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REVIEW

Fluid Resuscitation in Patients Presenting with Sepsis: Current Insights

Stephen Macdonald [1–3]

[1]Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research, Perth, WA, Australia; [2]Emergency Department, Royal Perth Hospital, Perth, WA, Australia; [3]University of Western Australia, Perth, WA, Australia

Correspondence: Stephen Macdonald, Emergency Department, Royal Perth Hospital, Level 6, Q Block, GPO Box 2213, Perth, WA, 6000, Australia, Email stephen.macdonald@health.wa.gov.au

Abstract: Intravenous (IV) fluid resuscitation is a key component of the initial resuscitation of septic shock, with international consensus guidelines suggesting the administration of at least 30mL/kg of isotonic crystalloid fluid. The rationale is to restore circulating fluid volume and optimise stroke volume. It is acknowledged that there is a paucity of high-level evidence to support this strategy, with most studies being observational or retrospective in design. In the past decade, evidence has emerged that a large positive fluid balance is associated with worse outcomes among patients with septic shock in intensive care who have already received initial resuscitation. Randomised trials undertaken in low-income countries have found increased mortality among patients with sepsis and hypoperfusion administered a larger fluid volume as part of initial resuscitation, however, translating these findings to other settings is not possible. This uncertainty has led to variation in practice with some advocating a more conservative fluid strategy coupled with the earlier introduction of vasopressors for haemodynamic support. This question is the subject of several ongoing clinical trials. This article summarises the current state of the evidence for IV fluid resuscitation in septic shock and provides guidance for practitioners in the face of our evolving understanding of this important area.

Keywords: shock, septic, fluid therapy, critical care

Introduction

Intravenous (IV) fluid resuscitation was first described during the cholera outbreaks of the 1830s and became adopted into routine practice during the early part of the 20th century.[1] Despite their widespread use in routine clinical care, it was not until recently that the safety and efficacy of IV fluids began to be systematically evaluated in a range of clinical settings. Specific questions that have been addressed are the use of crystalloid solutions versus albumin,[2,3] the safety of synthetic starch solutions,[4] and comparing the use of 0.9% sodium chloride to so-called "balanced" isotonic crystalloid fluids.[5–7]

Sepsis is a major global health challenge with an estimated 49 million incident cases and 11 million associated deaths each year.[8] Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection, whereas septic shock is a subset of sepsis in which particularly profound circulatory, cellular metabolic abnormalities are associated with greater risk of mortality than with sepsis alone.[9] Clinically septic shock is identified as a requirement for vasopressors to maintain a mean arterial blood pressure (MAP) of ≥65mmHg, and an elevated lactate of >2mmol/L, despite adequate fluid resuscitation. The most recent iteration of the Surviving Sepsis Campaign guidelines suggests 30mL/kg if IV crystalloid fluid should be administered within the first 3 hours of treatment, although this is designated as a "weak" recommendation based upon low-quality evidence.[10] It is useful to consider the different phases of fluid management in septic shock over the course of the acute illness. For example, one construct has characterised these as resuscitation, optimisation, stabilisation and evacuation phases.[11]

Physiological Rationale for Fluid Resuscitation

The rationale for delivering a fluid bolus in septic shock is to restore circulating fluid volume and optimise cardiac output. Hypovolaemia can occur as a consequence of reduced oral fluid intake, losses from the respiratory and

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gastrointestinal tract, and extravasation via leaky capillaries as part of the sepsis-associated systemic inflammatory response. According to the Frank-Starling principle, increasing preload leads to an increase in stroke volume, although sepsis-related myocardial dysfunction can alter this relationship.[12] Fluid responsiveness (FR) is defined as an increase in stroke volume of 15% in response to a fluid bolus, although this is demonstrable in only around 50% of patients with septic shock.[13] Alongside clinical examination (including pulse, respirations, blood pressure, mentation, peripheral perfusion), bedside assessment of FR is best assessed using dynamic techniques such as echocardiography, pulse pressure variability or non-invasive cardiac output monitoring in combination with passive leg raising (PLR) or administration of a fluid bolus. Static measures such as central venous pressure (CVP) do not correlate with FR.[14] While the optimal means of assessing fluid responsiveness remains a matter of debate, there is evidence this approach results in a smaller positive fluid balance and reductions in respiratory and renal failure,[15] although the effect on mortality is less clear.[16] It is important to recognise that the haemodynamic effects of an IV fluid bolus are typically not sustained.[17]

Evidence for Benefit of IV Fluid Resuscitation

A landmark trial by Rivers in 2001 demonstrated, in a single centre study of patients with septic shock, a 16% absolute mortality reduction with a bundle of care which included IV fluid resuscitation among a number of interventions targeting central venous oxygenation as a resuscitation target.[18] A decade later, the ProCESS,[19] PROMISE[20] and ARISE[21] trials found no difference in mortality with the Rivers early goal-directed therapy protocol and usual care.[22] However, mortality rates in both intervention and usual care groups were similar to or lower than the intervention group in the Rivers trial and the volume of intravenous fluids was also similar, with, on average, between 3.7L and 5L being administered within the first 6 hours across the three trials. Thus, IV fluid resuscitation had been adopted into usual practice.[23] While this has been associated with a reduction in mortality over time, this cannot be separated from other factors such as prompt assessment, antibiotics, source control, and management by an experienced clinician.

In an observational study of 1866 patients with septic shock, the administration of 30mL/kg of IV fluid was associated with a reduction in risk-adjusted mortality.[24] In a large single centre retrospective analysis from the United States, failure to achieve 30mL/kg of IV fluids within 3 hours was associated with increased odds of mortality.[25] Another retrospective study found a larger initial IV fluid volume to be associated with survival after adjustment for confounding variables.[26] A propensity-matched analysis of 5072 patients undergoing treatment for sepsis found an association between delay to administration of a fluid bolus and increased mortality.[27] A single centre ICU-based study found lower mortality associated with faster completion of an initial 30mL/kg IV fluid bolus.[28] Similar findings have been reported in sepsis patients with a history of congestive heart failure.[29] Conversely, a multicentre retrospective analysis did not find an association between mortality and time to completion of a fluid bolus up to 12 hours, although a small effect was found when patients who completed the fluid bolus between 12 and 24h are included.[30] An Australian study among patients with infection presenting to the ED found an association between a larger volume of IV fluid in the first 24 hours and reduced in-hospital mortality,[31] while a Chinese observational study found the lowest mortality among septic shock patients who received an initial IV fluid volume of 20–30mL/kg compared to both the group who received <20mL/kg and those who received >30mL/kg.[32]

Vasopressor Therapy and Relationship with Fluid Resuscitation

Closely related to IV fluid volume in the haemodynamic resuscitation of sepsis is the timing of initiation of vasopressors.[33] Early initiation of a vasopressor such as noradrenaline is associated with reduction in mortality as well as a reduction in the volume of fluids received within the first 6 hours of treatment.[34] In a randomised, double-blind placebo controlled trial, initiation of noradrenaline resulted in a higher proportion of patients achieving resolution of shock within 6 hours, but with no difference in the fluid volume administered between the groups.[35] As well as its action as a peripheral vasoconstrictor, noradrenaline also increases cardiac preload and stroke volume, effectively delivering a 'fluid bolus' presumably via reduced systemic venous capacitance.[36]

Evidence of Harm with IV Fluids in Sepsis

A number of observational studies have found a positive fluid balance to be an independent predictor of worse outcome among patients with septic shock.[37–40] Analysis of a database of 25,513 patients with sepsis found that mortality

exceeded that predicted when the fluid volume in the first 24 hours was greater than 6 litres, increasing by 2.3% for each additional litre.[41] However, there was also a small but significant reduction in mortality of 0.7% for each litre up to 5L. A systematic review and meta-analysis of 2051 patients with sepsis and/or acute respiratory distress syndrome found a fluid-sparing or de-resuscitation strategy in ICU resulted in increased ventilator-free days and reduced ICU length of stay, but with no difference in mortality.[42] While providing insights into overall fluid management over the course of illness in ICU, these data provide little guidance regarding the use of IV fluids in initial haemodynamic resuscitation.

In contrast, the publication of the Fluid Expansion as Supportive Therapy (FEAST) trial in 2011 was a pivotal moment in our understanding of the role of IV fluid resuscitation in sepsis.[43] This trial conducted among children (median age 2 years) with infection and hypoperfusion across 6 centres in Uganda, Tanzania and Kenya aimed to compare the effectiveness initial fluid resuscitation with 0.9% saline with 5% albumin solution. Because fluid resuscitation was not the norm for children with suspected sepsis in this setting, the trial also included a control arm who received no initial resuscitation fluid. The trial was stopped early after 85% of the planned 3600 participants were enrolled because of excess mortality in both fluid arms. The primary outcome of mortality at 48-hours post randomisation was 10.6%, 10.5% and 7.6%, respectively, in the albumin-bolus, saline-bolus, and no-bolus groups. This excess mortality signal in the fluid bolus groups persisted to 4 weeks. This trial was conducted in a resource-poor setting with limited access to critical care interventions, many participants were anaemic and 57% had malaria. Contrary to what might have been expected, a subsequent analysis found that the excess mortality in the fluid bolus groups was caused by haemodynamic collapse rather than neurological or respiratory complications of IV fluid administration.[44]

The phenomenon of a fluid bolus exacerbating shock was further explored in a preclinical ovine study of endotoxaemia.[45] Anaesthetised sheep were administered intravenous lipopolysaccharide until they developed hypotension and were then randomised to receive either bolus 0.9% saline or to commence on an infusion of noradrenaline to restore the target MAP. While the fluid group initially responded, all subsequently required noradrenaline to be commenced. After 4 hours, the noradrenaline dose required to maintain the target MAP in the fluid-bolus group continued to rise progressively in excess of that required in the no-bolus group up to 12 hours when the experiment concluded.

Further evidence of harm with fluids was demonstrated in a trial involving 212 adults with infection and hypotension presenting to the emergency department (ED) of a single hospital in Zambia who were randomised to a protocolised resuscitation strategy involving mandated fluid boluses versus usual care at clinician discretion.[46] The in-hospital mortality rate among the protocolised resuscitation group, who received a median of 3.5L of IV fluid in the first 6 hours from presentation was 48% compared to 33% in the usual care group who received a median of 2.0L in the same period (Relative Risk 1.46, 95% CI 1.03–2.05, p = 0.03). Like the FEAST trial, major differences in population characteristics and health system resources make translating these findings to high-income countries problematic.

Postulated mechanisms for how IV fluid administration may exacerbate organ failure and shock include oedema in critical organ beds (such as heart, kidneys lung and gut), reflex vasodilatation, the release of natriuretic peptides, flushing of cytokine-rich blood from shut-down capillary beds, and exacerbation of shedding of the endothelial glycocalyx.[11,47,48]

Does Limiting IV Fluid Administration Lead to Better Outcomes?

Several studies have investigated the question of whether restricting IV fluids in the setting of septic shock leads to better outcomes. A systematic review of 9 trials involving 637 participants found no significant difference in mortality between the two fluid resuscitation regimens.[49] Of the 9 trials, 8 involved patients with septic shock in the ICU while 1 trial enrolled patients in the ED. The largest trial had 151 participants, and there was a high risk of bias among the trials. It was concluded there is currently a low quality of evidence to support decisions on fluid therapy for adults with sepsis.

Recently, the multicentre randomised Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) trial compared a fluid restricted approach compared to usual care among patients admitted to ICU with septic shock who had already undergone initial IV fluid resuscitation.[50] The median volume of IV fluid prior to randomisation was approximately 3L, and the median fluid volume administered in the ICU was 1798mL (IQR 500–4366mL) in the restricted fluid group compared to a median of 3811mL (IQR 1861–6762mL). The primary outcome of 90-day mortality was 42.3% in the restricted group and 42.1% in the usual care group (Relative Risk 1.00, 95% CI 0.89–1.13, p = 0.96). There was no difference in the rate of serious adverse events. Of interest, in a pre-planned

subgroup analysis, the point estimates for mortality favoured the restrictive regimen for those patients who received >30mL/kg prior to randomisation and favoured the usual care fluid regimen for those who received <30mL/kg, however the statistical threshold for heterogeneity was not met; therefore, a null effect is not excluded.

CLASSIC demonstrates that a fluid restricted regimen among patients admitted to the ICU with septic shock do not benefit from a restricted fluid regimen, nor does this appear to be associated with harm. All participants in CLASSIC had received initial fluid resuscitation and were on vasopressors at the time of randomisation, so this trial does not address the question of fluid volume in initial haemodynamic resuscitation, nor the optimal timing of commencement of vasopressors. A number of other trials are addressing this particular aspect. The Crystalloid Liberal or Vasopressors Early in Sepsis (CLOVERS) trial (ClinicalTrials.gov NCT03434028) in the United States has recently ceased recruitment and the results are awaited. The Australasian Resuscitation in Sepsis Evaluation: Fluids or Vasopressors in Emergency Department Sepsis (ARISE FLUIDS) (ClinicalTrials.gov NCT04569942) and the Early Vasopressors in Sepsis (EVIS) (ClinicalTrials.gov NCT05179499) in the United Kingdom are currently in progress.

Summary

Emerging evidence over the past decade has led to a reappraisal of the role of IV fluid resuscitation in the management of haemodynamic instability in septic shock. While observational studies have found IV fluid resuscitation to be associated with both benefit and harm, there is a paucity of high-quality evidence to guide practice. It is important to make a distinction between initial haemodynamic resuscitation and ongoing fluid management. The Surviving Sepsis Campaign has recently downgraded its recommendation for initial administration of 30mL/kg of crystalloid fluid to a suggestion.[51] There is variation in practice ranging from generous initial fluid administration to a fluid-restricted strategy with early introduction of vasopressors.[52] Recognising the substantial clinical heterogeneity of sepsis, practitioners are increasingly focused on tailoring resuscitation to the individual patient by administering IV fluids more judiciously based upon an assessment of fluid responsiveness. This approach may lead to an overall reduction in fluid administration although the impact on clinical outcomes is unknown.

It is important for clinicians to appreciate that equipoise remains regarding the relative benefits/harms of IV fluids particularly during the initial phase of resuscitation. It is instructive to consider that a large multicentre trial of a fluid restricted strategy in patients undergoing elective major abdominal surgery demonstrated worse outcomes with this approach despite observational studies and smaller trials favouring this.[53] Several large-scale randomised trials are currently investigating different haemodynamic resuscitation regimens in septic shock, and it is anticipated that these will address the current evidence gap for the benefit of patients and clinicians.

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