Critical Review Form
Therapy

Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012 Oct 17;308(15):1566-72.

Objectives: **To test the hypothesis that "that a chloride-restrictive intravenous fluids strategy in critically ill patients might be associated with a decreased incidence and severity of AKI [acute kidney injury] compared with a chloride-liberal intravenous strategy." (pp. 1566-1567)**

Methods: **This prospective, open-label, before-and-after study was conducted in a 22-bed ICU at Austin Hospital in Melbourne, Australia. The control period from February 18 to August 17, 2008 was followed by a phase-out period from August 18, 2008 to February 17, 2009, and then an intervention period from February 18 o August 17, 2009. Consecutive patients admitted to the ICU during each of the 6-month study periods were enrolled.**

During the control period, clinicians were free to use chloride rich fluids, while during the intervention period, chloride-rich fluids were available only after prescription by the attending physician for a specific condition, such as hyponatremia, traumatic brain injury, and cerebral edema. In place of these fluids, lactated crystalloid, a balanced buffered solution, and a 20% albumin solution were used.

Primary outcomes Included the increase in creatinine and the incidence of AKI (as defined by the RIFLE system). Secondary outcomes included the need for renal replacement therapy (RRT), length of stay in the ICU and hospital, and survival to discharge. A multivariate sensitivity analysis was conducted for all outcomes, adjusting for sex, APACHE III score, diagnosis, operative status, and admission type (elective vs. emergent).

There were 760 patients enrolled during the control period and 773 patients enrolled during the intervention period. The cohorts were 61% and 62% male respectively, with mean ages of 60 and 60.5.

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 before and after study in which chloride-rich fluids were restricted during the intervention period to only those patients with diseases requiring administration of such fluids. No attempt was made to control for confounding factors, or to decrease the possibility of additional interventions occurring between the control and intervention period.
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. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. While the two groups were not randomized, they were analyzed according to the study period during which they were enrolled, regardless of the type and amount of fluids administered. Consecutive patients were enrolled in each study period, and no patients were excluded for the primary outcomes.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to gender, admission type, need for mechanical ventilation, comorbidities, baseline serum creatinine, and APACHE III score. Slight more patients in the control period had a metabolic diagnosis, while slightly more in the intervention period had a neurologic diagnosis; this is unlikely to be of clinical significance.
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). This was a non-blinded before and after study, and hence all participants were aware of treatment allocation. It seems unlikely that this would result in significant performance bias on the part of the patients.

2.	Were clinicians aware of group allocation?	Yes. This was a non-blinded before and after study, and hence all participants were aware of treatment allocation. It is possible that this would result in significant performance bias on the part of the clinicians.
3.	Were outcome assessors aware of group allocation?	Yes. This was a non-blinded before and after study, and hence all participants were aware of treatment allocation. It is unlikely that this would result in significant observer bias, as all of the outcomes were objective.
4.	Was follow-up complete?	No. For the primary outcome of increase in creatinine level from baseline, there were 104 (13.7%) patients in the control group and 110 (14.2%) in the intervention group without a baseline creatinine level available. For these patients, baseline GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Patients in the intervention period saw a significantly lower increase in serum creatinine compared to the control period: 14.8 µmol/L (95% CI 9.8-19.9 µmol/L) vs. 22.6 µmol/L (95% CI 17.5-27.7 µmol/L); p = 0.03, adjusted p = 0.007). • The incidence of AKI was significantly lower in the intervention period compared to the control period: 8.4% vs. 14%, p < 0.001; RR 1.6 (95% CI 1.2-2.2), NNT – 18.5. • The need for RRT was higher in the control period compared to the intervention period: 10% (95% CI 8.1-12%) vs. 6.3% (95% CI 4.6-8.1%). • After multivariate analysis, the adjusted odds of developing AKI were lower in the intervention group compared to the control group: OR 0.52 (95% CI 0.37-0.75). • After multivariate analysis, the odds of requiring RRT were significantly lower in the intervention group compared to the control group: OR 0.52 (95% CI 0.35-0.76). • ICU and hospital mortality and median ICU and hospital length of stay were not significantly different between the two groups.
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?	Not really. These were ICU patients rather than ED patients, and only about 22% were even admitted from the ED. Half the patients were post-operative, and about 30% were post-operative from elective surgeries.
2.	Were all clinically important outcomes considered?	Yes. The authors considered the effect of fluid choice on renal function, need for dialysis, ICU length of stay, and mortality. They did not address cost, though any effect on cost would likely be as a result of increased need for dialysis or increased length of stay.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a before and after study, and hence subject to a great deal of bias, including Hawthorne effect and performance bias. In addition, the patient population was largely post-operative, with less than a quarter admitted from the ED.

Limitations:

1. **This was a before and after study, with all of the inherent biases involved. Specifically, there is no way to control for other interventions that occurred with regards to seizure management in the interim.**

2. **This was a non-randomized, open-label (unblinded) study, open to several potential sources of bias as a result (selection bias, performance bias, recall bias, observer bias).**

3. **This was an ICU-based population, and half of the subjects were post-operative. Less than a quarter of the patients were admitted from the ED (external validity).**

Bottom Line:

In this prospective, before-and-after study conducted in Australia ICUs, patients given chloride-rich fluids were more likely to develop acute kidney injury (RR 1.6 (95% CI 1.2-2.2) and were more likely to require renal replacement therapy (10% vs. 6.3%). There was no significant effect on length of stay or mortality. Unfortunately, this was a before-and-after study, and hence subject to a great deal of potential bias. Additionally, the study population was potentially quite different from ours in the ED. Future prospective, randomized studies will need to be conducted in the ED setting to further evaluate the efficacy of balanced fluids compared to chloride-rich fluids.