

## 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  $\geq 3.96$  mg/dL with an increase of  $\geq 0.5$  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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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.<sup>1</sup> Globally, 0.9% sodium chloride (saline) is the most commonly used resuscitation fluid.<sup>2</sup> However, despite its widespread use, emerging data provide uncertainty about the safety of saline in patients who are critically ill.<sup>3-7</sup>

Most concern has focused on the hypothesis that the high chloride content of saline contributes to the development of acute kidney injury (AKI).<sup>3,4,8</sup> 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<sup>3,4,8</sup> and of death compared with saline.<sup>6,7</sup> Although it is biologically plausible that saline worsens renal function compared with buffered crystalloids,<sup>9,10</sup> 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<sup>11</sup> (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.<sup>11</sup> 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<sup>12</sup> and published before study recruitment had been completed.<sup>13</sup> Sta-

tistical 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 Hartmann solution contains calcium and is therefore incompatible with blood products preserved in citrate-based anticoagulation solutions, and that Hartmann solution contains more chloride than PL-148.<sup>14</sup> 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.<sup>15</sup> 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.<sup>15</sup>

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 ( $\Delta$  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)<sup>16</sup>; the use of RRT in the ICU and the requirements for RRT after hospital discharge; the indications for initiation of RRT in the ICU<sup>17</sup>; 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<sup>18</sup> 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.<sup>19</sup> 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<sup>12,13</sup> 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

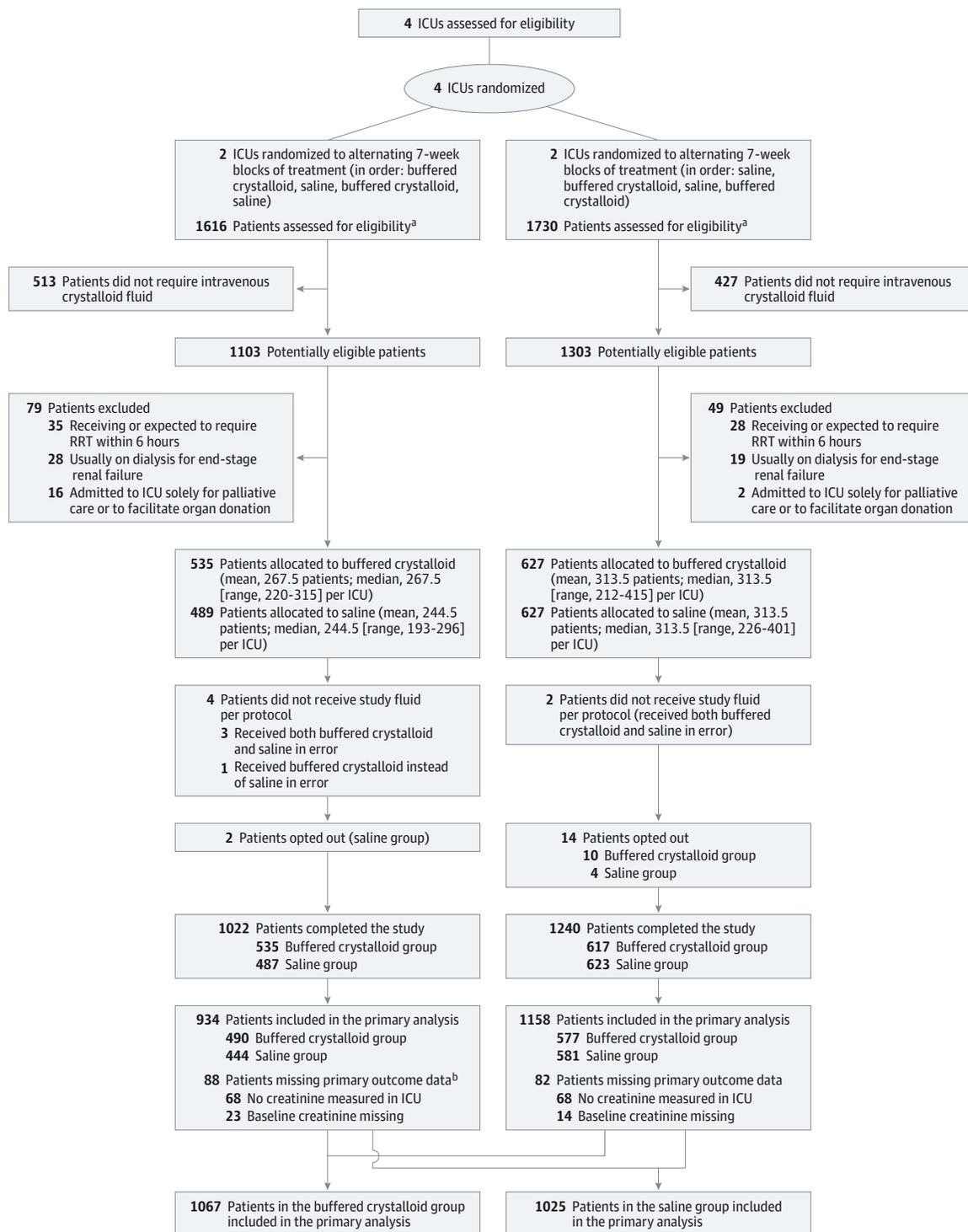
### Patients

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.

<sup>a</sup> 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.

<sup>b</sup> 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 <sup>a</sup>	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 <sup>a</sup>	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)

(continued)

Table 1. Characteristics of the Patients at Baseline (continued)

Characteristic	No. (%)	
	Buffered Crystalloid (n = 1152)	Saline (n = 1110)
APACHE II score, mean (SD) <sup>b</sup>	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)
<b>Buffered Crystalloid and Saline Administration in the 24 h Before Enrollment</b>		
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 <sup>a</sup>		
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 $\geq 25$	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  $\mu\text{mol/L}$ , multiply by 88.4.

<sup>a</sup> Diagnostic subgroups and admission diagnoses are based on the APACHE III-j admission diagnostic codes.

<sup>b</sup> 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			
<b>Primary Outcome</b>					
Acute kidney injury or failure <sup>a</sup>	102/1067 (9.6)	94/1025 (9.2)	0.4 (-2.1 to 2.9)	1.04 (0.80 to 1.36)	.77
<b>Secondary Outcomes (Renal Outcomes)</b>					
<b>RIFLE<sup>b</sup></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)			
<b>KDIGO stage<sup>c</sup></b>					
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
<b>RRT use and indications for RRT initiation</b>					
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 <sup>d</sup>	0.21 (0.16 to 0.25)	0.18 (0.13 to 0.23)	0.03 (-0.04 to 0.10) <sup>e</sup>		.42
<b>Service utilization, geometric mean (95% CI)</b>					
ICU, d	1.50 (1.41 to 1.60)	1.47 (1.39 to 1.57)	1.02 (0.94 to 1.11) <sup>f</sup>		.58
Hospital, d	7.45 (7.05 to 7.87)	7.33 (6.94 to 7.76)	1.01 (0.94 to 1.10) <sup>f</sup>		.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) <sup>f</sup>		.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
<b>Mortality</b>					
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.

<sup>a</sup> Based on serum creatinine levels in accordance with RIFLE criteria.

<sup>b</sup> 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).

<sup>c</sup> 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.

<sup>d</sup> Difference between the most recent preenrollment serum creatinine level and the peak serum creatinine level measured in the ICU up until day 90.

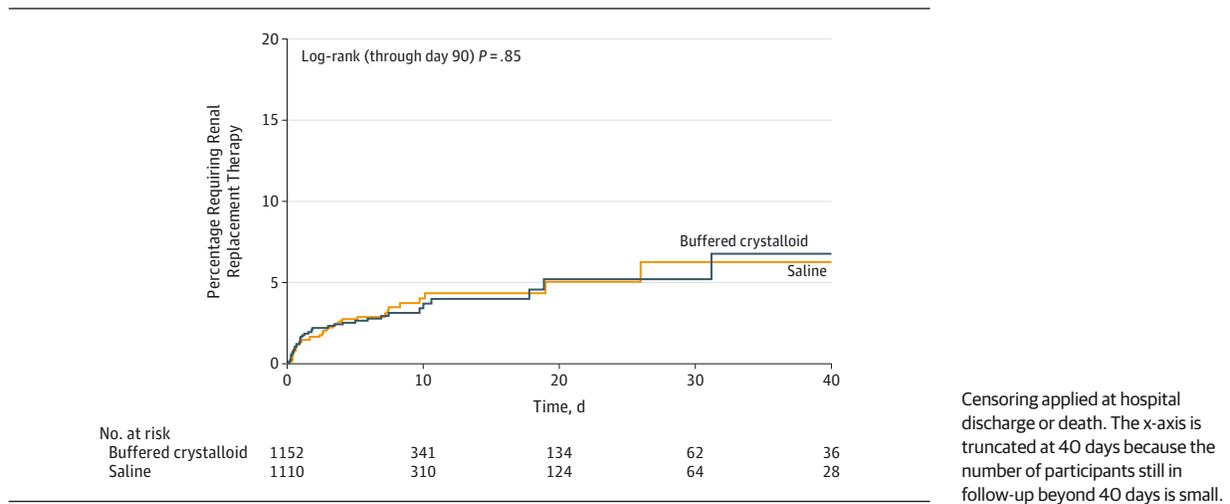
<sup>e</sup> This value is the mean difference (95% CI).

<sup>f</sup> This value is the ratio of geometric means (95% CI).

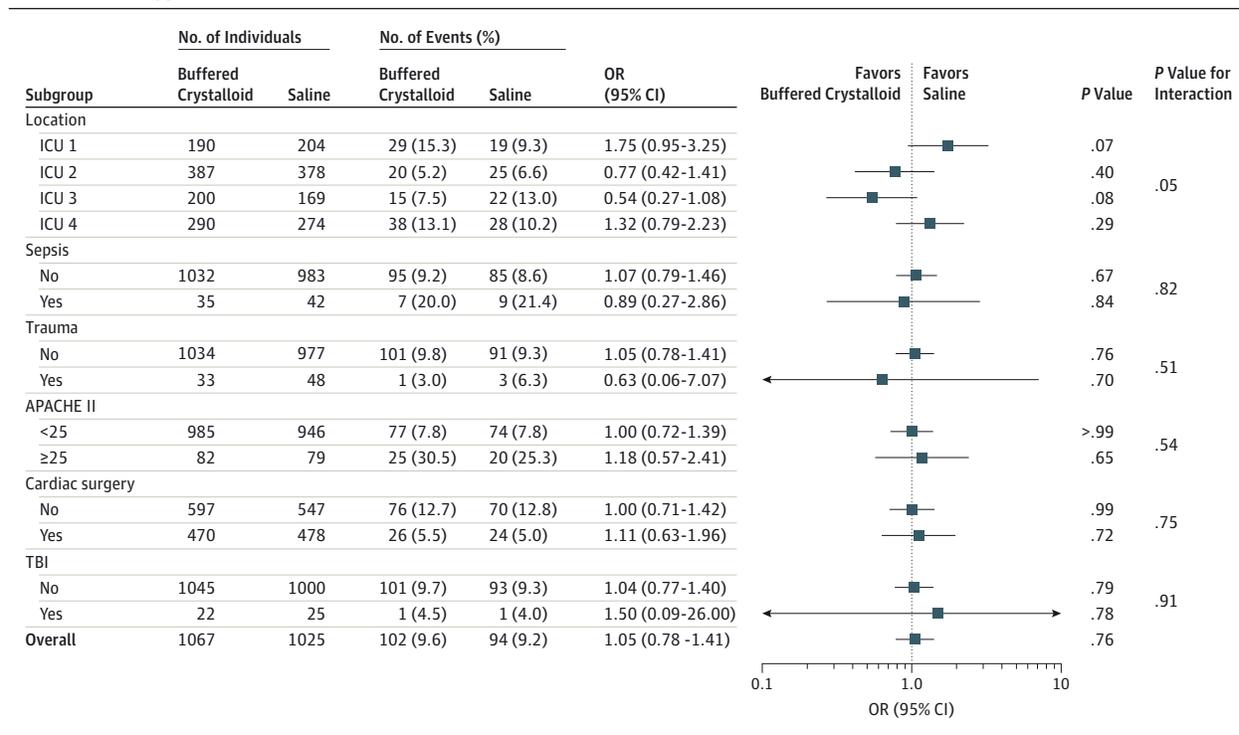
the saline group 90 days after enrollment ( $P = .85$ ) (Figure 2). There was, however, a significant interaction between the effect of treatment on AKI and study site ( $P = .05$ ) (Figure 3). There was no significant heterogeneity in the effect of treatment on AKI or failure in any of the predefined 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**



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



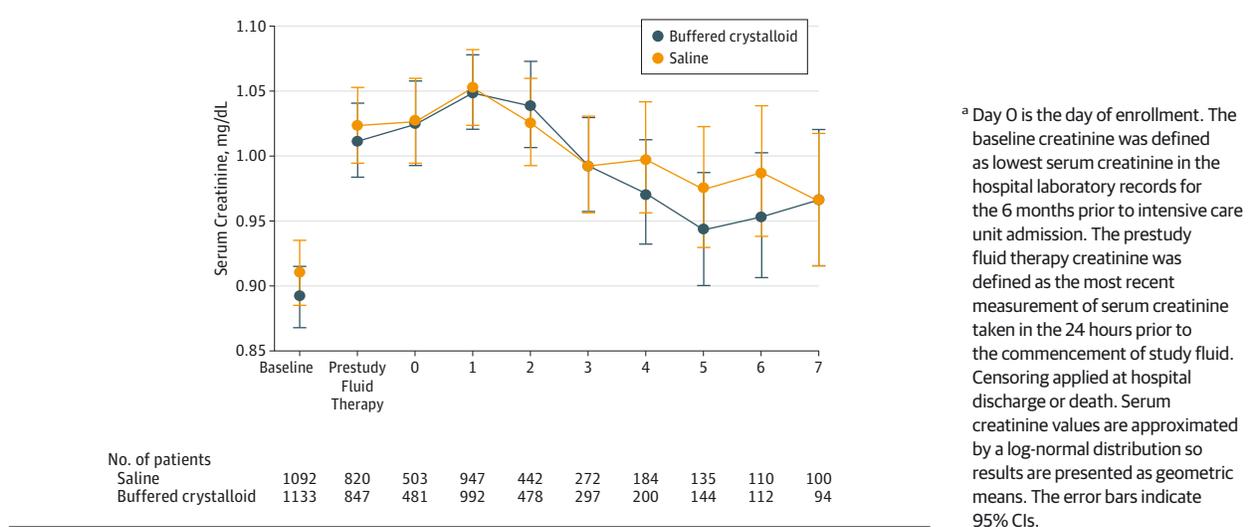
OR indicates odds ratio.

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<sup>a</sup>



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 heterogeneous 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 non-surgical patients with sepsis in which there was no significant association between use of balanced vs unbalanced crystalloids and acute renal failure.<sup>6</sup> 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.<sup>3</sup> However, in this study there were dif-

ferences 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.<sup>20</sup> 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 increase in major post-operative complications compared with buffered crystalloid solutions.<sup>5</sup> 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.<sup>5</sup>

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.<sup>12,13</sup> 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,<sup>10</sup> 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 pre-enrollment 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),<sup>21</sup> which demonstrated, in a population with similar baseline serum creati-

nine 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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