Critical Review Form
Therapy

PGY-2

Raghunathan K, Bonavia A, Nathanson BH, Beadles CA, Shaw AD, Brookhart MA, Miller TE, Lindenauer PK. Association between Initial Fluid Choice and Subsequent In-hospital Mortality during the Resuscitation of Adults with Septic Shock. Anesthesiology. 2015 Sep 28.

Objectives: **"To test the hypothesis that the specific mixture of IV fluids, colloids and different types of crystalloids, used during initial resuscitation, in severe sepsis, is associated with major in-hospital outcomes." (p. 2)**

Methods: **This retrospective cohort study was conducted using patients admitted to one of 360 US hospitals in the Premier healthcare alliance between January 2006 and December 2010. Adults inpatients age 18 years or older with a principal or secondary diagnosis of sepsis, who were in an ICU receiving vasopressors by the 2nd day of hospitalization, who received at least 3 consecutive days of antibiotics with blood cultures drawn, and who received at least 2 liters of crystalloid by day 2 were eligible for inclusion. Patients who underwent major surgery (excluding tracheostomy, dialysis catheter placement, and treatment of infectious processes) and those that were transferred were excluded.**

Patients were categorized in one of 4 groups, based on fluids received ONLY during hospital days 1 and 2: 1) Those who received only saline (the Sal group), 2) Patients receiving some balanced fluids such as LR (the Sal + Bal grop), 3) Patients who received saline and colloids (the Sal + Col group), and 4) Patients receiving all three fluid types (the Sal + Bal + Col group).

The primary outcome was in-hospital mortality. Secondary outcomes included hospital length of stay and cost per day among survivors. To adjust for potential baseline differences between the groups, risk adjustment was conducted based on the volume of fluid received in the first two days, and on 27 comorbidity categories from the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality. The authors also controlled for the use of organ supportive therapies (mechanical ventilation, dialysis, diuretics, vasopressors, inotropes, etc.) and other factors.

A total of 60,734 adult patients with a diagnosis of sepsis were identified. There were 44,347 subjects in the Sal group, representing 73% of the entire cohort. There were 11,038 subjects in the Sal + Col group, 3,651 in the Sal + Bal group, and 1,698 in the Sal + Bal + Col group.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No. This was a retrospective study in which patients were analyzed according to the type of fluid they received. The authors used several methods to adjust for imbalances in known confounders, including inverse probability weighting (IPW), propensity score matching (PSM), and logistic regression.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	No. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed according to which fluids they actually received.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients were of similar age and gender, however they differed with respect to medical comorbidities (e.g. CHF, hypertension, chronic pulmonary disease, liver disease, volume of fluid administered by day 2, and adjunctive therapy use). The authors attempted to control for these baseline differences using various statistical methods.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes (in theory), however it is unlikely that knowledge of fluids being received would affect the outcomes.
2.	Were clinicians aware of	Yes (in theory), however it is unlikely that knowledge

	group allocation?	of fluids being received would affect the outcomes. As this was not a prospective study, it is unlikely that performance bias would have any effect on outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors. While this could potentially lead to observer bias, the outcomes were fairly objective.
4.	Was follow-up complete?	Yes. All outcomes were considered within the hospital stay, and hence there was outcome data for all patients.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• In IPW analyses, risk-adjusted in-hospital mortality in the Sal group was 20.19%. Compared to this in-hospital mortality was lower in the Sal + Bal group (17.69%, $p < 0.001$), higher in the Sal + Col group (24.16%, $p < 0.001$), and similar in the Sal + Bal + Col group (19.23%, $p = 0.401$). • In logistic regression analyses, risk-adjusted in-hospital mortality in the Sal group was 21.35%. Compared to this in-hospital mortality was lower in the Sal + Bal group (18.83%, $p < 0.001$), higher in the Sal + Col group (25.36%, $p < 0.001$), and similar in the Sal + Bal + Col group (19.97%, $p = 0.138$). • In PSM comparisons, use of balanced fluids was associated with decreased mortality whether colloids were used (RR 0.84, 95% CI 0.76-0.92) or not (RR 0.78, 95% CI 0.70-0.89). • In PSM comparisons, colloids were associated with no significant change in mortality when balanced fluids were co-administered, and an increase in mortality when balanced fluids were not co-administered. • Secondary outcomes, hospital LOS, and costs per day were comparable among those receiving balanced fluids and those not receiving balanced fluids, but were higher among those receiving colloids compared to those who did not receive colloids.
2.	How precise was the estimate of the treatment effect?	See above.

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Mostly yes. While these were ICU rather than ED patients, they were septic patients requiring vasopressors to maintain hemodynamic stability, which we see quite frequently. It seems reasonable to assume that the choice of fluids for the initial resuscitation of such patients in the ED would have a significant effect on outcomes.
2.	Were all clinically important outcomes considered?	No. The authors considered mortality, LOS, and cost, but did not assess the incidence of acute kidney injury, the need for renal replacement therapy, or the need for other adjunctive therapies (e.g. mechanical ventilation).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study demonstrated a statistically significant decrease in mortality with the use of balanced fluids, and an increase in mortality with the use of colloid when balanced fluid was not co-administered, the lack of randomization makes it difficult to make firm conclusions based on these results . This was a retrospective study, and while various statistical methods were used to account for known confounders, these methods are far from perfect, and do not make up for lack of randomization. Additionally, there are always other confounders (both known and unknown) for which the authors are unable to balance the two groups. It may be there was an imbalance in one or more of these factors that led to the increase in mortality.

Limitations:

1. **This was a retrospective, observational study that lacked the benefits of randomization and blinding. Such studies often demonstrate association without causation.**

2. **The authors used propensity matching, inverse probability weighting, and logistic regression to balance known confounders; such methods are unable to take into account unknown confounders.**

3. **The study demonstrated a decrease in mortality with the use of balanced fluids without an associated decrease in ARF or need for dialysis, but does not discuss the theoretical physiology of such a finding.**

Bottom Line:

This large, observational study of patients with sepsis requiring vasopressors in the ICU demonstrated a decrease in mortality among patients given any amount of balanced fluids compared to those receiving only unbalanced fluids. There was no difference in the incidence of kidney injury between the groups. While these results are promising, further randomized clinical trials will need to be conducted to confirm the results of this study.