Critical Review Form
Therapy

PGY-3

Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014 Jul;42(7):1585-91.

Objectives: **To examine "the association between receipt of balanced fluids (vs not) during initial resuscitation and in-hospital mortality, renal morbidity, ICU, and hospital lengths of stay (LOS) in a large cohort of adults admitted with vasopressor-dependent sepsis." (p. 1586)**

Methods: **This retrospective cohort study was conducted using patients admitted to one of 360 US hospitals in the Premier healthcare alliance between November 2005 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 any type of surgery and those that were transferred were excluded, as were those with missing fluid exposure data.**

Patients who received only crystalloids with a strong ion difference (SID) of 0 (e.g. isotonic saline) were put in the "non-balanced fluid" group, while patients who received any amount of fluid with an SID > 0 (e.g. LR) were put in the "balanced fluids" group. Patients in this group were categorized based on the proportion of balanced fluid received in order to analyze the dose-response relationship. The primary outcome measure was in-hospital mortality occurring after hospital day 2. Secondary outcomes included acute renal failure (ARF) with and without dialysis, and hospital and ICU length of stay among survivors.

There were 654,855 critically ill adults meeting inclusion criteria; 100,685 underwent surgery; 356,483 were not in the ICU on day 2; 94,302 were not on vasopressors; 20,104 were dead or discharged by day 2; 4,216 did not receive 3 or more days of antibiotics; and 25,596 had missing or invalid fluid data. This left 53,448 patients, of whom 3,396 received balanced fluids and 50,052 received only non-balanced fluids. Patients in the balanced fluid group were propensity matched to 3,365 patients in the non-balanced fluid group. The mean age in the two groups was 64, and nearly 48% in each group was male.

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 in the balanced fluid group were propensity-matched to similar patients who received only non-balanced fluids.
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.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. After propensity matching, patients were similar with respect to age, gender, past medical history/comorbidities, use of co-interventions (e.g. mechanical ventilation, CVP monitoring, arterial line placement), and total crystalloid volume infused by day 2.
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 group allocation?	Yes (in theory), however it is unlikely that knowledge 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-hospital mortality was significantly lower in the balanced-fluid cohort compared to the control group: RR 0.86 (95% CI 0.78-0.94), NNT 31 (95% CI 19-78). • The relative risk of in-hospital mortality was lowered an additional 3.4% on average for every 10% increase in in the proportion of balanced fluids received. • There was no significant difference in the incidence of ARF requiring dialysis: RR 0.95 (95% CI 0.76-1.19). • There was no difference in the incidence of ARF without need for dialysis: RR 0.95 (95% CI 0.78-1.15). • There was no significant difference in hospital LOS among survivors: absolute difference (AD) -0.11 days (95% CI -0.55 to 0.34). • There was no difference in ICU LOS among survivors: AD -0.11 (95% CI -0.37 to 0.15).
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?	Yes. The authors considered mortality, incidence of AKI both with and without need for dialysis, and length of stay. They did not consider cost or the effect of fluid choice on the need for additional therapies (duration of vasopressor therapy, need for mechanical ventilation, etc.).
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, with an NNT of 31, it seems unusual that there was not a similar decrease in the incidence of AKI or the need for dialysis.

		This was a retrospective study, and while propensity-matching was used to balance the two cohorts as much as possible, 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 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.