EDITORIAL



# Assessing Toxicity of Intravenous Crystalloids in Critically Ill Patients

John A. Kellum, MD; Andrew D. Shaw, MB, FRCA

**Intravenous administration** of a specific fluid may have very different effects compared with enteral administration of the same fluid. For example, pure water is well tolerated when given orally, but is highly injurious (leading to hemolysis) when administered intravenously. Intravenous fluids are the most common intervention prescribed for hospitalized patients and may be administered for multiple reasons, such as for rehydration (as an alternative to the enteral route), as a vehicle or carrier for medication delivery, and to produce direct physiologic effects on cardiac output and electrolyte concentrations (as drugs). There are important differences in the composition, volume, and rate of administration of fluids for these different uses.

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Over the last 25 years, the safety and efficacy of intravenous fluids have been vigorously debated. First, the composition of lactated Ringer solution was changed from a racemic mixture of lactate ions to pure L-lactate when high concentrations of the D-isomer were found to be toxic, including cardiac and neural toxicity.[1] Next, the combination of several small studies examining the use of albumin for fluid resuscitation suggested an association with decreased survival.[2] Even though a subsequent large trial showed no overall mortality difference between albumin vs saline for fluid resuscitation of patients in the intensive care unit (ICU), there was evidence of toxicity in 1 predefined subgroup.[3] Subsequent analysis including detailed follow-up provided additional evidence that a 4% albumin solution was harmful for patients with increased intracranial pressure, probably related to its hypotonicity and the effect on intracranial pressure.[4] More recently, the use of hydroxyethyl starch was found to have an adverse effect on survival among patients with sepsis, apparently related to its effect on acute kidney injury (AKI).[5] A subsequent larger trial showed no significant difference between hydroxyethyl starch vs saline administration and mortality, and also demonstrated that hydroxyethyl starch was associated with a reduction in AKI but a small increase in the use of dialysis.[6] Importantly, trials showing harm used much larger volumes of starch and studied higher-risk patients.[7] As a result, most experts now accept that hydroxyethyl starch is at least mildly nephrotoxic, although disagreement exists as to whether the solution still has a role in the management of some patients.

Isotonic 0.9% sodium chloride (saline) solution is the most commonly used intravenous fluid in much of the world, and especially in North America.[8] The toxic potential of sodium chloride solutions was known at least as early as the late 19th century and was described by Cushing[9] among others. Although the sodium concentration of isotonic saline is only slightly higher than that of plasma, the higher than physiologic chloride concentration can lead to hyperchloremia and acidosis if isotonic saline is administered fast enough, and in large enough volumes.[10] Bolus administration of either isotonic saline or albumin in saline was found to increase short-term mortality in children with sepsis in Africa.[11] Although the mechanism of this toxicity is unclear, increased deaths appeared to be mainly related to late cardiovascular collapse—a known consequence of experimental hyperchloremic metabolic acidosis in septic animals.[12]

Numerous observational studies[13-15] and a sequential period trial[16] have suggested a signal of potential harm when saline administration was compared with administration of fluids with more physiologic chloride concentrations, although the kinds of adverse outcomes have varied. Some studies have shown increased AKI or dialysis,[13,16] whereas other reports have shown increased hospital mortality without an effect on AKI.[14] This heterogeneity of effect is important because it demonstrates 2 essential aspects about toxicity—that toxicity is dose dependent and that the manifestation of toxicity depends on the susceptibility of the population exposed. A high "dose" of a low-toxicity substance will cause harm in a susceptible patient, whereas a low dose of a highly toxic substance may be undetectable in a low-risk patient. Put more simply, if there is a hazard with saline administration, then healthier patients who receive small doses will deal with the hazard better than sicker patients who receive large doses.

In this issue of *JAMA*, Young and colleagues[17] report the 0.9% Saline vs Plasma-Lyte 148 for ICU fluid Therapy (SPLIT) trial, a multicenter study comparing 0.9% saline with a buffered electrolyte solution for fluid therapy among 2278 patients who were receiving treatment in 4 ICUs in New Zealand and required crystalloid fluid therapy. The indications for fluid were not specified, but presumably included both volume replacement as well as fluid resuscitation and other indications. The overall exposure to study fluids was small (a median of only 2 L) during the ICU stay, and most of the fluid administration occurred during the first 24 hours. The population was (at most) moderate risk (mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 14) and predominantly included postoperative patients. Overall, development of AKI within

90 days of enrollment (the primary outcome) occurred in only approximately 9%, and rates of renal replacement therapy (RRT) and in-hospital mortality (key secondary outcomes) were approximately 3% and 8%, respectively, with no significant differences between the buffered crystalloid group and the saline group (AKI, 9.6% for buffered crystalloid vs 9.2% for saline; RRT, 3.3% for buffered crystalloid vs 3.4% for saline; mortality, 7.6% for buffered crystalloid vs 8.6% for saline).

The study was well conducted with excellent adherence to study protocol and near-complete follow-up, and the results have high face validity. The authors conclude that fluid choice did not alter the risk of AKI and that "further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality."[17] This trial has set the stage for future studies, which should be guided both by the success of the trial in its protocol adherence and pragmatic elegance as well as by its limitations.

However, some important points merit discussion. First, it is unclear how much physiologic separation may have occurred between the 2 fluid administration groups. The authors did not report serum chloride data, which may have allowed an estimate of whether there was sufficient difference between the groups to permit a plausible effect on clinical outcomes. Second, the total exposure to these 2 fluids was minimal, approximately 2 L during the entire ICU stay. It is unlikely that this amount of fluid volume could have demonstrated a plausible hazard, and not in the study population that was at low risk for AKI or other adverse effects. Third, if the trial had been designed to test the efficacy of fluids on renal function, then the authors would have had to measure renal function or injury in a more granular fashion, perhaps including biomarkers or imaging studies. Prior studies in animals[18] or healthy volunteers[19] have shown important effects of fluids on the kidney. If the investigators had used the techniques used by Chowdhury et al,[19] then they would most likely have demonstrated similar changes in renal blood flow and function, but these do not necessarily lead to an increase in moderate-severe AKI, as measured by changes in serum creatinine. In the healthy kidney, substantial functional reserve must be exhausted before serum creatinine increases.

Another concern is whether the trial reported by Young et al is an effectiveness trial. The effectiveness of fluids for treating or preventing AKI would require the presence of (or risk for) fluid responsive AKI, and clinicians would need to understand that they were using the fluid for this indication. Instead, the SPLIT trial enrolled patients who received fluid for a variety of indications and the effectiveness for each indication was not assessed. Rather, adverse events were measured. Thus, the SPLIT trial, like the CHEST[6] and SAFE trials,[3] were actually toxicity studies, or at best were studies that accepted a broad assessment of effectiveness using mortality as a surrogate outcome. The surrogacy of the mortality end point is clear because few, if any, patients who are critically ill die for lack of 2 L of crystalloid.

This fundamental premise that large pragmatic studies can be used to assess the effectiveness of fluids on outcomes such as AKI, requirement for dialysis, and mortality should be carefully considered when the intervention is not being used specifically for these purposes. Drugs such as 0.9% saline or other electrolyte solutions might result in differences in these outcomes, but it will be as a result of differences in toxicity, not efficacy, and studies should be designed accordingly. In particular, such studies need to deliver a plausible dose of fluids to a population at sufficient risk for adverse outcomes to uncover the hazard, if one exists. If there is a hazard with one or another of these fluids, then it will be important to discover and quantify that risk, however small, because of the sheer enormity of the exposed population that receive intravenous fluids. This hazard will not be unmasked by treating healthier patients with small doses of fluids, but rather by treating sicker patients with larger fluid volumes.

In the meantime, the results of the trial by Young et al provide reassurance that neither 0.9% saline nor a low-chloride electrolyte solution appears to be particularly hazardous when the total dose used in patients at low to moderate risk is about 2 L. This is an important contribution to the care of patients in the ICU. However, the large body of "circumstantial" evidence that points to a harm signal for saline—with scant, if any, evidence of comparative benefit—should behoove intensivists and other clinicians to proceed with caution when ordering intravenous fluids.

## ARTICLE INFORMATION

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## REFERENCES

1. Chan L, Slater J, Hasbargen J, Herndon DN, Veech RL, Wolf S. Neurocardiac toxicity of racemic DL-lactate fluids. *Integr Physiol Behav Sci*. 1994;29(4):383-394.

2. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998;317(7153):235-240.

3. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.

4. Myburgh J, Cooper DJ, Finfer S, et al; SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357(9):874-884.

5. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 vs Ringer acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.

6. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group.

Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.

**7**. Shaw AD, Kellum JA. The risk of AKI in patients treated with intravenous solutions containing hydroxyethyl starch. *Clin J Am Soc Nephrol*. 2013;8(3):497-503.

**8**. Finfer S, Liu B, Taylor C, et al; SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*. 2010;14(5):R185.

**9**. Cushing H. Concerning the poisonous effect of pure sodium chloride solutions upon the nerve-muscle preparation. *Am J Physiol–Legacy Content*. 1901;6(2):77-90.

**10**. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during in vitro hemodilution. *Crit Care Med*. 2002;30(1):157-160.

**11**. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483-2495.

**12**. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125(1):243-248.

**13**. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared with Plasma-Lyte. *Ann Surg*. 2012;255(5):821-829.

**14**. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of intravenous crystalloid and in-hospital mortality among critically ill adults with sepsis. *Crit Care Med*. 2014;42(7):1585-1591.

**15**. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med*. 2014;40(12):1897-1905.

**16**. 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;308(15):1566-1572.

**17**. Young P, Bailey M, Beasley R, et al; for the SPLIT investigators and the ANZICS CTG. 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*. doi:10.1001/jama.2015.12334.

**18**. Zhou F, Peng Z-Y, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9% saline vs a balanced electrolyte solution on acute kidney injury in a rat model of sepsis. *Crit Care Med*. 2014;42(4):e270-e278.

**19**. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
## The SPLIT Randomized Clinical Trial

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**IMPORTANCE** Saline (0.9% sodium chloride) is the most commonly administered intravenous fluid; however, its use may be associated with acute kidney injury (AKI) and increased mortality.

**OBJECTIVE** To determine the effect of a buffered crystalloid compared with saline on renal complications in patients admitted to the intensive care unit (ICU).

**DESIGN AND SETTING** Double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand from April 2014 through October 2014. Three ICUs were general medical and surgical ICUs; 1 ICU had a predominance of cardiothoracic and vascular surgical patients.

**PARTICIPANTS** All patients admitted to the ICU requiring crystalloid fluid therapy were eligible for inclusion. Patients with established AKI requiring renal replacement therapy (RRT) were excluded. All 2278 eligible patients were enrolled; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analyzed.

**INTERVENTIONS** Participating ICUs were assigned a masked study fluid, either saline or a buffered crystalloid, for alternating 7-week treatment blocks. Two ICUs commenced using 1 fluid and the other 2 commenced using the alternative fluid. Two crossovers occurred so that each ICU used each fluid twice over the 28 weeks of the study. The treating clinician determined the rate and frequency of fluid administration.

**MAIN OUTCOMES AND MEASURES** The primary outcome was proportion of patients with AKI (defined as a rise in serum creatinine level of at least 2-fold or a serum creatinine level of ≥3.96 mg/dL with an increase of ≥0.5 mg/dL); main secondary outcomes were incidence of RRT use and in-hospital mortality.

**RESULTS** In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4% [95% CI, −2.1% to 2.9%]; relative risk [RR], 1.04 [95% CI, 0.80 to 1.36]; $P = .77$). In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95% CI, −1.6% to 1.4%]; RR, 0.96 [95% CI, 0.62 to 1.50]; $P = .91$). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95% CI, −3.3% to 1.2%]; RR, 0.88 [95% CI, 0.67 to 1.17]; $P = .40$).

**CONCLUSIONS AND RELEVANCE** Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI. Further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality.

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Editorial

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The administration of intravenous fluids to increase intravascular volume or maintain hydration is a frequent intervention in the intensive care unit (ICU), although the choice of fluid remains controversial.[1] Globally, 0.9% sodium chloride (saline) is the most commonly used resuscitation fluid.[2] However, despite its widespread use, emerging data provide uncertainty about the safety of saline in patients who are critically ill.[3-7]

Most concern has focused on the hypothesis that the high chloride content of saline contributes to the development of acute kidney injury (AKI).[3,4,8] One alternative to saline is a buffered crystalloid solution with an electrolyte composition that more closely resembles that of plasma, such as the prototype compound sodium lactate solutions or proprietary "buffered" or "balanced" crystalloid solutions.

Observational data suggest that buffered crystalloids may be associated with a decreased risk of AKI[3,4,8] and of death compared with saline.[6,7] Although it is biologically plausible that saline worsens renal function compared with buffered crystalloids,[9,10] the effects of buffered crystalloids have not been evaluated in randomized trials in the broad range of patients in the ICU to whom they might be administered if used in preference to saline.

We therefore designed and conducted a cluster randomized, double-crossover study 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. The aim of our study was primarily to determine the effect of specific fluid type on the development of AKI in this patient population.

## Methods

### Study Design and Oversight

The management committee designed the trial that was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). The study protocol[11] (trial protocol in Supplement 1) was approved by the New Zealand Northern B Health and Disability Ethics Committee (12-NTB-57). Because this study involved the systematic evaluation of treatments that were used commonly in the study hospitals and randomization occurred at the level of the participating ICU, a process of "opt-out consent" was prospectively approved by the ethics committee. Accordingly, patients or their next of kin were provided information about the study and given the opportunity to opt-out of the use of their data.

The 0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) trial was a prospective, investigator-initiated, multicenter, blinded, cluster-randomized, double-crossover study conducted in 4 tertiary ICUs in New Zealand.[11] Three study ICUs were adult or mixed (adult and pediatric) general medical and surgical ICUs and 1 ICU had a predominance of cardiothoracic and vascular surgical patients (eMethods in Supplement 2).

A predefined statistical analysis plan was reported[12] and published before study recruitment had been completed.[13] Statistical analyses were conducted at the Australian and New Zealand Intensive Care Research Center.

### Patients

All ICU patients receiving crystalloid fluid therapy as clinically indicated were eligible to be included. Patients who were on renal replacement therapy (RRT) for end-stage renal failure, were currently receiving RRT, or expected to require RRT within 6 hours were excluded. Patients who were admitted to the ICU solely for consideration of organ donation or for palliative care were excluded, as were those who were previously enrolled in the study.

### Study Randomization and Treatment

In New Zealand, there are 2 commercially available buffered crystalloid solutions: compound sodium lactate (Hartmann solution) and PL-148. We chose PL-148 as the comparator to saline in this study because PL-148 was used more commonly than Hartmann solution in the study centers before the trial began. Additional considerations were that the sodium in Hartmann solution contains calcium and was therefore incompatible with blood products preserved in citrate-based anticoagulation solutions, and that Hartmann solution contains more chloride than PL-148.[14] The composition of the study fluids is shown in eTable 1 in Supplement 2.

Participating ICUs were assigned to use blinded study fluid (either saline or buffered crystalloid) for alternating treatment blocks of 7 weeks, with the initial fluid determined by the study statistician using computer-generated randomization. Two ICUs initially used 1 fluid and the other 2 initially used the alternative fluid. Two crossovers occurred so that each ICU used each study fluid twice over the 28 weeks of the study. Study fluids appropriate for each study block were provided in 1000-mL bags labeled "fluid A" or "fluid B." The study fluids were macroscopically indistinguishable. Investigators and clinicians were blind to study fluid allocation for the duration of the study. Patients who remained in the ICU through 1 or more crossover periods continued to use the fluid to which they were originally assigned.

The treating clinician determined the rate and frequency of fluid administration. If possible, crystalloid treatment during investigations and procedures performed outside the ICU was with the assigned study fluid. Open-label saline and buffered crystalloid solution were available for use in situations in which there was a specific clinical indication for either fluid. No restrictions were placed on the use of other fluids or therapies (eMethods in Supplement 2). For the purpose of determining the duration of follow-up, study enrollment (time zero) was defined as the time when study fluid was first administered.

### Outcome Measures

The primary outcome was the proportion of patients with AKI, defined as a degree of renal dysfunction of injury or greater (based on the use of a 5-category scoring system to evaluate risk, injury, failure, loss, and end-stage renal failure [RIFLE]) based solely on defined thresholds of serum

creatinine.[15] The RIFLE system is a validated consensus definition that classifies patients as having different degrees of AKI such that, in brief, a 50% increase in serum creatinine is labeled as "risk," a doubling in serum creatinine is labeled as "injury," a trebling in serum creatinine is labeled as "failure," persistent failure is labeled as "loss," and lack of recovery and need for chronic dialysis is labeled as "end-stage" AKI.[15]

Secondary outcomes within the 90-day follow-up period were the difference between the serum creatinine measured immediately before study enrollment and the peak serum creatinine in the ICU (Δ creatinine); the cumulative incidence of AKI as defined by RIFLE category; the cumulative incidence of AKI solely on defined thresholds of serum creatinine (Kidney Disease: Improved Global Outcomes [KDIGO] criteria)[16]; the use of RRT in the ICU and the requirements for RRT after hospital discharge; the indications for initiation of RRT in the ICU[17]; 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; and ICU and in-hospital all-cause mortality and cause-specific mortality, censored at 90 days after enrollment.

Both the primary outcome and the risk of in-hospital mortality were examined in 5 predefined subgroup pairs. These subgroups were based on Acute Physiology and Chronic Health Evaluation (APACHE) III-j admission diagnoses[18] and the calculated APACHE II illness severity score (ranging from 0-71, with higher scores indicating an increased risk of mortality) in the 24 hours prior to first fluid administration.[19] The subgroups were the presence or absence of each of the following: an admission diagnosis of sepsis, an admission diagnosis of trauma with or without a diagnosis of traumatic brain injury, a cardiac surgical admission diagnosis, and a preenrollment APACHE II score of 25 or higher.

### Statistical Analysis

Because of its cluster randomized, double-crossover design, this study was conducted for a specific period and had no fixed sample size. The trial was partly performed to establish the feasibility of using a cluster randomized, double-crossover design to investigate fluid therapy in the ICU and, as there are no established statistical methodologies for prospectively determining sample sizes for cluster randomized, double-crossover studies with binary outcome variables, we did not perform sample size calculations.

We conducted all analyses on an intention-to-treat basis in accordance with the statistical analysis plan[12,13] and did not impute missing values unless stated. We compared binary outcomes using relative risks (RRs) with 95% CIs and $\chi^2$ tests. Continuous outcomes were compared using mixed linear modeling with results reported as differences or ratios with 95% CIs as appropriate. We compared survival time and the proportion of patients requiring RRT from enrollment to day 90 using log-rank tests and presented these as Kaplan-Meier curves. The volumes of fluids administered were compared using Wilcoxon rank sum tests. Causes of death were compared using a $\chi^2$ test or Fisher exact test when numbers were small. As missing data for the primary outcome exceeded 5%, we performed additional sensitivity analyses to account for extreme case scenarios in accordance with the statistical analysis plan. First, all missing patients were assigned to have AKI and, second, all missing patients were assigned to not have AKI.

For the predefined subgroups, we assessed the primary outcome and in-hospital mortality using the same method implemented in the main analysis and assessed the heterogeneity of treatment effects among subgroup pairs by fitting an interaction between treatment and subgroup.

At the end of the study, all clinicians at each study center were asked to provide their best guess as to whether fluid A was saline or buffered crystalloid solution. The proportion of clinicians who guessed correctly is presented along with the 95% CI for the proportion calculated by the modified Wald method.

All analyses were performed using SAS (SAS Institute), version 9.4. A 2-sided *P* value of .05 or less was considered significant. No adjustment was made for multiple comparisons; therefore, secondary outcomes should be interpreted as exploratory. Additional details of the statistical analyses are outlined in the eMethods in Supplement 2.

## Results

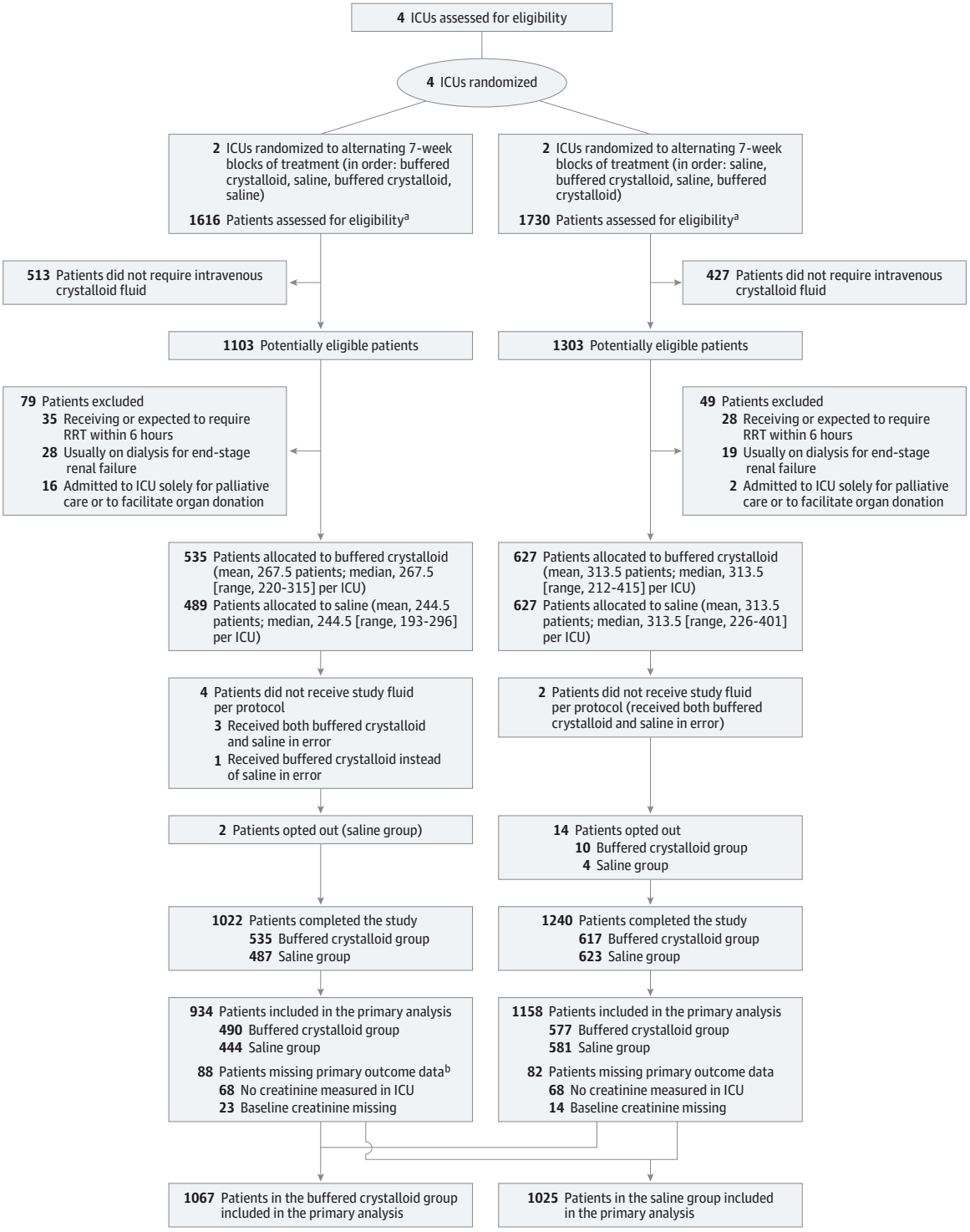
### Patients

From April 2014 through October 2014, all 2278 eligible patients were enrolled, with 1162 patients assigned to the buffered crystalloid group and 1116 assigned to the saline group (**Figure 1**). Of the enrolled patients, 1152 of 1162 patients (99.1%) in the buffered crystalloid group and 1110 of 1116 patients (99.5%) in the saline group were analyzed. The 2 groups of patients had similar baseline characteristics (**Table 1**; eTable 2 in Supplement 2). The mean age of enrolled patients was around 60 years and approximately two-thirds were men. Most patients were admitted to the ICU following elective surgery, most commonly cardiovascular surgery, and relatively few had comorbidities. The mean (SD) APACHE II illness severity scores were 14.1 (6.9) for the buffered crystalloid group and 14.1 (6.7) for the saline group.

### Fluid Therapy

The buffered crystalloid and saline groups received similar volumes of study fluid, (median [IQR], 2000 mL [1000-3500 mL] for buffered crystalloid vs 2000 mL [1000-3250 mL] for saline; *P* = .63) with most fluid administered in the first day in the ICU (eFigure 1 and eFigure 2 in Supplement 2). The volumes of study fluids, open-label saline and buffered crystalloid solution, nonstudy fluids, and blood products administered are shown in eTables 3 to 5 in Supplement 2 along with the proportion of patients who received each of these on each study day. Fifty-five of 87 clinicians (63%) responded to the survey to provide their best guess as to whether fluid A was saline or buffered crystalloid solution. Of these, 36 clinicians (66% [95% CI, 52%-77%]) correctly guessed that fluid A was buffered crystalloid solution.

Figure 1. Flow of Clusters and Participants Through the SPLIT Trial




ICU indicates intensive care unit; RRT, renal replacement therapy; SPLIT, 0.9% Saline vs Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy.

[a] All patients admitted to 1 of the study ICUs during the 28 weeks of recruitment were screened for study enrollment except for 2 patients who decided not to participate in the study prior to ICU admission.

[b] Patients could have both types of missing data.

Table 1. Characteristics of the Patients at Baseline

| Characteristic | No. (%) Buffered Crystalloid (n = 1152) | Saline (n = 1110) |
|---|---|---|
| Age, mean (SD), y | 60.10 (16.79) | 60.95 (16.25) |
| Men | 739 (64) | 746 (67) |
| Weight, mean (SD), kg | 80.4 (20.1) | 80.7 (20.0) |
| Ethnicity | | |
| New Zealand European | 749 (65) | 723 (65) |
| Maori | 116 (10) | 110 (10) |
| Pacific Island peoples | 90 (8) | 91 (8) |
| Other | 197 (17) | 186 (17) |
| Comorbidities | | |
| Chronic respiratory disease | 27 (2) | 30 (3) |
| Chronic cardiovascular disease | 12 (1) | 23 (2) |
| Leukemia/myeloma | 9 (1) | 7 (1) |
| Immunosuppression by disease | 17 (1) | 12 (1) |
| Immunosuppression by therapy | 46 (4) | 50 (5) |
| Hepatic failure | 5 (<1) | 7 (1) |
| Cirrhosis | 8 (1) | 12 (1) |
| Lymphoma | 14 (1) | 5 (<1) |
| AIDS | 1 (<1) | 1 (<1) |
| Metastatic cancer | 25 (2) | 31 (3) |
| Source of admission to ICU | | |
| Operating room | 822 (71) | 798 (72) |
| After elective surgery | 650 (56) | 642 (58) |
| After emergency surgery | 172 (15) | 156 (14) |
| Emergency department | 168 (15) | 148 (13) |
| Hospital floor | 87 (8) | 88 (8) |
| Another hospital (excluding from another ICU) | 43 (4) | 47 (4) |
| Another ICU | 32 (3) | 29 (3) |
| Operative admission diagnoses[a] | 822 (71) | 798 (72) |
| Cardiovascular | 560 (49) | 548 (49) |
| Gastrointestinal | 98 (9) | 87 (8) |
| Gynecological | 6 (1) | 11 (1) |
| Neurological | 38 (3) | 35 (3) |
| Musculoskeletal / skin | 18 (2) | 13 (1) |
| Renal | 17 (1) | 23 (2) |
| Respiratory | 48 (4) | 59 (5) |
| Trauma | 17 (1) | 7 (1) |
| Other postoperative | 20 (2) | 15 (1) |
| Nonoperative admission diagnoses[a] | 330 (29) | 312 (28) |
| Respiratory | 70 (6) | 59 (5) |
| Cardiovascular | 54 (5) | 52 (5) |
| Neurological | 47 (4) | 50 (5) |
| Sepsis | 41 (4) | 43 (4) |
| Metabolic | 40 (3) | 23 (2) |
| Trauma | 40 (3) | 61 (5) |
| Gastrointestinal | 18 (2) | 12 (1) |
| Renal | 4 (<1) | 0 |
| Musculoskeletal/skin | 1 (<1) | 3 (<1) |
| Hematological | 0 | 1 (<1) |
| Other medical diseases | 15 (1) | 8 (1) |
| APACHE II score, mean (SD)[b] | 14.1 (6.9) | 14.1 (6.7) |
| Mechanical ventilation | 768 (67) | 731 (66) |
| Serum creatinine, mg/dL | | |
| Baseline (before illness), mean (SD) | 0.98 (0.76) | 0.99 (0.68) |
| No. of patients | 1133 | 1092 |
| Most recent, mean (SD) | 1.18 (1.00) | 1.15 (1.15) |
| No. of patients | 847 | 820 |
| Time from ICU admission to first fluid, median (IQR), h | 1.17 (0.22-3.80) | 1.25 (0.17-3.50) |
| **Buffered Crystalloid and Saline Administration in the 24 h Before Enrollment** | | |
| Buffered crystalloid | | |
| Fluid volume, median (IQR), mL | 1200 (0-3000) | 1000 (0-3000) |
| Proportion of patients who received fluid | 726 (63) | 675 (61) |
| Saline | | |
| Fluid volume, median (IQR), mL | 0 (0-875) | 0 (0-1000) |
| Proportion of patients who received fluid | 343 (30) | 351 (32) |
| Subgroups[a] | | |
| Sepsis | 41 (4) | 43 (4) |
| Trauma | 40 (3) | 61 (5) |
| Traumatic brain injury | 25 (2) | 32 (3) |
| Cardiac surgery | 475 (41) | 485 (44) |
| APACHE II score ≥25 | 95 (8) | 87 (8) |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range.

SI conversion factor: to convert creatinine to μmol/L, multiply by 88.4.

[a] Diagnostic subgroups and admission diagnoses are based on the APACHE III-j admission diagnostic codes.

[b] Scores on the APACHE II range from 0 to 71, with higher scores indicating an increased risk of death.

## Outcomes

### Primary Outcome

In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4% [95% CI, −2.1% to 2.9%]; RR, 1.04 [95% CI, 0.80 to 1.36]; $P = .77$) (**Table 2**). Primary outcome data were missing for 170 of 2262 patients (7.5%). This was either because no baseline serum creatinine was available in the medical record or because the serum creatinine was not measured in the ICU. The baseline serum creatinine was missing for 19 of 1152 patients (1.6%) in the buffered crystalloid group and 18 of 1110 patients (1.6%) in the saline group, and the peak serum creatinine in the ICU was missing for 68 of 1152 patients (5.9%) in the buffered crystalloid group and 68 of 1110 patients (6.1%) in the saline group. Sensitivity analyses accounting for extreme case scenarios for missing data did not meaningfully alter the results (eTable 6 in Supplement 2).

### Secondary Outcomes

There was no significant difference in the probability of requiring RRT between the buffered crystalloid group and

Table 2. Outcomes for Patients in the Intensive Care Unit Receiving Buffered Crystalloid vs Saline Fluid Therapy

| Variable | No./Total No. (%) | | Absolute Difference (95% CI) | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|---|
| | Buffered Crystalloid | Saline | | | |
| **Primary Outcome** | | | | | |
| Acute kidney injury or failure[a] | 102/1067 (9.6) | 94/1025 (9.2) | 0.4 (−2.1 to 2.9) | 1.04 (0.80 to 1.36) | .77 |
| **Secondary Outcomes (Renal Outcomes)** | | | | | |
| RIFLE[b] | | | | | |
| Risk | 123/1067 (11.5) | 107/1025 (10.4) | 1.1 (−1.6 to 3.8) | 1.10 (0.86 to 1.41) | .44 |
| Injury | 46/1067 (4.3) | 57/1025 (5.6) | −1.2 (−3.1 to 0.6) | 0.78 (0.53 to 1.13) | .19 |
| Failure | 54/1067 (5.1) | 36/1025 (3.5) | 1.5 (−0.2 to 3.3) | 1.44 (0.95 to 2.18) | .09 |
| Loss | 2/1067 (0.2) | 1/1025 (0.1) | 0 | 1.92 (0.17 to 21.16) | >.99 |
| End-stage renal failure | 0/1067 (0) | 0/1025 (0) | | | |
| KDIGO stage[c] | | | | | |
| 1 | 194/1067 (18.2) | 194/1025 (18.9) | −0.7 (−4.1 to 2.6) | 0.96 (0.80 to 1.15) | .69 |
| 2 | 43/1067 (4.0) | 46/1025 (4.5) | −0.5 (−2.2 to 1.3) | 0.90 (0.60 to 1.4) | .67 |
| 3 | 62/1067 (5.8) | 58/1025 (5.7) | 0.2 (−1.8 to 2.1) | 1.03 (0.73 to 1.45) | .93 |
| RRT use and indications for RRT initiation | | | | | |
| RRT use | 38/1152 (3.3) | 38/1110 (3.4) | −0.1 (−1.6 to 1.4) | 0.96 (0.62 to 1.50) | .91 |
| Oliguria | 10/1152 (0.9) | 11/1110 (1.0) | −0.1 (−0.9 to 0.7) | 0.88 (0.37 to 2.05) | .83 |
| Hyperkalemia with serum potassium >6.5 mEq/L | 4/1152 (0.3) | 2/1110 (0.2) | 0.2 (−0.3 to 0.6) | 1.93 (0.35 to 10.50) | .69 |
| Acidemia with pH <7.20 | 13/1152 (1.1) | 9/1110 (0.8) | 0.3 (−0.5 to 1.1) | 1.39 (0.60 to 3.24) | .52 |
| Serum urea nitrogen >70 mg/dL | 5/1152 (0.4) | 10/1110 (0.9) | −0.5 (−1.1 to 0.2) | 0.48 (0.17 to 1.41) | .20 |
| Serum creatinine >3.39 mg/dL | 16/1152 (1.4) | 13/1110 (1.2) | 0.2 (−0.7 to 1.1) | 1.19 (0.57 to 2.45) | .71 |
| Organ edema | 6/1152 (0.5) | 11/1110 (1.0) | −0.5 (−1.2 to 0.2) | 0.53 (0.20 to 1.42) | .23 |
| Other renal failure-related indication | 3/1152 (0.3) | 9/1110 (0.8) | −0.6 (−1.2 to 0.1) | 0.32 (0.09 to 1.18) | .09 |
| Other non-renal failure-related indication | 0/1152 (0) | 2/1110 (0.2) | −0.2 (−0.4 to 0.1) | | .24 |
| Ongoing use after hospital discharge | 0/1152 (0) | 0/1110 (0) | | | |
| Δ Creatinine, mean (95% CI), mg/dL[d] | 0.21 (0.16 to 0.25) | 0.18 (0.13 to 0.23) | 0.03 (−0.04 to 0.10)[e] | | .42 |
| Service utilization, geometric mean (95% CI) | | | | | |
| ICU, d | 1.50 (1.41 to 1.60) | 1.47 (1.39 to 1.57) | 1.02 (0.94 to 1.11)[f] | | .58 |
| Hospital, d | 7.45 (7.05 to 7.87) | 7.33 (6.94 to 7.76) | 1.01 (0.94 to 1.10)[f] | | .72 |
| Mechanical ventilation, h | 15.32 (13.83 to 16.97) | 14.24 (12.82 to 15.82) | 1.05 (0.91 to 1.21)[f] | | .48 |
| Use of mechanical ventilation | 790/1152 (68.6) | 751/1110 (67.7) | 0.9 (−2.9 to 4.8) | 1.01 (0.96 to 1.07) | .65 |
| ICU readmission required during index hospital admission | 80/1152 (6.9) | 57/1110 (5.1) | 1.8 (−0.2 to 3.8) | 1.35 (0.97 to 1.88) | .08 |
| Mortality | | | | | |
| Death in ICU | 76/1152 (6.6) | 80/1110 (7.2) | −0.6 (−2.7 to 1.5) | 0.92 (0.68 to 1.24) | .62 |
| Death in hospital | 87/1152 (7.6) | 95/1110 (8.6) | −1.0 (−3.3 to 1.2) | 0.88 (0.67 to 1.17) | .40 |

Abbreviations: ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, risk, injury, failure, loss, end-stage renal failure; RRT, renal replacement therapy.

SI conversion factors: to convert creatinine to μmol/L, multiply by 88.4; urea nitrogen to mmol/L, multiply by 0.357.

[a] Based on serum creatinine levels in accordance with RIFLE criteria.

[b] RIFLE categories: risk (1.5-1.9 times increase from baseline serum creatinine), injury (2-2.9 times increase from baseline serum creatinine), failure (≥3 times increase from baseline serum creatinine or increase in serum creatinine to ≥3.96 mg/dL with a rise of ≥0.5 mg/dL), loss (persistent loss of kidney function for >4 wk), end-stage renal failure (dialysis-dependent for >3 mo).

[c] KDIGO stages: stage 1, 1.5 to 1.9 times increase from baseline serum creatinine or 0.3 mg/dL or higher increase in serum creatinine; stage 2, 2 to 2.9 times increase from baseline serum creatinine; stage 3, 3 times or higher increase or increase in serum creatinine to 4 mg/dL or higher or start of RRT.

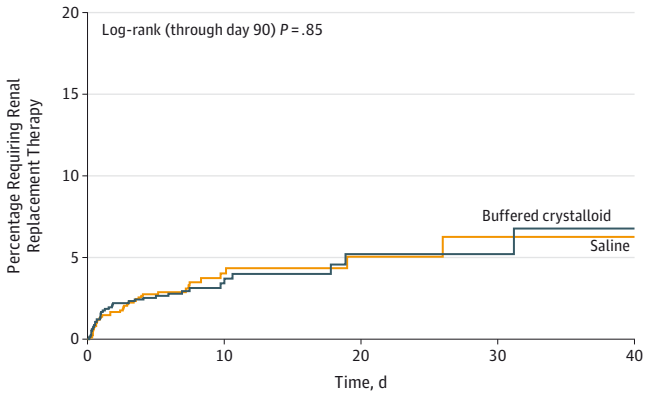
[d] Difference between the most recent preenrollment serum creatinine level and the peak serum creatinine level measured in the ICU up until day 90.

[e] This value is the mean difference (95% CI).

[f] This value is the ratio of geometric means (95% CI).

the saline group 90 days after enrollment (*P* = .85) (**Figure 2**). There was, however, a significant interaction between the effect of treatment on AKI and study site (*P* = .05) (**Figure 3**). There was no significant heterogeneity in the effect of treatment on AKI or failure in any of the predefined subgroups (Figure 3). RRT was used in 38 of 1152 patients (3.3%) receiving buffered crystalloid and 38 of 1110 patients (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) (Table 2). The indications for initiation of RRT were similar between the groups

**Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial**

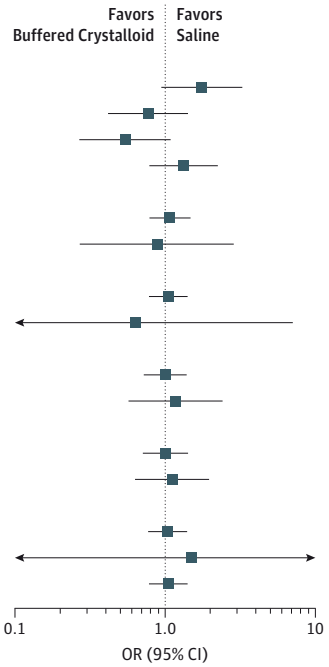



| No. at risk | | | | | |
|---|---|---|---|---|---|
| Buffered crystalloid | 1152 | 341 | 134 | 62 | 36 |
| Saline | 1110 | 310 | 124 | 64 | 28 |

Censoring applied at hospital discharge or death. The x-axis is truncated at 40 days because the number of participants still in follow-up beyond 40 days is small.

**Figure 3. Risk of Acute Kidney Injury by Subgroup for Patients Admitted to the Intensive Care Unit Receiving Buffered Crystalloid vs Saline Fluid Therapy**

| Subgroup | No. of Individuals: Buffered Crystalloid | No. of Individuals: Saline | No. of Events (%): Buffered Crystalloid | No. of Events (%): Saline | OR (95% CI) | *P* Value | *P* Value for Interaction |
|---|---|---|---|---|---|---|---|
| Location | | | | | | | |
| ICU 1 | 190 | 204 | 29 (15.3) | 19 (9.3) | 1.75 (0.95-3.25) | .07 | .05 |
| ICU 2 | 387 | 378 | 20 (5.2) | 25 (6.6) | 0.77 (0.42-1.41) | .40 | |
| ICU 3 | 200 | 169 | 15 (7.5) | 22 (13.0) | 0.54 (0.27-1.08) | .08 | |
| ICU 4 | 290 | 274 | 38 (13.1) | 28 (10.2) | 1.32 (0.79-2.23) | .29 | |
| Sepsis | | | | | | | |
| No | 1032 | 983 | 95 (9.2) | 85 (8.6) | 1.07 (0.79-1.46) | .67 | .82 |
| Yes | 35 | 42 | 7 (20.0) | 9 (21.4) | 0.89 (0.27-2.86) | .84 | |
| Trauma | | | | | | | |
| No | 1034 | 977 | 101 (9.8) | 91 (9.3) | 1.05 (0.78-1.41) | .76 | .51 |
| Yes | 33 | 48 | 1 (3.0) | 3 (6.3) | 0.63 (0.06-7.07) | .70 | |
| APACHE II | | | | | | | |
| <25 | 985 | 946 | 77 (7.8) | 74 (7.8) | 1.00 (0.72-1.39) | >.99 | .54 |
| ≥25 | 82 | 79 | 25 (30.5) | 20 (25.3) | 1.18 (0.57-2.41) | .65 | |
| Cardiac surgery | | | | | | | |
| No | 597 | 547 | 76 (12.7) | 70 (12.8) | 1.00 (0.71-1.42) | .99 | .75 |
| Yes | 470 | 478 | 26 (5.5) | 24 (5.0) | 1.11 (0.63-1.96) | .72 | |
| TBI | | | | | | | |
| No | 1045 | 1000 | 101 (9.7) | 93 (9.3) | 1.04 (0.77-1.40) | .79 | .91 |
| Yes | 22 | 25 | 1 (4.5) | 1 (4.0) | 1.50 (0.09-26.00) | .78 | |
| **Overall** | 1067 | 1025 | 102 (9.6) | 94 (9.2) | 1.05 (0.78 -1.41) | .76 | |

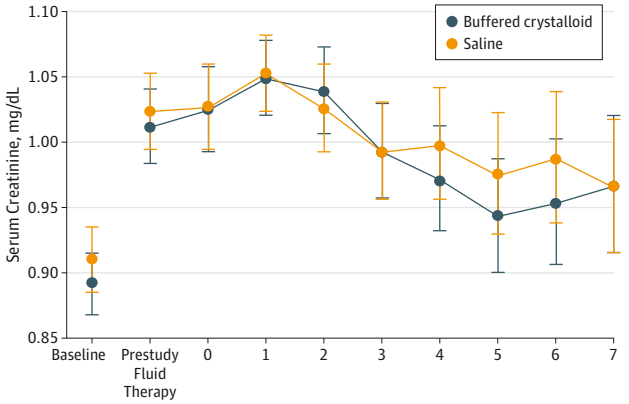



OR indicates odds ratio.

and there was no significant between-group difference in Δ creatinine, daily serum creatinine to day 7 (**Figure 4**), or the rates of AKI based on the RIFLE and KDIGO classifications (Table 2). No patient in either group required RRT after hospital discharge.

There were no significant between-group differences in service utilization (days in the ICU, days in the hospital, use or duration of mechanical ventilation, and requirement for ICU readmission) (Table 2). There were no significant between-group differences in the rates of death in the ICU or in the hospital or in the cause-specific mortality within the 90-day follow-up period (eTable 7 in Supplement 2). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95% CI, −3.3% to 1.2%]; RR, 0.88 [95% CI, 0.67 to 1.17]; *P* = .40) (Table 2). There was

Figure 4. Daily Serum Creatinine for the Buffered Crystalloid vs Saline Groups[a]




| No. of patients | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Saline | 1092 | 820 | 503 | 947 | 442 | 272 | 184 | 135 | 110 | 100 |
| Buffered crystalloid | 1133 | 847 | 481 | 992 | 478 | 297 | 200 | 144 | 112 | 94 |

[a] Day 0 is the day of enrollment. The baseline creatinine was defined as lowest serum creatinine in the hospital laboratory records for the 6 months prior to intensive care unit admission. The prestudy fluid therapy creatinine was defined as the most recent measurement of serum creatinine taken in the 24 hours prior to the commencement of study fluid. Censoring applied at hospital discharge or death. Serum creatinine values are approximated by a log-normal distribution so results are presented as geometric means. The error bars indicate 95% CIs.

no significant difference in the probability of survival between the buffered crystalloid group and the saline group (eFigure 3 in Supplement 2). There was no significant heterogeneity in the effect of treatment on in-hospital mortality up to day 90 in any of the predefined subgroups (eFigure 4 in Supplement 2). The main results were similar after adjustment for baseline covariates and when nested within individual sites (eTable 8 in Supplement 2).

There was 1 reported serious adverse event that was judged by a site principal investigator to be potentially related to study treatment. This serious adverse event occurred in a patient who was admitted to the ICU following a renal transplant and assigned to the buffered crystalloid group. This patient developed lactic acidosis and progressive multiorgan failure culminating in circulatory collapse and death. No specific cause of death was identified at autopsy.

## Discussion

In this cluster randomized, double-crossover trial, there was no significant difference in the primary outcome of incidence of AKI or failure within 90 days after enrollment in a heterogenous population of ICU patients who received a buffered crystalloid or saline for crystalloid fluid therapy. There was no significant difference in the key secondary outcome, use of RRT, between treatment groups; no patients in either treatment group required RRT after hospital discharge. There was no significant difference in in-hospital mortality between treatment groups.

Our results are consistent with a retrospective study of nonsurgical patients with sepsis in which there was no significant association between use of balanced vs unbalanced crystalloids and acute renal failure.[6] In contrast, our results were at variance to a previous observational cohort study in which removing chloride-rich fluids from a single ICU was associated with a reduction in the incidence of AKI and reduced requirements for RRT.[3] However, in this study there were differences in albumin use in the phases before and after treatment and 1 of the fluids, of which its use was discontinued, was a synthetic gelatin-based colloid. The use of gelatins has previously been associated with an increased risk of AKI in patients with sepsis.[20] A retrospective study of patients undergoing major abdominal surgery that used multivariate logical regression and a propensity score reported that saline was associated with a significant reduction in major postoperative complications compared with buffered crystalloid solutions.[5] Although this study did not demonstrate a significant increase in the risk of renal complications, saline use was associated with an increased risk of requiring dialysis compared with buffered crystalloid solutions.[5]

Compared with previous observational studies, our trial design incorporated a number of features that reduce the risk of bias. We published our statistical analysis plan before completing recruitment to mitigate analysis bias.[12,13] Study fluids were labeled only as fluid A and fluid B to mitigate ascertainment bias. Despite blinding, however, by the end of the study, two-thirds of clinicians were able to correctly guess the assigned treatment. Saline use is associated with the development of hyperchloremia and metabolic acidosis,[10] and the occurrence of these phenomena may have led clinicians to correctly deduce which fluid was which over the course of a block of treatment. Although this may potentially have led to ascertainment bias, we did not detect any major differences in co-interventions between treatment groups. Furthermore, because our primary end point was derived from serum creatinine measurements, it is not subject to observer bias. Although allocation of patients to fluid A or fluid B within a particular treatment block was not concealed, the risk of selection bias was negligible because 99.3% of all eligible patients were included in the study and analyzed. Our study was conducted in 4 New Zealand centers potentially reducing the external validity of our study findings. However, one notable feature of our trial is that all patients admitted to the ICU who received crystalloid fluid therapy were eligible for study participation except for those

with established renal failure and those patients admitted to the ICU for palliative care. Our findings were consistent with a treatment effect that lies between a relative decrease of 20% and a relative increase of 36% in AKI arising from use of a buffered crystalloid for crystalloid fluid therapy instead of saline. Although we demonstrated a significant interaction between study treatment and study center, we are not aware of any variations in care or differences in patient population between sites that are likely to have accounted for this and consider it as most likely a chance finding.

The most important limitation of our study is that we did not perform sample size calculations. An additional limitation is that more than 90% of patients were exposed to intravenous fluids before enrollment and the majority of preenrollment fluid was buffered crystalloid. Although the CIs around the point estimate of treatment effect in relation to the risk of AKI did not encompass the large treatment effect suggested by previous observational studies, the CIs were wide and the possibility of a clinically significant effect on AKI was not excluded by this exploratory study. Moreover, because we studied a heterogeneous population with an overall low incidence of AKI, our findings do not preclude the possibility of significant beneficial or harmful renal effects from using buffered crystalloids in higher-risk groups. Although the volumes of fluids administered to patients were small, they were similar to those administered in the Crystalloid vs Hydroxyethyl Starch Trial (CHEST),[21] which demonstrated, in a population with similar baseline serum creatinine levels to ours, that the use of hydroxyethyl starch for fluid resuscitation in patients who were critically ill significantly increased RRT use compared with saline.

Our study did not exclude the possibility of a clinically important increase or decrease in the risk of in-hospital mortality with the use of buffered crystalloid solutions compared with saline. We studied a heterogeneous population of patients who were critically ill with a low overall mortality. However, our data were consistent with a treatment effect that lies between a relative decrease of 33% and a relative increase of 17% in in-hospital mortality arising from the use of a buffered crystalloid instead of saline. The observed point estimate of a 12% RR reduction in in-hospital mortality, which did not differ significantly in 5 predefined subgroup pairs, provides new information that will inform the design of a pivotal randomized clinical trial designed to definitively establish the relative safety and efficacy of a buffered crystalloid solution and saline in ICU patients requiring intravenous fluid therapy.

## Conclusions

Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI. Further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality.

### ARTICLE INFORMATION

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## REFERENCES

1. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369(13):1243-1251.

2. Finfer S, Liu B, Taylor C, et al; SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*. 2010;14(5):R185.

3. 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;308(15):1566-1572.

4. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2015;41(2):257-264.

5. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255(5):821-829.

6. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. *Crit Care Med*. 2014;42(7):1585-1591.

7. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med*. 2014;40(12):1897-1905.

8. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- vs low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg*. 2015;102(1):24-36.

9. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24.

10. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. *Crit Care*. 2010;14(4):226.

11. Reddy SK, Bailey MJ, Beasley RW, et al. A protocol for the 0.9% saline vs Plasma-Lyte 148 for intensive care fluid therapy (SPLIT) study. *Crit Care Resusc*. 2014;16(4):274-279.

12. Reddy SK, Young PJ, Beasley RW, et al. Overview of the study protocols and statistical analysis plan for the Saline vs Plasma-Lyte 148 for Intravenous Fluid Therapy (SPLIT) research program. *Crit Care Resusc*. 2015;17(1):29-36.

13. Young P, Bailey M, Beasley R, et al. The statistical analysis plan for the 0.9% Saline vs Plasma-Lyte 148 for Intensive care fluid Therapy (SPLIT) study. http://wellingtonicu.com/Data/Trials/SPLITSAP.pdf. Accessed April 13, 2015.

14. Young PJ, Joannidis M. Crystalloid fluid therapy: is the balance tipping towards balanced solutions? *Intensive Care Med*. 2014;40(12):1966-1968.

15. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy, and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. *Crit Care*. 2004;8(4):R204-R212.

16. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care*. 2013;17(1):204.

17. Bellomo R, Cass A, Cole L, et al; RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627-1638.

18. Pilcher D, Hicks P, Slater A, Huckson S, O'Sullivan E. APD data dictionary for software programmers. http://www.anzics.com.au/Downloads/ANZICS%20APD%20Dictionary%20V4_Programmer.pdf. Accessed April 20, 2015.

19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.

20. Bayer O, Reinhart K, Sakr Y, et al. Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. *Crit Care Med*. 2011;39(6):1335-1342.

21. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.