DEM Journal Club

# Article Appraisal

**Article:** Balanced Crystalloids versus Saline in Noncritically Ill Adults (SALT-ED Trial) by Self et al, NEJM 2018

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## Background and Study Objective(s):

Administration of intravenous (IV) fluid is a very common intervention in the emergency department (ED). Normal saline (NS) is typically the most frequently used crystalloid, despite increasing evidence that it may cause harm by inducing hyperchloremic metabolic acidosis and renal injury. Balanced crystalloid (BC) solutions such as Ringer's Lactate and Plasmalyte-A are closer to physiologic electrolyte concentrations and pH levels, and may provide a more expensive but possibly safer alternative. Previous studies have compared the effects of NS and BC use, mainly in critically ill patients in a critical care setting. However, no studies have evaluated their use in the non-critically ill population. It is unclear if there is any harm caused by administration of NS over BC in this less ill but significantly larger population. This trial sought to investigate the effects of routine administration of NS versus BC in non critically ill patients in the ED.

## Study Design:

This was a single-center, pragmatic, unblinded, multiple-crossover trial performed in a tertiary care center in the United States. The trial population consisted of adults (≥18 years) who received at least 500 mL of IV fluid in the ED and were subsequently hospitalized outside of the ICU. The entire ED crossed over every month during the 16-month trial and alternated the use of NS or BC. Trial protocol guided only the type of crystalloid given, all other aspects of care were determined by treating clinicians. Selection of IV fluids after the patient's transfer from the ED to the ward was not included as part of the trial intervention. Relative contraindications to the use of BC included hyperkalemia and brain injury. Providers had the option of ordering off-protocol crystalloids if they believed an alternative was specifically indicated. Patients who received off-protocol fluids were included in the primary analysis according to intention-to-treat principles, but a secondary per-protocol analysis was also performed. The primary outcome was hospital-free days to day 28. The trial included three key secondary outcomes: major adverse kidney events within 30 days (MAKE-30), acute kidney injury of stage 2 or higher, and in-hospital death. MAKE-30 was a composite of death, new renal-replacement therapy (RRT), or persistent renal dysfunction (Cr ≥200% of baseline) at the earliest of hospital discharge or 30 days after the index ED visit.

## Results:

A total of 13347 patients were included in the trial after an enrolment period of 16 months, with 6708 receiving BC and 6639 receiving NS. Baseline characteristics were similar among the groups. The median crystalloid volume received was 1079 mL. Of those who received BC, 95.3% received Ringer's Lactate. There was no difference in the primary outcome of hospital length of stay. Secondary outcomes showed a significantly lower rate of MAKE-30 in the BC (4.7%) compared to NS (5.6%) group with an adjusted odds ratio of 0.82 and a 95% confidence interval of 0.70-0.95. The major contributing factor to the difference in the MAKE-30 composite outcome was a 0.7% increase in the rate of patients experiencing a 200% increase in creatinine above baseline at 30-days. With a 0.9% absolute reduction in MAKE-30, there was a number needed to treat of 111 for BC. The largest benefit was found in patients presenting with renal dysfunction, in which the rate of MAKE-30 was 28% in the BC group and 37.6% in the NS group. There were no significant differences in other secondary outcomes including stage 2 acute kidney injury and in-hospital death.

## Validity of Results:

One of the major limitations of this study is that physicians and patients were not blinded to the type of IV fluid administered, which could introduce bias. Furthermore, fluids administered after hospital admission and those used as medication carriers were not controlled for in this trial, and these are confounding factors that make it difficult to draw definitive conclusions about the direct impact of fluids given in the ED. Providers also had the option of ordering off-protocol crystalloids and these patients were included in the primary analysis which could dilute the results of the study. However, an additional per-protocol analysis did account for this. With regards to outcomes, the differences were primarily driven by a change in creatinine, and it is unclear whether this actually has long term patient-centered implications. Finally, the use of composite outcomes makes it difficult to interpret the findings and decipher how meaningful each component of the endpoint actually is.

## Generalizability of Results:

The study was conducted in a tertiary care teaching hospital with a similar patient volume to our practice setting. It is important to note that it was conducted in a private hospital where intervention and admission rates are likely higher than are seen in our public funded system. It is also difficult to draw any conclusions on the effect of Plasma-Lyte use in this setting, as over 95% of patients in the BC group received Ringer's Lactate.

## The Bottom Line:

In non-critically ill adults admitted to the hospital and treated with BC or NS in the ED, there was no difference in hospital-free days. A composite secondary outcome demonstrated a small but statistically significant decrease in adverse renal events with the use of BC compared to NS, but this result was primarily driven by doubling of creatinine, not mortality or need for RRT; and we don't know the long term or patient-centered implications of this finding. Patients with a baseline creatinine ≥110 appeared to have largest benefit from BC for avoiding adverse renal events. This data is the current best evidence in the IV fluid debate, although it does not provide unequivocal evidence for using BC. A properly blinded RCT would be the next step. In the meantime, many experts are arguing that we should be switching to BC if we haven't done so already. Although the risk difference is modest for each patient, the implications on a population level may be substantial owing to the millions of patients who receive isotonic crystalloids annually. Since LR and NS are similar in terms of cost and availability, it may be time to consider a culture shift in the ED with regards to our historically prominent use of NS.