Fluid Resuscitation in Sepsis: “Get the Balance Right”*

*See also p. 386.

**Key Words:** critical ill; fluid output; intensive care unit

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When you think you’ve got a hold of it all, you haven’t got a hold at all. (from “Get the Balance Right”, Depeche Mode)

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On the one hand, fluid administration represents a mainstay of therapy in hemodynamically unstable patients and is probably the most common intervention in critical care overall. Accordingly, the upgraded recommendations of the surviving sepsis guideline favor an aggressive fluid resuscitation for as long as the patient continues to improve hemodynamically (1). On the other hand, it is well known that a positive fluid balance represents an independent predictor of mortality in critically ill patients (2, 3). Probably because of this quandary, fluid resuscitation is currently one of the most intensively discussed topics in critical care. Already in 2000, Alsous et al (4) hypothesized based on a small retrospective study in pediatric patients “that negative fluid balance achieved in any of the first 3 days of septic shock portends a good prognosis.” More recently, it was proposed that early positive fluid balance and late negative balance are positively associated with survival (5). But how to achieve a negative fluid balance? The majority of studies and debates currently focus on fluid input: assessing how to restrict fluid volumes, identifying the variables that are most reliable to guide fluid resuscitation, testing different solutions, and evaluating varying methods to determine fluid responsiveness. But there is another component of fluid balance, namely the fluid output.

In this issue of Critical Care Medicine, Sakr et al (6) present the very interesting results of their planned substudy of an observational multinational prospective audit, the so called “Intensive Care Over Nations database” (7). The authors concluded that a “higher cumulative fluid balance at day 3 but not in the first 24 hours following ICU admission was independently associated with an increase in the hazard of death.” At first sight, these findings support the current approach to stabilize the patient with “aggressive” fluid resuscitation initially and then be restrictive as soon as possible. However, this conclusion is put in perspective by a closer look at the data: Fluid input on day 1 with less than 3.5 L was relatively low suggesting that hemodynamic stabilization took already place before ICU admission. The authors attributed this issue to an increased awareness for sepsis, a circumstance that has also been discussed as a potential reason for the failure of “early goal-directed therapy” as proclaimed by Rivers et al (8) in the recent randomized, controlled trials (9–11). Nevertheless, the relevance of a negative fluid balance within the first three ICU days for the patients’ outcome is reinforced by the present study.

The second major finding is that the reduced fluid balance in survivors was exclusively caused by higher fluid outputs, whereas there was no difference in fluid input between survivors and nonsurvivors. This discovery raises (at least) two questions: what are the reasons for the reduced fluid output (summarizing diuresis, extracorporeal fluid elimination, and drainage fluid in the present study) and how does this information influence clinical practice? With regard to the first question, the authors tried to adjust for differences in renal function by including Sequential Organ Failure Assessment renal subscores in the multivariable analysis. Trusting this valid statistical approach, there must have been additional factors contributing to the reduced fluid output in nonsurvivors such as insufficient perfusion pressures and/or a lack of intravascular volume. Based on the observational design and the high number of participating centers worldwide, the applied strategies and goal variables for hemodynamic therapy probably differed substantially throughout the study. Unfortunately, the authors did not provide information about differences between survivors and nonsurvivors in respect to vasopressor support and hemodynamic parameters. As a consequence, we can only speculate on the role of perfusion pressures as a potential cause for the lower fluid output. However, one would assume that mean arterial pressure was probably comparable between both groups.

Under the premise that renal function, vasopressor support, and hemodynamics were comparable between survivors and nonsurvivors, the most conclusive explanation would be differences in capillary leakage. The increased vascular permeability does not only lead to a reduction of intravascular volume but
also increases intercellular edema formation. Both finally result in an impairment of urine output. This assumption is supported by the fact that the absolute differences in fluid output and fluid balance, respectively, are already present on day 1 and remain almost constant during the following days.

Regarding the second question, the impact of the proposed study on clinical practice primarily exists in an additional prognostic factor in septic patients: the cumulative fluid balance at day 3. Contrary to most of the recent studies that focus on the initial resuscitation bundle (1-, 3-, and 6-hr periods), the present results emphasize the role of the “management bundle” beyond day 1. Furthermore, the awareness for fluid output as important component of fluid balance is reinforced. Whether this knowledge leads to new therapeutic strategies remains to be determined.

Just increasing fluid output in every septic patient will probably be associated with detrimental consequences. But preventing or attenuating vascular leakage would be desirable. In this context, highly selective vasopressin-1a-receptor agonists have been reported not only to stabilize cardiovascular hemodynamics but also to attenuate endothelial permeability (12, 13). However, clinical trials are required to verify these experimental studies. For now, let us close with the title of the above referred to song that nicely summarizes the most important rule for fluid resuscitation in sepsis: “Keep the balance right.”

REFERENCES


Septic Cardiomyopathy: Getting to the Heart of the Matter*

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Sepsis is often accompanied by profound changes in the cardiovascular system, classically described as an initial hypodynamic state prior to resuscitation, followed by a hyperdynamic state with high cardiac output and low systemic vascular resistance. However, some patients also suffer from a reversible myocardial stunning known as “septic cardiomyopathy,” which manifests primarily as a depression in both right and left ventricular contractility (1). This septic cardiomyopathy is difficult to study since native physiologic variables are often augmented by clinical interventions such as fluid resuscitation and inotropes/vasopressors. Further, due to the obvious difficulty in sampling the heart directly, most studies on the underlying pathophysiology have focused on either circulating cytokines in a clinical setting, or on cellular or animal models (2). These prior studies have suggested that the dysregulated immune response in sepsis may be coupled to myocardiologic changes in nitric oxide production and signaling, mitochondrial function, and/or calcium-regulated contractility.

In this issue of Critical Care Medicine, Matkovich et al (3) report on a genome-wide expression profiling study of...