 3 h in patients with sepsis and hypoperfusion, with further fluid administration guided by repeated assessment of haemodynamic and perfusion parameters.[3] The rationale is to restore circulating volume and optimise cardiac output. However, these recommendations are based on low-quality evidence. The difficulty is compounded by the clinical heterogeneity of sepsis. Accurately assessing volume status in an individual patient is challenging, and only around half of patients with septic shock are found to be 'fluid responsive'.[4]

With the widespread adoption of a protocolised approach to resuscitation in septic shock, patients typically receive at least 4 L of fluid during the first 6 h.[5] This approach, which also includes early antibiotics, senior clinician involvement and surgical source control where indicated, has been associated with substantial reductions in sepsis mortality in the past two decades.[6] More recently, accumulating evidence has challenged aggressive, liberal fluid resuscitation among critically ill patients.[7] Seminal clinical trials undertaken in Africa found an association between early rapid volume administration and higher mortality among patients with sepsis and hypoperfusion.[8,9] Translation of these findings to industrialised countries such as Australia and New Zealand is problematic because of substantial differences in sepsis aetiologies; time to presentation; and limited access to critical care interventions such as ventilation, vasopressor support and dialysis. A pilot randomised trial among ICU patients with sepsis in Scandinavia found a lower incidence of acute kidney injury with volume restriction, although over 4 L of fluid were administered prior to randomisation.[10] These findings have challenged the conventional theoretical basis for volume resuscitation and highlighted the potential detrimental effects of i.v. fluids. For example, the mechanistic effects of exogenous fluids on the structure and function of the endothelium and endothelial glycocalyx in systemic inflammation remain incompletely understood.[11] A recent expert statement recommends judicious, titrated fluid boluses and earlier vasopressor introduction.[1] Yet for the practising emergency physician, the question of the right amount of volume for an individual patient, and the closely related question of when to introduce vasopressors, remains a dilemma for which there is a paucity of high-quality evidence to inform practice.[12]

The international, multicentre Restrictive *versus* Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial, recently published in the *New England Journal of Medicine*, randomised 3000 high-risk patients (the majority from Australia and New Zealand) undergoing elective major abdominal surgery to a liberal *versus* restricted perioperative fluid management regimen.[13] Outcome assessment was blinded to group allocation, and protocol compliance was high. There was no difference in the primary outcome of 1 year disability-free survival between the liberal fluid group, who received a median of 6.1 L (interquartile range 5.0–7.4 L) in the first 24 h, and the restricted fluid group, who received a median of 3.7 L (interquartile range 2.9–4.9 L). However, contrary to expectations based on previous smaller trials, the rates of surgical site infections and acute kidney injury (including need for dialysis) were significantly higher in the restricted fluid group. Clearly, translating these findings to critically ill acute patients in the ED is not possible. Nevertheless, this demonstrates the importance of undertaking high-quality, large, randomised, multicentre clinical trials to confirm or refute the findings of smaller studies and to inform everyday clinical practice surrounding a universal intervention.

Back in the ED, the question of fluid volume and timing of vasopressors in non-traumatic shock remains unanswered. For sepsis, given its high prevalence, substantial mortality and morbidity rates and associated costs of care, finding the optimal resuscitation strategy is a high priority. This is now being addressed, with a large multicentre phase III randomised trial recently commencing recruitment in the USA.[12] An Australian ED pilot trial has recently completed and is scheduled to report its findings later this year.[14] Active planning is in progress for a further large multicentre collaborative trial led by the ACEM Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group to assess the impact of a smaller volume/early vasopressor resuscitation strategy compared to the conventional larger volume/later

vasopressor approach on patient-centred outcomes.

Over-aggressive fluid resuscitation without demonstrable clinical improvement in perfusion parameters is likely to have downstream adverse consequences, similar to the use of vasopressors in a hypovolaemic, under-resuscitated patient. Although guidelines recommend routine administration of 2–3 L initially in an average adult with septic shock, the dilemma is whether to persist with fluid boluses in the absence of clinically suspected hypovolaemia and at what stage to introduce a vasopressor infusion. This decision is often made with the operational and resource considerations of securing an ICU bed in mind. Although recent clinical studies have pointed to a more fluid-restricted approach being preferable, the findings of the RELIEF trial caution against the premature adoption of fluid management strategies based on a limited evidence base. In the meantime, we endorse the recommendations made by the authors of the expert statement and echo their call for high-quality research in this area.[1] Wherever possible, eligible patients should be enrolled in clinical trials designed to resolve this important question.

Competing interests

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References

1. Perner A, Cecconi M, Cronhjort M *et al*. Expert statement for the management of hypovolemia in sepsis. *Intensive Care Med*. 2018; **44**: 791–8.
2. Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 801–10.
3. Rhodes A, Evans LE, Alhazzani W *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017; **43**: 304–77.
4. Loflin R, Winters ME. Fluid resuscitation in severe sepsis. *Emerg. Med. Clin. North Am*. 2017; **35**: 59–74.
5. PRISM Investigators, Rowan KM, Angus DC *et al*. Early, goal-directed therapy for septic shock – a patient-level meta-analysis. *N. Engl. J. Med*. 2017; **376**: 2223–34.
6. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014; **311**: 1308–16.
7. Silversides JA, Major E, Ferguson AJ *et al*. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med*. 2017; **43**: 155–70.
8. Maitland KKS, Opoka RO, Engoru C *et al*. Mortality after fluid bolus in African children with severe infection. *N. Engl. J. Med*. 2011; **364**: 2483–95.
9. Andrews B, Semler MW, Muchemwa L *et al*. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension. *JAMA* 2017; **318**: 1233–40.
10. Hjortrup PB, Haase N, Bundgaard H *et al*. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med*. 2016; **42**: 1695–705.
11. Myburgh JA, Mythen MG. Resuscitation fluids. *N. Engl. J. Med*. 2013; **369**: 1243–51.
12. Self WH, Semler MW, Bellomo R *et al*. Liberal versus restrictive intravenous fluid therapy for early septic shock: rationale for a randomized trial. *Ann. Emerg. Med*. 2018. https://doi.org/10.1016/j.annemergmed.2018.03.039.
13. Myles PS, Bellomo R, Corcoran T *et al*. Restrictive versus liberal fluid therapy for major abdominal surgery. *N. Engl. J. Med*. 2018; **378**: 2263–74.
14. Macdonald SPJ, Taylor DM, Keijzers G *et al*. REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial. *Trials* 2017; **18**: 399.

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