Journal Club Eastern Virginia Medical School
Therapy Article

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CITATION: Semler MW et al Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018 Mar 1;378(9):829-839.

I. **WHAT IS BEING STUDIED?**	
1. Study Objective	"To determine the effect of isotonic crystalloid composition on clinical outcomes in critically ill adults we compared the use of balanced crystalloids with the use of saline in patients in medical (SMART-MED) and nonmedical (SMART-SURG) intensive care units (ICUs).
2. Study Design	Cluster randomized, unblinded, multiple crossover trial (pragmatic) among five ICU settings in a single institution between 6/2015-4/2017
3. Inclusion Criteria	All adult ICU patients during study period. Readmitted ICU patients that were previously enrolled,
4. Exclusion Criteria	Patients already receiving renal replacement.
5. Interventions Compared	"Patients in the saline group received 0.9% sodium chloride when intravenous isotonic crystalloid was administered, whereas patients in the balanced crystalloids group received either lactated Ringer's solution or Plasma-Lyte A, according to the preference of the treating clinician."
6. Outcomes Evaluated MAKE (major adverse kidney event) composite of: • Death • new renal-replacement therapy • or persistent renal dysfunction (defined as a final inpatient creatinine value >220% of baseline)	Primary: • The proportion of patients who met one or more criteria for a major adverse kidney event within 30 days. Secondary Clinical Outcomes : • In-hospital death before ICU discharge or at 30 days or 60 days, • ICU-free days

	• Ventilator-free days • Vasopressor-free days • Days alive and free of renal-replacement therapy during the 28 days after enrollment Secondary Renal Outcomes • New receipt of renal-replacement therapy, • Persistent renal dysfunction • Acute kidney injury of stage 2 or higher • The highest creatinine level during the hospital stay • The change from baseline to the highest creatinine level • The final creatinine level before hospital discharge
II. **Are the results of the study valid**	
1. Was the assignment of patients randomized?	Not really. The only randomization was cluster randomization of ICU's to use saline during even-numbered months and balanced fluids during odd months or vice versa. ED's and OR's were randomized in the same cluster with the ICU's in order to have same fluids utilized. Individual patients were not randomized.
2. Was randomization concealed (blinded)?	No, patients, clinicians and investigators were aware.
3. Were patients analyzed in the groups to which they were randomized?	Clinicians had the opportunity to override (off-protocol) research allocation if they felt that there was a reason to select the other type of IV fluid. Though the authors state they applied intention-to-treat analysis they do not provide separate analysis of per-protocol data. .
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Very similar. Table 1. The only disease based comparisons were sepsis (15%), TBI (8.6%) and CKD (17.4%)
III. **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. Non blinded and patients could be aware if the fluid they were receiving.
2. Were clinicians aware of group	Yes

allocation?	
3. Were outcome assessors aware of group allocation?	Probably. " Patients, clinicians, and investigators were aware of group assignments. Likely investigators were data assessors. No mention otherwise.
4. Was follow-up complete?	Uncertain. 30 day mortality not available in all patients, survival to discharge prior to 30 days used as surrogate.No description of how f/u was performed, number lost to f/u not provided.
IV. What were the results? Answer the questions posed below	
1. How large was the treatment effect? (Difference between treatment and control group).	Primary Outcome: Composite MAKE • 14.3% in the balanced crystalloids group and 15.4% in the saline group had a major adverse kidney event. OR 0.91; (95% CI, 0.84 to 0.99; ARR 1.1% **NNT= 90.9..** • Among patients with **sepsis**, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline. ARR=4.4% NNT= 25 OR 0.80; (95% CI, 0.67 to 0.97); p = 0.02 Secondary Clinical Outcomes: No statistically significant differences between groups for individual components of composite outcome • In-hospital death OR 0.90 (95% CI 0.80 to 1.01) p=0.06 • New RRT OR 0.84 (95% CI 0.68 to 1.02) p= 0.08 • Final creat >200% baseline OR: 0.96 (95% CI 0.84 to 1.11) p= 0.60 • ICU free days OR 1.00 (95% CI 0.89 to 1.13) p=0.94 • Ventilator free days OR= 1.06 (0.97 to 1.16) p= 0.22 • Vasopressor free days OR= 1.05 (0.97 to 1.14) p= 0.26 Secondary Renal Outcomes: • No differences reported

2. What was the estimated treatment effect at a 95% confidence interval? (Precision)	See above
V. **Will the results help me in caring for my patients? (Applicable?)**	Maybe? Appear to be a paucity of other diagnoses. NNT for primary outcome was 90.
1. Were the study patients similar to my patient?	Difficult to broadly apply to my patient population. These patients admitted to single center (Vanderbilt) ICU. Over 80% of study patients were Caucasian. Only 50% of study patients came from the ED. We have a significantly higher percentage of African Americans. Unable to find median weight for Norfolk, likely heavier than 80 kg. Also, on pg 832 in the last paragraph, it says that the patients received a median of 1000 mL BC and 1020 NS. This seems inconsistent with sepsis protocols. Seems like low median IVF rates
2. Were all clinically important outcomes considered?	No economic analysis was included.
3. Are the likely treatment benefits worth the potential harm and costs?	Subgroup analysis suggests an NNT of 25 for use of balanced fluids in septic ICU patients for In-patient mortality.

Study Limitations
- Single center mostly Caucasian patients
- Clinicians not blinded which may predispose to intervention bias.
-Composite outcomes have been demonstrated to be problematic and biased. One example is the error of giving equal weighting given to each composite (i.e. death and AKI) . Individually, none of the individual items in the composite demonstrated statistical significance.
No report on how follow-up was obtained or how many were lost to follow-up.
No description of standardization of data abstraction or kappa scores for data assessors.

Clinical Bottom Line:
Pragmatic study with inherent weaknesses demonstrates composite primary outcome with statistical significance in favor of balanced fluids though the NNT is 95. Among patients with sepsis, there appears to be evidence to suggest a decrease in in-patient mortality in favor of balanced fluids NNT=25