Critical Review Form
Therapy

PGY-2

Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018 Mar 1;378(9):829-839.

Objectives: **"To determine the effect of isotonic crystalloid composition on clinical outcomes in critically ill adults...We hypothesized that the use of balanced crystalloids would result in a lower overall incidence of death, new renal-replacement therapy, and persistent renal dysfunction than saline." (p. 830)**

Methods: **This unblinded, "cluster-randomized," multiple-crossover trial was conducted in five ICUs at Vanderbilt Medical Center between June 1, 2015 and April 30, 2017. Adults aged 18 years or greater admitted to a participating ICU were enrolled. Patients who were discharged from the hospital and later readmitted to the ICU were eligible for reenrollment. The type of crystalloid administered was "randomized" base on calendar month, alternating between saline and balanced cystalloids. During months when balanced crystalloids were administered, clinicians could choose to administer either lactated Ringer's solution or Plasma-Lyte A. Clinicians could also choose to administer off-protocol fluids if they were felt to be indicated. Patients admitted during one calendar month, who remained in the ICU at the start of another month may have received both types of crystalloid.**

The primary outcome was a major adverse renal event by the time of discharge or within thirty days, defined as death, need for new renal replacement therapy, or a persistent renal dysfunction (final inpatient creatinine ≥ 200% of baseline). Secondary outcomes included in-hospital death before ICU discharge or at 30 days or 60 days, number of ICU-free days, ventilator-free days, vasopressor-free days, and days alive and free of renal-replacement therapy during the 28 days following enrollment.

A total of 15,802 patients were enrolled in the trial, 7942 in the balanced crystalloid group and 7860 in the saline group. The median age was 58 years and 57.6% were male. More than a third of patients were on mechanical ventilation and a quarter were receiving vasopressors at the time of enrollment.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. The type of isotonic crystalloid was assigned according to calendar month. This type of quasi randomization does not allow for blinding of

		interventions and is subject to systematic bias.
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?	N/A as the study was not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "Analyses were conducted at the level of each patient's hospitalization in an intention-to-treat fashion." (p. 832) "Only 426 patients (5.4%) in the balanced-crystalloids group and 343 patients (4.4%) in the saline group received any volume of unassigned crystalloid as a result of remaining in the ICU from one calendar month to the next." (p. 832) The authors do not report the percent of patients in each group treated off protocol at clinician discretion.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, race, presence of pre-existing renal dysfunction, source of ICU admission (i.e. ED vs. OR vs. ward), presence of sepsis, need for mechanical ventilation and vasopressors, predicted risk of in-hospital death, and baseline creatinine level.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
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. This study was not randomized and hence it was impossible to blind clinicians to fluid choice. As a result, performance bias may have affected the 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. As all outcomes measures were made during hospitalization, no patients were lost to follow-up.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• The primary outcome (major adverse renal event) occurred slightly less frequently in the balanced

		crystalloid group compared to the saline group: 14.3% vs. 15.4% (adjusted OR 0.90, 95% CI 0.82-0.99). ○ There was, however, no statistically significant difference in any of the individual components of this composite outcome (incidence of death, new need for renal replacement therapy, or persistent renal dysfunction). ○ There was also no <u>unadjusted</u> difference in the incidence or a major adverse renal event (RR 0.93, 95% CI 0.86-1.00). • Among patients with sepsis, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (adjusted OR, 0.80; 95% CI, 0.67 to 0.97). • Mortality before hospital discharge and within 30 days of ICU admission did not differ significantly between the balanced crystalloid and saline groups: 10.3% vs. 11.1% (adjusted OR 0.90, 95% CI .80-1.01). • There was no significant difference between the groups with regards to death before ICU discharge, death before 60 days, ICU-free days, ventilator-free days, or vasopressor-free days.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. This study was conducted in a large, urban, tertiary care center with what is likely a similar mix of medical, surgical, and trauma patients. This was, unfortunately, a single-center study, and its results are less generalizable than a multi-center study would be.
2.	Were all clinically important outcomes considered?	No. The authors considered the most relevant outcomes (mortality, hospital LOS, and renal impairment), but did not look at cost or need for electrolyte repletion.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This observational study demonstrated a small but statistically significant reduction in the composite outcome of major renal adverse events with a NNT of 91. This difference was only observed after statistical adjustment of outcomes for certain confounders, and was not present when the raw data was analyzed without adjustment. Additionally, there was no statistically significant difference observed for any of the individual components of the outcome. Given that the median

		volume of fluid administered in the study was only 1 liter, it is quite possible that patients receiving larger volumes would see a larger, more consistent benefit. In subgroup analysis, a much larger benefit was seen when looking only at septic patients, who are likely to receive larger volume resuscitation. Further randomized studies specifically looking at patients receiving large-volume resuscitation, or looking only at septic patients, should be undertaken to see if this effect is consistent.

Limitations:

1. **Neither patients, clinicians, nor outcome assessors were blinded to group allocation, raising the possibility of performance bias and observer bias.**

2. **This was not a randomized controlled trial. Instead, group allocation was dictated by the month in which the patient presented.**

3. **The method of establishing a baseline creatinine varied between patients depending on information available: in approximately half of patients a lowest value in the 12 months prior to hospitalization was used; in nearly 40% a lowest value between hospital and ICU admission was used; and about 10% of patients had an predicted value estimated by calculation.**

4. **The primary outcome was a composite outcome whose individual components did not achieve statistical significance. Additionally, the reported odds ratio for the composite outcome has been adjusted for certain prognostic factors and does not represent the raw results (which did not achieve statistical significance).**

Bottom Line:

This pseudo-randomized study of all patients admitted to the ICU at Vanderbilt University Medical Center found a very small decrease in the composite outcome of major renal adverse events with the use of balanced crystalloids versus saline, with a NNT of 91. This effect was only observed after statistical adjustment of the outcomes for certain prognostic factors and was not seen for the raw data or the individual components of the composite. Further randomized studies should be undertaken to evaluate this possible effect size, perhaps focusing on patients receiving large-volume resuscitation or on patients with sepsis.