CHEST

Fluid Management in Sepsis Hypotension and Septic Shock

Time to Transition the Conversation From Fluid Responsive to Fluid Refractory?

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Management of IV fluid (IVF) delivery has been, and will remain, an essential component in the management of critically ill patients, especially those with septic shock. However, definitive literature to support fluid resuscitation at presentation or hours later has been elusive, although literature builds with regards to the potential harms of a positive fluid balance in the critically ill.[1,2] In this issue of *CHEST*, Douglas et al[3] publish data from FRESH (Fluid Response Evaluation in Sepsis Hypotension and Shock), adding to the growing evidence that dynamic evaluations of fluid responsiveness can improve outcomes. Similar to our previous single-center study, fluid management after initial resuscitation that is guided by bioreactance monitoring to determine "fluid responsiveness" was associated with a lower fluid balance and better outcomes.[4] In FRESH, the authors wrote that "dynamic-measure guided resuscitation was associated with lower net fluid balance and reductions in the risk of renal and respiratory failure" when compared with usual care. The authors went on to state that "lack of fluid responsiveness adequately identifies a group of patients with sepsis-associated hypotension that should not have further IV fluids infused."

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The Surviving Sepsis Guidelines recommend continued assessment of hemodynamics and, where available, the use of dynamic measures to assess fluid responsiveness after the initial resuscitation.[5] In accordance with these guidelines, the FRESH investigators assessed for dynamic changes in stroke volume after initial resuscitation in the ED via the use of bioreactance technology with a passive leg raise. Bioreactance is one of multiple methods capable of evaluating whether a volume challenge changes cardiac stroke volume and/or cardiac output. Bioreactance is validated to be concordant with invasive measures of cardiac output.[6] Advantages of noninvasive hemodynamic monitoring devices such as bioreactance are that they do not require specialized training, are easy to apply, and do not have significant interoperator assessment variability. In FRESH, Douglas et al[3] demonstrated that bioreactance technology enables the identification of a patient group unlikely to have cardiac output increased by fluid administration and therefore at risk to be harmed by continued volume loading. Identification of these patients may be equally as important as identifying patients considered "fluid responsive," if not more so.

Is Volume Responsiveness a Meaningful Term?

Many methods exist and have been evaluated in attempts to identify patients who are "fluid responsive." However, this term is ultimately ambiguous and may not be clinically meaningful. We may be able to identify patients in whom IVFs will increase stroke volume and/or cardiac output in the short term. But, how do we know that these patients benefit clinically from this intervention, in the short or long term?

"Volume responsive" does not necessarily equate to clinically meaningful improvement with volume expansion. Approximately one-half of patients with septic shock will experience increased cardiac output with a volume challenge.[7] At the same time, it is reported that only one-half of patients that increase oxygen delivery can increase oxygen uptake at the cellular level.[8] In this scenario, only one of four patients with septic shock will experience increased oxygen uptake with IVFs, yet all patients remain at risk for the

negative consequences of volume loading. Perhaps the most troubling consideration is that, even if an infusion of IVF augments a patient's cardiac output and oxygen uptake, the benefit might be short-lived. Sanchez et al[9] report that <6% of an infused colloid bolus remained in the intrathoracic blood volume one hour after infusion among septic patients, which is significantly less than observed in nonseptic patients. The benefits of fluid administration may last only minutes, yet the potential harm remains with every bolus.

We propose that the identification of patients with septic shock who are unlikely to benefit from IVFs, irrespective of timing from presentation or initial volume resuscitation, may lead to further measurable clinical benefits. Transitioning our dialogue to the identification of patients as fluid refractory, rather than labeling them as fluid responsive, may help curtail the reflex to "give another bolus" and ultimately achieve improved outcomes.

What About Guidelines for Resuscitation?

It is important to note that FRESH was conducted in a common scenario where patients who presented to an ED had initial resuscitation, as suggested by current guidelines.[10] At an average initial volume resuscitation of >2 L before enrollment, the median IVF resulted in >30 mL/kg for the median BMI at the time of enrollment. This important publication should solidify ICU practice for many physicians and health systems that are incorporating stroke volume guided resuscitation into daily patient care. It also may change practice for others who are not using dynamic guidance to make decisions about IVFs for patients with recurrent hypotension after initial volume resuscitation. However, learning from FRESH does not challenge guidelines about the initial 30 mL/kg of crystalloid resuscitation for septic shock. Guidelines recommend rapid administration of 30 mL/kg of crystalloid for sepsis-related hypotension or a lactate value ≥4 mmol /L, which is a strong recommendation with low quality evidence.[10] Should we apply this dynamic physiologic evaluation for assessment of patients who are unlikely to benefit from volume expansion from the time of initial evaluation? At the time of first evaluation in FRESH, 58% of patients were categorized as non-fluid responders or "fluid refractory." Importantly, during the efforts to enroll the 124 patients in the study, nearly five times that many (587 patients) were excluded because they had already received >3 L of fluid.[3] The question becomes, would patients benefit further by evaluation for fluid refractory status after only 1 L of fluid or even before any fluid administration?

If similar positive outcomes were found by refraining from IVF infusion in patients who are identified as fluid refractory, we would have the ability to change management paradigms and guidelines. Not all septic patients have the same history. Patients with immunocompromise and poor nutritional status with acute derangements from gram-negative bacteremia may need different volume management than patients with 7 days of *Clostridium difficile* diarrhea and poor PO intake. Application of easy-to-use technology to assess and identify patients who are unlikely to benefit from potentially harmful interventions has the chance to move the needle in sepsis management and outcomes for some of our most vulnerable patients. We look forward to evaluating this approach as the next frontier in sepsis management.

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