

Early Fluid Resuscitation in Severe Sepsis

Anand Shah

Story From the Front Line

A man in his 60s with a history of heart failure with reduced ejection fraction, hypertension and chronic kidney disease presented to the emergency room after being found on the ground of his bathroom at his assisted living facility. He described several days of diarrhea, weakness, and subjective fevers. On initial assessment, he was tachycardic with a blood pressure of approximately 110/60. He was in no acute distress but had a tender abdomen and appeared mildly confused and fatigued. His labs were notable for an elevated white blood cell count to 14, an acute kidney injury with creatinine of 2.8 from baseline 1.5, and a lactate of 4.2. He was started on ceftriaxone and metronidazole for presumed intra-abdominal infection and 3 liters of lactated ringers were ordered based on a weight of 100 kg and the patient was admitted to the ICU and discharged two days later.

Teachable Moment

The most recent Surviving Sepsis Campaign Guidelines, published in 2016, recommend that at least 30 ml/kg of IV crystalloid fluid be given within the first 3 hours during initial resuscitation of a patient with sepsis. This recommendation is a strong recommendation. Data behind this comes from 4 large trials – the Rivers trial, PROCESS, PROMISE, and ARISE. In the Rivers trial, patients were administered fluids with a goal CVP of 8-12 mm Hg and on average received nearly 5L within the first 6 hours of treatment. Since then, PROCESS, PROMISE, and ARISE have provided data suggesting parts of the Rivers protocol were either not beneficial or harmful and have suggested less fluid than in EGDT are appropriate. In ARISE, patients in the usual care group were given on average 1.7 L (vs 2L in the EGDT group), an average of 34.6 ml/kg. In PROCESS, patients were initially given at least 20 ml/kg but this was subsequently simplified to a fluid challenge of at least 1L. Ultimately, in the first 6 hours, patients in the EGDT group received 2.8 L, patients in the protocol based standard therapy received 3.3 L, and patients in the usual care group received 2.3 L (all between 28 to 30.5 ml/kg). In PROMISE, patients received on average 2L in the first 6 hours vs 2.2 L in the EGDT group, though ultimately received more IV fluids during hospitalization than the EGDT group did.

Despite the results of the trials above, other trials have suggested a lack of benefit or harm to early fluid boluses. There are many observational and retrospective studies of patients with sepsis that demonstrate a correlation between worse outcomes and increased fluid administration and positive fluid balance. The theory behind this is that fluid resuscitation only transiently increases cardiac output and tissue perfusion, that excess fluid can cause edema in organs and subsequent tissue damage, and that some vascular dysfunction is resistant to fluid repletion. However, to date, it appears no prospective, randomized trials have been conducted to investigate this question. The CLOVERS trial, being conducted currently, seeks to compare a liberal fluid resuscitation strategy with a restrictive strategy. The outcome of this trial could change fluid management in sepsis dramatically.

There have also been two RCTs performed in Africa that demonstrate increased mortality associated with aggressive fluid resuscitation. The FEAST trial, evaluating treatment of children with shock in resource limited settings, randomized children to receive 20-40 ml/kg of IV fluids or to receive no bolus initially. All received appropriate antibiotics and maintenance fluids. In this trial, 48 hour mortality was increased in the fluid bolus group (10.6% for albumin bolus, 10.5% for saline bolus, and 7.3% for no bolus). Another trial of a Simplified Severe Sepsis Protocol conducted in Zambia randomized patients to receive at least 2L of IV fluids within 1 hour and another 2 L in the following 4 hours vs usual care with fluid determined by the clinical. Patients in the protocol group received on average 3.5L within the first 6 hours vs 2 L in the usual care group. Mortality was higher in the sepsis protocol group (48.1% vs 33.0%), and patients in the sepsis protocol group had more frequent worsening of hypoxemia and tachypnea. There have also been animal models that demonstrate potential risks of fluid resuscitation. Admittedly, these trials were performed in very different patient populations, with more malnourished patients included and patients at higher risk for TB and malaria among other differences. However, they and other animal models raise the question of the optimal amount of fluid that should be administered during initial resuscitation of patients with sepsis.

For now, standard of care in the USA remains aggressive fluid resuscitation in all patients with sepsis despite the potential risks associated with blind, aggressive fluid resuscitation. Based on guidelines and current data, our patient was appropriately resuscitated with 30 ml/kg of fluids initially and apparently suffered no harm. However, future data may suggest more conservative fluid administration would be more appropriate in patients like him and others at risk for harm from excess fluid resuscitation.

References

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