CRITICAL CARE

COMMENTARY

Totem and Taboo: Fluids in sepsis

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Abstract

The need for early, rapid, and substantial fluid resuscitation in septic patients has long been an article of faith in the intensive care community, a tribal totem that is taboo to question. The results of a recent multicenter trial in septic children in Africa, published in *The New England Journal of Medicine*, powerfully challenge the fluid paradigm. The salient aspects of the trial need to be understood and reflected upon. In this commentary, we discuss the background to and findings of the trial and explain why they will likely trigger a re-evaluation of our thinking about fluids in sepsis, a re-evaluation that is already happening in the treatment of acute respiratory distress syndrome and acute kidney injury and in postoperative care.

Current guidelines for the acute management of severe sepsis in pediatric and adult patients place prime importance on early, rapid, and substantial infusion of intravenous fluids [1,2]. The immediate aim is to correct a possible fluid responsive hypodynamic circulation [1-3]. Beyond this, the common assumption is that expansion of effective circulating volume will attenuate hypotension, ameliorate the perceived impaired peripheral and end-organ perfusion, and correct abnormalities of base deficit and lactate. Curiously, this assumption is held despite the well-known fact that cardiac output is often elevated in septic adults [4-6] and children [7,8] even though myocardial performance may be impaired [9]. Furthermore, in children, sepsis-induced myocardial dysfunction [10] may increase the chance of fluid unresponsiveness. In fact, in both adults and children, no controlled data exist that increases in cardiac output due to volume expansion are beneficial or even reliably achieved [11]. Moreover, no human data show that substantial (>20 mL/kg) fluid resuscitation reliably improves blood pressure or end-organ perfusion (an elusive outcome given that organ blood flow cannot be accurately measured in septic humans). Finally, experimental data show that organ perfusion is supranormal in hyperdynamic sepsis [12] and that fluid resuscitation may increase mortality [13].

The publication of FEAST (Fluid Expansion As Supportive Therapy in critically ill African children) [14] challenges the widely held totemic beliefs in the protective power of fluids in severe sepsis. It also breaks the taboo that has made any challenge to fluid therapy in the sepsis paradigm an act of unspeakable tribal treason. Yet FEAST is the first large and randomized study of the relationship between volume and composition of intravenous fluids and clinical outcome in acute severe sepsis. The results challenge the status quo.

FEAST enrolled Sub-Saharan African children with a severe febrile illness (prostration, coma, or respiratory distress) and clinical evidence of impaired peripheral perfusion. Overall, 3,141 patients without severe hypotension were randomly assigned to one of three groups (n = 1,047 in each group): 20 to 40 mL/kg boluses of 5% albumin or 0.9% saline or no bolus fluids (FEAST A). All three groups were given intravenous maintenance fluids (2.5 to 4 mL/kg per hour), blood transfusion if the hemoglobin was less than 5 g/dL (20 mL/kg over the course of 4 hours), and appropriate antibiotics, antimalarials, anticonvulsants, antipyretics, and blood sugar management as indicated. The primary endpoint was mortality at 48 hours.

By 8 hours, the median cumulative volumes (including transfused blood) received were 40, 40, and 10.1 mL/kg for the albumin bolus, saline bolus, and control arms, respectively. Most of this difference occurred over the course of the first two hours. Overall 48-hour mortality was 9.5% and most deaths occurred within 24 hours, but a striking difference was found between the control group and the bolus fluid groups: 48-hour mortality rates were 7.3%, 10.6%, and 10.5% for the control, albumin bolus, and 0.9% bolus groups, respectively. The 48-hour mortality of the combined bolus group had increased by 45% (P = 0.003).

Not only are the overall results clinically and statistically significant but a dose effect is evident. After 2,535 subjects had been enrolled, the initial sample size was

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increased because of a lower-than-expected mortality rate. As part of this amendment, the bolus volume was increased from 20 to 40 mL/kg. However, enrollment was ceased after a further 606 subjects (total of 3,141 subjects) because of safety concerns about excess harm to the bolus groups. The postamendment mortality of the bolus groups (12.1%) was higher than that in preamendment group (10.2%), and there was no change between preamendment and postamendment outcomes for the control patients. The postamendment effect suggests that mortality increased because the dose of bolus fluids increased.

What conclusions can intensivists working in modern ICUs draw from FEAST? First, the pediatric nature of the cohort (median age of 2 years) should invite caution in extrapolating these findings to an adult population. Second, 59% of the patients had malaria, although the adverse effect of bolus fluids was significant in both malarial and nonmalarial subgroups. Third, there was insufficient information about the causes of death, details of which would allow a more insightful analysis of the mechanisms linking bolus fluid administration to mortality. Finally, and very importantly, the FEAST 'package' did not include ICU admission or the use of mechanical ventilation, inotropic or vasopressor drugs, or continuous renal replacement therapy (CRRT).

There is no evidence that, when ICU supports are available, volume expansion of the order of 40 mL/kg (the largest volume in FEAST) increases 48-hour mortality. Yet there is a growing body of evidence that a positive fluid balance might contribute to significant morbidity in patients with sepsis [15], acute respiratory distress syndrome [16], acute kidney injury [17], or major surgery [18]. It is, therefore, biologically and physiologically plausible that excessive fluid administration is harmful but that, owing to the masking effects of other supportive interventions, such harm is not immediately recognized in a Western context. Thus, mechanical ventilation, inotropes, vasopressors, and CRRT prevent increases in early mortality but at the price of delayed and unrecognized increases in the risk of a more prolonged subsequent organ failure [16,17]. Relevant to such reflections, the failure of short-term physiological gain to translate into medium- or long-term clinical benefit has a long and sad history in critical care medicine [16,19,20].

FEAST will undoubtedly cause robust debate and anxiety as the totemic status of fluids in sepsis becomes undermined. This is a result that Sigmund Freud, the author of *Totem and Taboo* [21], would have anticipated. His and our answer is the need to confront and more fully investigate. To question the role of fluids in severe sepsis can no longer be considered taboo.

Abbreviations

CRRT, continuous renal replacement therapy; FEAST, Fluid Expansion As Supportive Therapy in critically ill African children; ICU, intensive care unit.

Competing interests

The authors declare that they have no competing interests.

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