EVMS Emergency Medicine Journal Club
Therapy Worksheet

Resident Stu Glass **Date: 3/24/18**

CITATION: Young P 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 Oct 27; 1701-10.

A. What is being studied? (Answer below)	**Comments**
1. Study Objective	"to determine the comparative effectiveness of a buffered crystalloid and saline for crystalloid based fluid therapy in a heterogeneous population of patients treated in the ICU.
2. Study Design	Cluster randomized, double blind, double-crossover RCT in 4 different ICU's in New Zealand and Australia.
3. Inclusion Criteria	All patients in ICU receiving crystalloid fluid were eligible – they instead utilized an "opt-out" consent strategy
4. Exclusion Criteria	Patients on RRT or expecting to require RRT. Patients admitted for palliative care or organ donation omitted
5. Interventions Compared	Saline and Buffered crystalloid PL-148 were randomly assigned in blind fashion at 7 wk tx blocks with 2 crossovers (each ICU used each fluid twice over the 28 weeks) There were 5 predefined subgroups assessed for primary outcome and in-hospital mortality. 1. diagnosis of sepsis, 2. diagnosis of trauma with a TBI 3. diagnosis of trauma w/o TBI 4. cardiac surgical admission 4. a pre-enrollment APACHE II score of 25 or higher.
6. Outcomes Evaluated **RIFLE:** • a 50% increase in serum creatinine is labeled as **"risk,"**	**Primary** proportion of patients with AKI as defined by RIFLE Criteria(increase in creatinine by 2 fold or cr >3.96 with an increase >0.5

• a doubling in serum creatinine is labeled as "**injury,"** • a trebling in serum creatinine is labeled as **"failure,"** • persistent failure is labeled as "loss," • lack of recovery and need for chronic dialysis is labeled as **"endstage"** AKI.	**Secondary**: within 90D • difference between the serum creatinine measured before study enrollment and the peak serum creatinine • the cumulative incidence of AKI defined by thresholds of (Kidney Disease: Improved Global Outcomes [KDIGO] criteria) • the use of RRT in the ICU and the requirements for RRT after hospital discharge • the proportion of patients requiring, and the duration of, mechanical ventilation; • the proportion of patients requiring ICU readmission during their index hospital admission • the ICU and hospital length of stay • in-hospital all-cause mortality • cause-specific mortality, censored at 90 days after enrollment.
B. Are the results of the study valid? Answer questions below	
1. Were patients randomized?	No. Initial fluid used by participating ICU's was randomized using computer generated randomization. Patients however, got the fluid assigned to that ICU for the given block during their length of stay. Pts that remained through a crossover period continued to get the original fluid they were assigned.
2. Was randomization concealed (Blinded)	Yes. it was double blinded – both to physicians and investigators. Physicians were asked to "best guess" fluid and 66% guessed correctly which may suggest bias.
3. Were patients analyzed in the groups to which they were randomized?	Yes. Intention-to-treat analysis was used and all missing patients were assessed both with and w/o presumption of AKI
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes in almost all aspects the patients were almost identical except (Table 1) • Higher proportion of CV disease and trauma in saline group • Higher proportion of respiratory and 'metabolic' in buffered group.

C. Did experimental and control groups retain a similar prognosis after the study started (answer the questions below)?	
1. Were patients aware of group allocation?	no
2. Were clinicians aware of group allocation?	No. Clinicans did control the rate and volume of fluids administered however There was also open label fluid available for specific situations requiring it but these patients were not included in final analyses
3. Were outcome assessors aware of group allocation?	Not sure. Investigators and clinicians were blinded. No specific mention of data assessors.
4. Was follow-up complete?	The study did follow up patients up to day 90 after administration of fluid. However, the followup is truncated to 40 days because the number of participants beyond 40 days is extremely small The Kaplan Meier curves are pretty similar up to 40 days. I would like to see how they compare beyond that mark however – etable7
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	**Primary:** • 90 day AKI buffered crystalloid group, 9.6% vs.9.2% in NaCl group absolute difference, 0.4% [95%CI, −2.1%to 2.9%] RR, 1.04 [95%CI, 0.80 to 1.36]; P = .77) CI crosses 1.0 (insignificant. **Secondary: (See Figure 3)** There were no statistically significant differences in any of the predefined subgroups regardless of fluids used. RRT was used in (3.3%) receiving buffered crystalloid and (3.4%) receiving saline (absolute difference, −0.1% [95% CI, −1.6 to 1.4%]; RR, 0.96 [95% CI, 0.62 to 1.50]; P = .91) While there was some missing date they took this into account by either assuming all or none had AKI and gave similar rates of AKI in both groups (moving RR to 1.05 and 1.01 respectively)

2. How precise was the estimated treatment effect at a 95% confidence interval?	See above.
D. How can I apply the results to patient care	
IV. Were the study patients similar to my patients?	They did include ED patients admitted to the ICU however the overwhelming majority of patients were from the OR (71 & 72%) and most of these were after elective surgery in patients with low co-morbidity rates. No reporting on pre-ICU infusion fluid type and rate Emergent surgery and ED patients were 2 and 3 Other than that, I would say that in general they are not that similar. If you look at the comorbidities and admission diagnoses they are not overwhelmingly sick patients. The majority are cardiac patients which we do see a lot of in the ED but it is unclear if we are seeing this specific subset. Over 65% were Caucasian and male. However, maybe the most important concept is that the median volume of fluid given was about 2L. The patients simply were not given that much fluid. How can we apply this to patients presenting to the ED requiring large volume resusc (sepsis, honk, dka, etc)
1. Were all clinically important outcomes considered?	I think they did consider the clinically important outcomes. No economic analysis.
2. Are the likely treatment benefits worth the potential harms and costs?	Well the study shows that in a composite of all patients there appeared to no difference in type of fluid that stated, predefined subgroups That are important to us such as sepsis (4%), Trauma (4%) and Apache >25 (8%) represented a minority of their patients.

Limitations:

No sample size determinations so subgroups such as septic patients (4%) and others were not powered sufficiently to draw any conclusions.

Fluids quantities generally less than what we typically use which limits applicability applicable to ED patients.

The other, and maybe more important limitation, is that this study was performed in mainly mild to moderately ill patients. It really doesn't answer whether the findings type would hold true in much sicker patients

While it did a good job of minimizing bias I think that there was probably a large amount of ascertainment bias as 2/3 of the physicians could accurately identify the fluids being given. This is likely related to the physiology of the fluids and it could have significantly impacted the study given that they are the ones who controlled the rate and volumes given.

Clinical Bottom Line:

In a composite of generally healthy patients most of whom were elective post-op patients, being admitted to the ICU, there does not appear to be a difference in rates of 90 day AKI when comparing NaCL to buffered solutions .