CRITICAL CARE

COMMENTARY

How much fluid resuscitation is optimal in septic shock?

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See related research by Smith and Perner, http://ccforum.com/content/16/3/R76

Abstract

Smith and Perner report an observational cohort study of 164 patients with septic shock. For patients still alive on day 3, higher compared with lower fluid volume resuscitation was associated with lower 90-day mortality. This association of a relationship between fluid intake and decreased mortality aligns with the randomized controlled trial of early goal-directed therapy and later observational studies. I suggest careful individualization of fluid resuscitation to achieve adequate mean arterial pressure (about 60 to 70 mmHg) and normalization of arterial lactate levels in septic shock.

Trial registration: ISRCTN94845869

Despite decades of use, how much fluid is optimal during resuscitation of patients who have septic shock remains uncertain. Excessive fluid increases intravascular pressure, and with increased permeability of sepsis this increases fluid accumulation and organ dysfunction. Conversely, inadequate fluid resuscitation causes tissue hypoxia secondary to inadequate global oxygen delivery. Furthermore, excessive doses of vasopressors (consequent to inadequate fluid resuscitation) constrict the microvasculature, leading to tissue hypoxia.

Smith and Perner report an observational cohort study of 164 patients with septic shock [1]. They recorded fluid intake and correlated fluid intake to clinical outcomes. For patients still alive on day 3, higher compared with lower fluid volume resuscitation (10.9 l vs. 4.3 l) was associated with significantly lower 90-day mortality (40% vs. 62%, $P = 0.03$). This association of a relationship between fluid intake and decreased mortality aligns with the randomized controlled trial (RCT) of early goal-directed therapy (EGDT) by Rivers and colleagues [2]. In particular, Rivers and colleagues found that fluid and vasopressor resuscitation titrated to increase and maintain central venous oxygen saturation above 70% in patients who had septic shock was associated with increased fluid intake in the emergency department (first 6 hours) and with significantly decreased mortality [2].

Accordingly, sepsis guidelines [3] and Russell [4] have recommended EGDT fluid management for the first 6 hours of septic shock. Rivers and colleagues' RCT is being repeated in three large multicenter RCTs in the UK, the USA and Australia, and the results of those RCTs are awaited with considerable interest around the globe. Many case–control studies (often before and after implementation of sepsis guidelines, one component of which is use of Rivers and colleagues' protocol) suggest that EGDT bundles improve outcomes [5-16], including a meta-analysis [9] (Table 1).

Based on observational studies that found a positive association of early clearance of arterial lactate and better clinical outcomes [17], Jones and colleagues performed a RCT to compare titration of emergency resuscitation of patients who have septic shock with central venous oxygen saturation and with serial decrease of arterial lactate (which is less invasive). They found that arterial lactate was not inferior to central venous oxygen saturation-guided resuscitation [18]. As a result, it is reasonable to target normalization of arterial lactate to guide fluid intake and vasopressor use in patients with septic shock.

The strengths of Smith and Perner's study were that it was an observational cohort from six hospitals with no exclusions and that they carefully recorded volumes and types of fluids administered over the first 3 days of septic shock [1]. The study thus scores high on generalizability.

Several aspects of the study require consideration, however. First, their study was small, and so the clinical community would like to see other larger cohorts used to address this problem. Second, nutritional fluids were not included in the calculations of fluid intake and fluid balance. The total of all fluids given should be used in assessing effects of fluid administration. Indeed, Smith and Perner found that their higher volume group received

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Table 1. Relevant cohort studies of high versus low fluid volume in sepsis and septic shock

Study	Clinical condition studied	Randomized, controlled interventions	High fluid group mortality	Low fluid group mortality (*P* value for high vs. low fluid comparison)
Randomized controlled trials				
Rivers and colleagues [2]	Severe sepsis and septic shock	EGDT vs. usual care	30.5%[a] (EGDT)	46.5% (usual care; $P = 0.009$)
Observational cohort studies				
Smith and Perner [1]	Septic shock	NA	24%	65%[b] ($P < 0.001$)
Carlsen and Perner [15]	Septic shock	NA	38%	29% ($P = 0.36$)
McIntyre and colleagues [16]	Septic shock	NA	45%	44%
Vincent and colleagues [11]	Sepsis	NA		Odds ratio 1.1 per liter increase[b]
Gao and colleagues [8]	Sepsis	NA	29%	55% ($P = 0.045$)[c]
Jones and colleagues [10]		NA	18%	27% (95% CI = +5% to –21%)[d]
Nguyen and colleagues [14]	Sepsis	NA	26%	39%[e]

CI, confidence interval; EGDT, early goal-directed therapy; NA, not applicable. [a]Statistically significant in favor of high fluid group compared with low fluid group (that is, high fluid group had lower mortality). [b]Statistically significant in favor of low fluid group compared with high fluid group (that is, low fluid group had lower mortality). [c]Comparison of compliant (high fluid group) versus noncompliant to sepsis bundle. [d]McIntyre and colleagues evaluated first 6 hours of fluids given. [e]Completion of EGDT within 6 hours (high fluid group) or not.

significantly less volume of nutrition compared with the lower volume group (2.9 l vs. 3.4 l) [1]; the addition of nutritional fluids could alter the results and their interpretation.

One should not confuse early resuscitation fluid intake with studies of overall later fluid balance, which have sometimes found association of more positive fluid balance with increased mortality [19,20]. However, the cause–effect relationship is not resolved in such observational studies; more positive fluid balance could alter outcomes or could simply be a marker of increased endothelial injury and third-spacing of fluids in sicker patients (who have increased mortality because of increased endothelial injury and not necessarily due to more positive fluid balance).

In summary, Smith and Perner report a small observational cohort [1] that must be placed in context of prior studies. Rivers and colleagues' RCT of EGDT and other observational studies show that more positive fluid intake is associated with decreased mortality. The ongoing RCTs of EGDT in Australia, the USA and the UK will provide clearer evidence about how much fluid resuscitation is optimal in septic shock. Until then, I suggest careful individualization of fluid resuscitation to achieve adequate mean arterial pressure (about 60 to 70 mmHg) and normalization of arterial lactate levels in septic shock.

Abbreviations

EGDT, early goal-directed therapy; RCT, randomized controlled trial.

Competing interests

JAR reports holding stock in and is on the board of Sirius Genomics Incorporated, which has submitted patents owned by the University of British Columbia and licensed to Sirius Genomics that are related to the genetics of sepsis and its treatment. The University of British Columbia has also submitted a patent related to the use of vasopressin in septic shock. JAR is an inventor on these patents. JAR also reports receiving consulting fees from Ferring Pharmaceuticals (which manufactures vasopressin and is developing selepressin), from Astra Zeneca (which is developing anti-TNFα), from BioCritica (which used to sell activated protein C in the USA), from MedImmune, from Grifols (which sells albumin) and from Sirius Genomics Inc. JAR also reports having received grant support from Sirius Genomics, Ferring Pharmaceuticals, Astra Zeneca and Eli Lilly that is provided to and administered by University of British Columbia. JAR has received speaking honoraria from Pfizer and Eli Lilly.

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