Fixed minimum fluid volume for resuscitation: Con

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The Surviving Sepsis Campaign guideline recommends a minimum volume of 30 ml/kg body weight during initial fluid resuscitation for patients with septic shock [1]. This document acknowledges the limited evidence supporting this recommendation. No randomised trial has specifically assessed different fluid volumes in adults with septic shock. We believe that this recommendation may be challenged for the reasons given below.

Complex circulatory failure in sepsis

The circulatory failure of patients with early septic shock is often complex with varying degrees of hypovolemia, vasodilatation, vascular hypo-reactivity and myocardial depression [2].

Are all patients with septic shock hypovolemic?

In general, patients with early septic shock do not have significant external fluid losses to justify the input of many litres of fluid. The reduced circulating blood volume is more likely to be due to internal compartment shifts from capillary leak and from pooling of blood in the small vessels, so called unstressed volume [3]. Presently, we cannot quantify these internal 'losses'. It may be more meaningful to ask how many patients with early septic shock improve their circulation in response to fluid? In the three recent Early Goal Directed Therapy trials the use of vasopressors ranged from 46-67% [4] so approximately half responded to fluid alone. In these trials there was, however, significant variability in fluid administered and fewer than 20% of patients had both hypotension and hyperlactatemia, which significantly increases mortality risk {Singer, M. 2016). Of note, the median volume delivered in the Emergency Department in the 2.5-3 hours before trial entry was 2.2 litres; assuming a median body weight of 70 kg, only half actually got the recommended 30 ml/kg as initial resuscitation. Over the 6 hours after trial entry patients received on average an extra 2.3 litres, again with wide variation. If patients are not in need of extra fluid, there seems little justification to give it.

Unclear balance between benefits and harms from fluid resuscitation

Even if the septic patient does improve his/her circulation with fluid alone, benefit may only result if fluid leads to sustained improvements in tissue perfusion and organ function and, ultimately, patient-centred outcomes. Clearly, this will be a function of illness severity plus ongoing fluid losses and compartmental shifts.

The randomised FEAST trial in 3141 African children with fever and an impaired circulation showed increased mortality with a 20-40 ml/kg fluid bolus given on top of maintenance fluid versus maintenance given alone [5]. This mortality excess appeared to be driven by circulatory failure despite initial improvements in the circulation [6], suggesting the children were compromised by the additional fluid and with no capacity to support them with mechanical ventilation or pressor administration. Other studies in patients with septic shock also suggest harm from excessive fluid; these data arise from both retrospective analyses [7, 8] and from CLASSIC, a recent prospective feasibility trial from Scandinavia in which ICU patients were randomly assigned to restriction of resuscitation fluid versus standard care, albeit after an initial 30 ml/kg of fluids before randomisation [9]. Together with the recently updated systematic review of trials assessing conservative vs liberal fluid strategies in adults with sepsis or ARDS [10], these results indicate potential harm from excess fluid. We do not know at which volume the potential benefit of fluid turns into harm in an individual patient with septic shock; one size cannot fit all so it is more rational to target a meaningful physiological endpoint rather than offer a blanket recommendation of a fixed volume.

Therapeutic alternatives

Vasodilatation and myocardial depression occur frequently in patients with septic shock. Patients presenting with these phenotypes may benefit from early use of vasopressor or inotropic agents rather than fluids, however a balance needs to be struck against harm induced by catecholamines [11, 12]. No high-quality data yet support these approaches. Alternatively, other strategies also warrant investigation including corticosteroids, avoidance of excess sedation, and even beta-adrenergic blockade, which all may

improve the circulatory status in selected patients. A careful “watchful waiting” conservative approach may also be indicated in patients with hypotension yet maintained organ perfusion.

In any case, a therapeutic strategy based on the patient’s history, a thorough clinical examination and, in selected patients, more advanced hemodynamic monitoring will better identify those who will benefit from fluids, vasopressors or inotropes. Many patients with early septic shock are likely to improve with fluid alone. However, using 250 to 500 ml boluses followed by regular re-assessments of the circulation constitutes a reasonable protocol, as some patients will be harmed from too much fluid. This individualised approach is likely to be superior to the fixed volume approach as long as the latter has not been proven to benefit the majority of patients with early septic shock in trials with low risk of bias.

Conflicts of Interest

AP is member of the steering committee and Danish national investigator of the Sepsis Act vasopressin trial in septic shock sponsored by Ferring Pharmaceuticals; his department is reimbursed for his time. The department also receives research funds from Fresenius Kabi (the EAT-ICU nutrition trial) and CSL Behring (the INSTINCT trial on immunoglobulins for NSTI).

MS was a co-investigator of the UK Department of Health-funded LeoPARDs trial examining the role of levosimendan in septic shock, and Clinical PI of a multicentre sepsis biomarker study conducted by the UK Ministry of Defence (DSTL). He is Co-PI of a sub-study of the EU Innovative Medicines Initiative Combacte-Magnet Program. He sits on advisory boards for Biotest assessing the role of immunoglobulins in septic shock, and Bayer’s novel amikacin nebuliser therapy for hospital-acquired pneumonia. He chaired the Data Monitoring Committee for InflaRx’s Phase II trial of a novel C5a inhibitor. He sits on an Advisory Board for Deltex Medical (manufacturer of the CardioQ oesophageal Doppler haemodynamic monitor); his University holds shares in the company and his department receives unrestricted grant support. He is also developing

a novel tissue oxygen sensor (manufactured by Oxford Optronix) supported by the Wellcome Trust and the UK Department of Health that is shortly to undergo clinical trials.

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