AAEM Clinical Practice Statement

What is the Preferred Resuscitation Fluid for Patients with Sepsis and Septic Shock?

Chair: Steve Rosenbaum, MD, FAAEM

Authors: Michael E. Winters, MD, FAAEM
Robert Sherwin, MD, FAAEM

Reviewers: Lisa Mills, MD FAAEM
Michael Abraham, MD FAAEM
Grzegorz Waligora, MD

Reviewed and approved by the AAEM Board of Directors (3/17/2017).

Answer: Crystalloid solutions remain the resuscitative fluid of choice for patients with sepsis and septic shock. Balanced crystalloid solutions may improve patient-centered outcomes and should be considered as an alternative to 0.9% normal saline (when available) in patients with sepsis. The use of albumin does not improve mortality in patients with sepsis of any severity. Hydroxyethyl starch solutions are associated with increased mortality and should not be used to resuscitate patients with severe sepsis or septic shock.

Fluid resuscitation is a critical component to the emergency department (ED) management of patients with sepsis and septic shock. Fluids are administered to patients with sepsis in order to augment cardiac output and improve tissue perfusion and oxygenation. Recent evidence has suggested that the composition of fluids used in sepsis resuscitation may affect patient-centered outcomes.

Fluids have traditionally been separated into crystalloid and colloid solutions. Crystalloid solutions can be further divided into balanced and unbalanced solutions. The term balanced solution is commonly used to refer to solutions that contain different electrolyte concentrations that more closely resemble the composition of plasma and minimally affect acid-base equilibrium. Examples of balanced solutions include Ringer's lactate, Ringer's acetate, Hartmann's solution, and Plasma-Lyte. In contrast, unbalanced solutions do not have physiologic concentrations of electrolytes and can adversely affect acid-base equilibrium. The most common unbalanced fluid solution is 0.9% normal saline (NS). Colloid solutions primarily include albumin, hydroxyethylstarch (HES) solutions, dextrans, and gelatins. The choice of which intravenous fluid solution to administer to the patient with sepsis is often based on availability, cost, provider training (medical versus surgical), and geographic location.

Normal saline is one of the most common fluids administered to ED patients with sepsis. Importantly, 0.9% NS is not a true physiologic solution. In large volumes, 0.9% NS will reliably produce a hyperchloremic metabolic acidosis. In addition to its acid-base effects, 0.9% NS contains supraphysiologic amounts of chloride. In fact, the concentration of chloride in 0.9% NS is approximately 40% higher than the concentration of chloride in plasma. This supraphysiologic dose of chloride increases systemic inflammation and has been associated with adverse effects on the renal, circulatory, pulmonary, gastrointestinal, and coagulation systems.[1-3] In a prospective, open-label study of over 1500 critically ill patients, Yunos and colleagues demonstrated a lower rate of kidney injury by restricting the use of high-chloride containing solutions (0.9% saline, 4% succinylated gelatin solution, 4% albumin solution) and resuscitating patients with Hartmann solution, a balanced solution (Plasma-Lyte 148), or chloride-poor 20% albumin.[4] Importantly, this trial did not demonstrate a change in patient mortality. In a recent retrospective review, Shaw and colleagues demonstrated an increase in in-hospital mortality in patients with the systemic inflammatory response syndrome who received an intravenous fluid with a high chloride concentration. [5]

In contrast to 0.9% NS, balanced crystalloid solutions contain significantly lower concentrations of chloride. Instead of large amounts of chloride, balanced solutions contain organic anions (i.e., lactate, gluconate, citrate, acetate) which

act as physiologic buffers and are rapidly converted to bicarbonate upon administration. In addition, balanced solutions have less of an adverse effect on acid-base equilibrium than 0.9% NS. Balanced solutions also contain varying amounts of cations (i.e., potassium, calcium). In a large retrospective cohort, Raghunathan and colleagues demonstrated a lower in-hospital mortality among patients with sepsis who received a balanced solution as a component of their fluid resuscitation compared to patients who received only 0.9% NS. [6] Among 6,730 patients in a propensity-matched cohort, receipt of balanced fluids was associated with a lower in-hospital mortality (19.6% vs 22.8%). Mortality was lower among patients who received a larger proportion of balanced fluids. There was no significant difference in the prevalence of acute renal failure or in-hospital and ICU lengths of stay. Similarly, Rochwerg and colleagues demonstrated that balanced solutions may be superior to saline for fluid resuscitation in sepsis in a 6-node network meta-analysis.[7] The only prospective, randomized trial comparing the effect of a balanced solution with 0.9% NS was recently published in the *Journal of the American Medical Association*.[8] In this trial, Young and colleagues demonstrated no difference in acute kidney injury, renal replacement therapy, need for mechanical ventilation, intensive care unit length of stay, or mortality in over 2300 patients randomized to receive either Plasma-Lyte or 0.9% NS.[8] Importantly, the trial did not enroll critically ill patients with sepsis. In fact, the majority of patients were post-operative surgical patients who received an average of just 2 liters of intravenous fluid.

Current international guidelines for the management of patients with sepsis and septic shock suggest albumin administration in addition to crystalloids when patients require a large amount of crystalloids for initial resuscitation [9]. The authors of these guidelines, however, state that this is a weak recommendation based on low quality of evidence. In a systematic review and meta-analysis, Patel and colleagues failed to demonstrate a change in mortality among patients with sepsis of any severity who received albumin as part of their fluid therapy. [10] Similarly, Caironi and colleagues were unable to demonstrate an improvement in mortality among 1800 patients with severe sepsis or septic shock who were randomized to receive crystalloid alone or a 20% albumin solution. [11] Importantly, this trial was not designed to assess albumin as a resuscitative fluid. Rather, the primary objective of the study was to correct hypoalbuminemia. At this time, the body of evidence does not support the use of albumin as a resuscitative fluid for patients with sepsis.

Many critically ill patients across the world receive HES solutions for resuscitation. HES solutions are defined by their molecular weight and degree of hydroxyethylation. Recent evidence has demonstrated significant harm with the use of HES solutions. In a multicenter, parallel-group trial in 26 centers in Scandinavia, Perner and colleagues demonstrated a higher 90-day mortality and increased risk of renal replacement therapy in patients who received a HES solution compared with patients treated with Ringer's acetate.[12] Myburgh and colleagues demonstrated an increased risk of adverse events in intensive care unit patients who received a HES solution.[13] More recently, Zarychanski and colleagues demonstrated an increase in mortality and acute kidney injury among critically ill patients treated with a HES solution.[14] Based upon these trials and numerous others, HES solutions should no longer be used in the management of patients with sepsis.

References:

1. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol* 1989; 256:152-7.
2. Hadimioglu N, Saadawy I, Saglam T, et al. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. *Anesth Analg* 2008; 107:264-9.
3. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effect of 2-L infusion of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012; 256:18-24.
4. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012: 308:1566-72.
5. Shaw AD, Raghunathan K, Peyerl FW, et al. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med* 2014; 40:1897-905.
6. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill patients with sepsis. *Crit Care Med*. 2014; 42:1585-91.

7. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med*. 2014; 161:347-355.
8. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit. The SPLIT randomized clinical trial. *JAMA* 2015; 314:1701-10.
9. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017. [epub ahead of print].
10. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014; 349: g4561.
11. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370:1412-21.
12. Perner A, Haase N, Guttormsen AB, et al. Hydroxethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *NEJM*. 2012; 367:124-34.
13. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *NEJM*. 2012; 367:1901-11.
14. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation a systematic review and meta-analysis. *JAMA*. 2013; 309:678-88.