Fluid Therapy in Resuscitated Sepsis*

Less Is More

Lakshmi Durairaj, MD; and Gregory A. Schmidt, MD, FCCP

Fluid infusion may be lifesaving in patients with severe sepsis, especially in the earliest phases of treatment. Following initial resuscitation, however, fluid boluses often fail to augment perfusion and may be harmful. In this review, we seek to compare and contrast the impact of fluids in early and later sepsis; show that much fluid therapy is clinically ineffective in patients with severe sepsis; explore the detrimental aspects of excessive volume infusion; examine how clinicians assess the intravascular volume state; appraise the potential for dynamic indexes to predict fluid responsiveness; and recommend a clinical approach. ***(CHEST 2008; 133:252–263)***

Key words: fluids; fluid responsiveness; preload resuscitation; sepsis

Abbreviations: CVP = central venous pressure; EGDT = early goal-directed therapy; FACTT = Fluid and Catheter Treatment Trial; GEDV = global end-diastolic volume; LVEDA = left ventricular end-diastolic area; MAP = mean arterial pressure; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; PEEP = positive end-expiratory pressure; PLR = passive leg raising; PPV = pulse pressure variation; Pra = right atrial pressure; RVEDVI = right ventricular end-diastolic volume index; $Scvo_2$ = central venous oxyhemoglobin saturation; SPV = systolic pressure variation; Svo_2 = mixed venous oxyhemoglobin saturation; TEE = transesophageal echocardiography

"O Lord, methought what pain it was to drown,
what dreadful noise of waters in my ears!
What sights of ugly death within my eyes!"

Clarence, in Shakespeare's Richard III, act 1, scene 4, 1. 21-3

Fluids in Early Severe Sepsis

In the first hours of severe sepsis, venodilation, transudation of fluid from the vascular space into tissues, reduced oral intake, and heightened insensible loss combine to produce hypovolemia. Along with ventricular dysfunction, arteriolar dilation, and vascular obstruction, volume depletion contributes to impaired global perfusion, threatening the function of critical organs. Treating hypovolemia is a central tenet of early management of severe sepsis[1]: fluid should be infused to raise the intravascular volume, augment tissue perfusion, stave off organ failure, and enhance survival.

A study of sepsis resuscitation emphasizes the pivotal role of early and aggressive fluid therapy. Subjects presenting with severe sepsis or septic shock were randomized to 6 h of "standard therapy" guided by central venous pressure (CVP) [≥ 8 to 12 mm Hg] and mean arterial pressure (MAP) [≥ 65 mm Hg], or to 6 h of early goal-directed therapy (EGDT) guided also by central venous oxyhemoglobin saturation ($Scvo_2$) [≥ 70%].[2] By targeting resuscitation to $Scvo_2$, rather than simply to the conventional hemodynamic indexes, the EGDT subjects were administered more fluid in the first 6 h (4,981 ± 2,984 mL vs 3,499 ± 2,438 mL; $p < 0.001$), as well as more dobutamine and packed RBC transfusion. Standard treatment (relying on CVP and MAP) was clearly inferior, leading to more persis-

*From the Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, University of Iowa Carver College of Medicine, Iowa City, IA.
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Correspondence to: Gregory A. Schmidt, MD, FCCP, Professor of Medicine, Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, University of Iowa Carver College of Medicine, Iowa City, IA 52242; e-mail: gregory-a-schmidt@uiowa.edu
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tent lactic acidosis, greater organ dysfunction, and higher in-hospital mortality (46.5% vs 30.5%).[2]

This study has changed practice in many emergency departments, where there is greater emphasis on recognizing sepsis early, measuring $Scvo_2$, and resuscitating urgently.[3,4] It is far less clear how these results should inform ICU practice, however. First, the hemodynamic state of subjects in the EGDT trial differed dramatically from that of the typical ICU patient with severe sepsis. Most notably, subjects presenting to the emergency department had a mean $Scvo_2$ of 49%, a value indicating a gross deficit of oxygen transport in relation to demand and far lower than the usual septic ICU patient (in whom the $Scvo_2$ is usually $> 65\%$ and often $\geq 80\%$).[5,6] Second, time may be an important factor. The EGDT protocol was terminated after 6 h of severe sepsis, following which subjects were managed by clinicians blinded to the study group assignment. Thus, any impact of EGDT derives from this 6 h of treatment, not later ICU care. In a metaanalysis[7] of studies of hemodynamic optimization in critically ill subjects, most studies with early interventions (defined as before the occurrence of organ failure, within 24 h of trauma or within 12 h after surgery) showed lower mortality rates. In contrast, targeting supranormal cardiac index and oxygen delivery later conferred no benefit whatsoever.[8–10] In the largest of these trials with negative findings, Gattinoni and colleagues[10] randomized 762 subjects to three goal-directed arms: normal cardiac index, supranormal cardiac index, or mixed venous oxyhemoglobin saturation (Svo_2) $\geq 70\%$. There was no difference in morbidity or mortality between any of the treatment groups. Since the target in both the Gattinoni et al[10] trial and the EGDT trial of goal-directed hemodynamic therapy was nearly equivalent ($Scvo_2$ is quite similar, although not identical, to Svo_2), the disparate results are intriguing. Several key differences between these studies may explain their results (*eg*, the EGDT study enrolled only septic subjects, whereas the earlier trial included other subsets of critical illness), but the element of time (and the difference in initial hemodynamic state) stands out as a biologically plausible hypothesis. The point to emphasize is that what is beneficial early (more fluids) is not necessarily beneficial later in the course of critical illness.

Fluids in Resuscitated Sepsis

Initial resuscitation transforms a hypovolemic, hypodynamic circulation into one where oxygen transport is normal or high, at least at the whole-body level, in most septic adults.[2,11] In contrast to the average patient entering the EGDT trial, once fluids, antimicrobials, vasoactive drugs, and perhaps blood have been administered, these resuscitated patients usually display elevated CVP, cardiac output, and Svo_2. There is no longer global hypoperfusion as judged by any measure of oxygen transport, even when hypotension, lactic acidosis, and organ dysfunction persist. Nevertheless, the circulation remains grossly impaired, and MAP rarely is restored to normal. Indeed, persistent hypotension and progressive organ failures often prompt further fluid administration. It is this state of "resuscitated sepsis" that we emphasize here.

This clinical scenario (severe sepsis following initial resuscitation, but with persistent hypotension, oliguria, or other potential marker of incomplete fluid therapy) occurs daily in any busy ICU. When given additional fluid, some patients will respond: BP, cardiac output, oxygen delivery, $Scvo_2$, or urine output increases. Other patients will not: hemodynamics fail to improve and the fluid bolus is ineffective, at best. Moreover, ineffective fluid challenges often lead to additional boluses, culminating in a grossly edematous patient (still hypotensive and oliguric). How can we ensure sufficient volume resuscitation of those who will benefit, while limiting potential harm in those who will not? How to manage fluids in such a patient is an everyday problem that has been little studied and is probably little informed by studies of unresuscitated patients in their first 6 h. This important clinical dilemma was described recently as "a real challenge."[12]

Fluids May Be Harmful in Critical Illness

Fluid infused into the vascular space ultimately equilibrates with other fluid compartments. Unnecessary fluid (*ie*, fluid that does not enhance perfusion) will cause or exacerbate edema in lungs, heart, gut, skin, brain, and other tissues. At times, this creates clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome,[13,14] or cerebral edema and herniation. Further, there is some evidence that excess fluid can be harmful by more subtle means. Multiple studies have correlated positive fluid balance with reduced survival in ARDS[15,16] or sepsis.[17] In a study[18] of critically ill patients (45% of whom had sepsis) a pulmonary artery catheter (PAC) was compared with pulse contour analysis for hemodynamic monitoring. While the monitoring technique had no effect on several outcomes, a secondary logistic regression analysis identified positive fluid balance as a significant predictor of mortality (odds ratio, 1.0002 for each milliliter per day, $p = 0.0073$). Positive fluid balance may also impede liberation from mechanical ventilation. In a study[19] of 87 patients receiving venti-