ORIGINAL ARTICLE

Balanced Fluid or 0.9% Saline in Children Treated for Septic Shock

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ABSTRACT

BACKGROUND

Whether treatment with balanced crystalloid fluid leads to better outcomes than 0.9% saline in children treated for septic shock is debated.

METHODS

In this pragmatic clinical trial conducted at 47 emergency departments in five countries, patients (2 months to <18 years of age) with suspected septic shock and abnormal perfusion were randomly assigned to receive fluid resuscitation with either balanced fluid or 0.9% saline for up to 48 hours. The primary outcome was a major adverse kidney event (a composite of death, new renal-replacement therapy, or persistent kidney dysfunction) at 30 days after enrollment or hospital discharge, whichever occurred first.

RESULTS

Of 9041 enrolled patients, 277 (6.1%) in the balanced-fluid group and 282 (6.2%) in the 0.9%-saline group withdrew from the trial, leaving 4235 and 4247 patients, respectively, for analysis. A primary-outcome event occurred in 137 patients (3.4%) in the balanced-fluid group and in 124 (3.0%) in the 0.9%-saline group (difference, 0.4 percentage points; 95% confidence interval [CI], −0.5 to 1.3; risk ratio, 1.10; 95% CI, 0.88 to 1.40; P=0.85). The median number of hospital-free days during 28 days after enrollment was 23 (interquartile range, 19 to 25) in both groups. Hyperchloremia occurred in 868 patients (31.4%) in the balanced-fluid group and in 1383 (49.0%) in the 0.9%-saline group; hypernatremia in 52 (1.8%) and 89 (3.1%), respectively; and hyperlactatemia in 260 (19.8%) and 228 (16.7%). No differences in other safety outcomes or adverse events were seen.

CONCLUSIONS

Among children treated for septic shock, no significant difference was seen in the incidence of death, new renal-replacement therapy, or persistent kidney dysfunction when fluid resuscitation was administered with balanced fluid as compared with 0.9% saline. (Funded by Eunice Kennedy Shriver National Institute of Child Health and Human Development and others; PRoMPT BOLUS ClinicalTrials.gov number, NCT04102371.)

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Crystalloid fluid is commonly used to resuscitate children with septic shock.[1] Options for crystalloids include 0.9% sodium chloride (saline) or balanced fluid, such as lactated Ringer's solution or Plasma-Lyte. Despite its widespread use,[2,3] 0.9% saline contains a supraphysiologic concentration of chloride that is associated with hyperchloremia, metabolic acidosis, and decreased renal blood flow.[4,5] In contrast, balanced fluid has an electrolyte composition that more closely resembles that of human plasma[6] and has been shown to be associated with lower frequencies of acute kidney injury, receipt of renal-replacement therapy, and death than 0.9% saline in some studies involving adults[7-14] and in some involving children.[15-17] However, other studies have shown that balanced fluid does not provide any benefit[18-22] or is associated with harm.[23] Consequently, the Surviving Sepsis Campaign issued a conditional recommendation for treatment with balanced fluids over 0.9% saline in children with septic shock.[24]

To determine whether resuscitation with balanced fluid would result in a lower frequency of major adverse kidney events within 30 days than resuscitation with 0.9% saline in children treated for septic shock, we conducted the Pragmatic Pediatric Trial of Balanced versus Normal Saline Fluid in Sepsis (PRoMPT BOLUS). We hypothesized that resuscitation and maintenance hydration with balanced fluid would lead to a lower incidence of major adverse kidney events within 30 days than that with 0.9% saline.

Methods

Trial Design and Oversight

We conducted a multicenter, pragmatic, open-label, interventional trial in which children with suspected septic shock treated in an emergency department between August 25, 2020, and October 31, 2025, were randomly assigned to receive either balanced crystalloid fluid or 0.9% saline for resuscitation and maintenance hydration. The trial was conducted at 47 sites from the Pediatric Emergency Care Applied Research Network (PECARN) in the United States, the Pediatric Emergency Research Canada (PERC) network in Canada, the Pediatric Research in Emergency Departments International Collaborative (PREDICT) in Australia and New Zealand, and in Costa Rica. A data and safety monitoring board oversaw the trial. Regulatory oversight of human subjects was conducted separately within each country (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol showed feasibility in a pilot trial,[25] and methodologic details were published previously.[26] The protocol and statistical analysis plan are available at NEJM.org. An international steering committee oversaw all trial activities, including data collection, and vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Patients

Children (2 months to <18 years of age) with suspected septic shock who were being treated with fluid resuscitation for abnormal perfusion in an emergency department were eligible for enrollment if the total volume of crystalloid fluid administered before enrollment was confirmed as 40 ml per kilogram of body weight or less. All the clinicians in the participating emergency departments screened patients during routine care, but only those trained regarding trial procedures could enroll patients. Patients who met the eligibility criteria could be enrolled at any time before leaving the emergency department through either discharge or admission to the hospital. Eligible patients could be enrolled more than once. Patients were excluded if the treating clinician determined that administration of either fluid type would be unsafe (see the Supplementary Appendix for additional details).

Because of the narrow therapeutic window to begin fluid resuscitation, enrollment adhered to the Exception from Informed Consent Requirements for Emergency Research of the Code of Federal Regulations (21 CFR 50.24) in the United States[27] and to ethically approved alternative processes to prospective informed consent in Australia, Canada, Costa Rica, and New Zealand.[28,29] Additional details are provided in the Supplementary Appendix.

Randomization

Trial patients were assigned to receive either balanced fluid or 0.9% saline. Randomization was performed with a permuted-block method, with stratification according to site (see the Supplementary Appendix). Treatment assignment was concealed with the use of serially numbered, opaque envelopes for efficiency of enrollment concurrent

with clinical management. Fluid-type assignment was revealed after eligibility was confirmed and the patient was enrolled.

INTERVENTION

We compared treatment with a predominantly balanced fluid and treatment with 0.9% saline, acknowledging that routine care often includes multiple fluid types (Fig. S1 in the Supplementary Appendix). Balanced fluids could be lactated Ringer's solution, Plasma-Lyte, or Hartmann's solution, depending on availability or clinician preference (Table S1). The assigned trial fluid was preferentially used for all fluid administered as a bolus and as the base fluid for maintenance hydration until 11:59 p.m. on the day after trial enrollment (Table S2). The end of the intervention phase was timed to ensure that all patients would receive trial fluid for 24 to 48 hours, which is the duration of most fluid resuscitations for septic shock and which provided a pragmatic end to the intervention phase.[14]

Each site established procedures to promote protocol adherence (see the Supplementary Appendix). Other than fluid type, all decisions regarding the timing and rate of fluid administration and the volume of fluid remained at the discretion of the treating clinicians. Alternative fluid types were allowed for clinical indications (e.g., hyponatremia). Maintenance fluids were included because they constitute a substantial proportion of total crystalloid fluid administration.[25,30] Nonisotonic fluids (e.g., 0.45% saline) are not recommended as maintenance fluid in children and were discouraged.[31,32] Hospital fluid supplies were used without changes to labeling.

Patients and clinicians were aware of treatment assignment as a practical necessity and to reduce the risk that clinicians might attribute electrolyte changes to the trial fluid and stop adhering to the protocol. However, the senior biostatistician and all the investigators remained unaware of the aggregate outcomes until enrollment was complete.

DATA COLLECTION

Data obtained during clinical care were extracted from the medical record (see the Supplementary Appendix) and monitored for quality within the PECARN, PERC, and PREDICT networks. A central data coordinating center at Children's Hospital of Philadelphia collated the data across networks for interim and final analyses. The site of infection and diagnosis of septic shock were ascertained by the lead investigator at each site with all available data. Acute kidney injury at presentation was determined with the use of thresholds for serum creatinine level recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[33,34]

OUTCOMES

The primary outcome was a major adverse kidney event — defined as a composite of death from any cause, initiation of renal-replacement therapy, or persistent kidney dysfunction — within 30 days after trial enrollment or hospital discharge, whichever occurred first.[35] Patients were considered to have had a primary-outcome event if they met one or more criteria for a major adverse kidney event. Renal-replacement therapy included treatment with any renal-replacement method that was started during the hospitalization. Persistent kidney dysfunction was defined as a final serum creatinine level at least 200% of that at baseline and a minimum increase of at least 0.3 mg per deciliter. The baseline serum creatinine level was recorded as the lowest value available between 12 months and 24 hours before enrollment. If such data were unavailable, the baseline level was imputed according to median creatinine values for age and sex (see the Supplementary Appendix).[36]

Secondary effectiveness outcomes included the components of the primary outcome, length of hospital stay, number of hospital-free days during the 28 days after enrollment, and death from any cause before hospital discharge and within 90 days after randomization. Safety outcomes included electrolyte abnormalities within 4 days after enrollment, arterial or venous thrombosis, and cerebral edema diagnosed during clinical care. Data regarding adverse events were collected for 7 days after enrollment (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Details regarding sample-size determination were published previously.[26] In brief, we calculated that the enrollment of 8800 patients would provide 95% power to detect an absolute reduction in the risk of a primary-outcome event from 6.0% among children treated with 0.9% saline (on the basis of preliminary data[36]) to 4.3% among

children treated with balanced fluid, with a type I error of 0.05. To account for withdrawal from the trial among patients enrolled through exception from informed consent or deferred consent, the final enrollment target was increased by approximately 4% to 9178.

The primary analysis included all the patients who had undergone randomization, except those whose parent or other legally authorized representative made the decision to withdraw the patient from the trial or declined deferred consent without allowance for data use. Patients who were later determined not to have met eligibility criteria were retained in the primary analysis to avoid bias from differential assessment of eligibility. Multiple imputation was used to account for missing outcome data, with the assumption that the data were missing at random (see the Supplementary Appendix).

The primary outcome and other binary outcomes were compared with a Cochran–Mantel–Haenszel test, with stratification according to trial site. Continuous outcomes were compared with the van Elteren test, with stratification according to trial site. Death within 90 days was estimated with the Kaplan–Meier method, and a mixed-effects Cox proportional-hazards model was used to compare groups, with random intercepts for trial site. The proportional-hazards assumption was assessed through visual inspection of log–log survival plots and through testing of Schoenfeld residuals and was not violated.

Sensitivity analyses included patients with complete primary-outcome data and a per-protocol analysis of patients who received at least 75% of their total crystalloid fluid volume as their assigned trial fluid during the intervention phase. We also conducted a tipping-point analysis to assess the robustness of the primary analysis of a major adverse kidney event at 30 days with respect to departures from the missing-at-random assumption. For safety outcomes with more than 30% missing data, additional sensitivity analyses were performed (see the Supplementary Appendix).

Prespecified subgroup analyses were conducted for age, sex, coexisting cancer, acute kidney injury at presentation, total fluid volume during the intervention phase, and country of enrollment (see the Supplementary Appendix). Additional post hoc analyses evaluated the measured as compared with the imputed creatinine level at baseline and the initial severity of acidosis and hyperlactatemia. Subgroup analyses were performed with multiple imputed data.

Interim analyses for efficacy were performed after enrollment of 15%, 40%, and 70% of the participants with the use of a group sequential design with symmetric two-sided O'Brien–Fleming boundaries to control the overall type I error rate at 0.05. A two-sided P value of less than 0.044 at the final analysis indicated statistical significance for the primary outcome. Because of multiplicity, statistical significance is not reported for secondary effectiveness outcomes, and unadjusted P values are reported for safety outcomes. All analyses were performed with SAS, version 9.4 (SAS Institute), or R, version 4.4.1 (R Foundation for Statistical Computing).

RESULTS

TRIAL PATIENTS

A total of 9041 patients were enrolled; 4512 were randomly assigned to receive balanced fluid and 4529 to receive 0.9% saline (Figs. S2, S3, and S4 and Table S3). Of these patients, 277 (6.1%) in the balanced-fluid group and 282 (6.2%) in the 0.9%-saline group were not included in the analysis because a parent or other legally authorized representative made the decision to withdraw the patient from the trial or declined consent without allowance for data use. Therefore, the analysis included 4235 patients assigned to receive balanced fluid and 4247 assigned to receive 0.9% saline.

BASELINE CHARACTERISTICS

The characteristics of the patients were similar in the two treatment groups (Table 1 and Tables S4 and S5). The median age was 6.8 years (interquartile range, 2.8 to 12.8), and 50.8% were boys. The site of infection was most often respiratory (in 46.6% of the patients) (Table S6), and only 5.8% of the patients were determined not to have sepsis (Table S7). At presentation, 1172 patients (13.8%) had stage 1 acute kidney injury, 415 (4.9%) had stage 2, and 432 (5.1%) had stage 3 (Table 1 and Table S8).

Treatments for sepsis through the intervention phase are shown in Table S9. Overall, 1207 patients (14.2%) received vasoactive medications, and 822 (9.7%) underwent invasive mechanical ventilation. Treatment with bicarbonate occurred

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Balanced Fluid (N=4235)	0.9% Saline (N=4247)
Median age (IQR) — yr†	6.8 (2.8–12.8)	6.8 (2.8–12.8)
Male sex — no./total no. (%)	2166/4232 (51.2)	2136/4242 (50.4)
Coexisting conditions — no./total no. (%)		
Hematogenous or solid-tumor cancer	603/4224 (14.3)	613/4236 (14.5)
Bone marrow or solid-organ transplant	165/4224 (3.9)	158/4236 (3.7)
Cardiomyopathy or heart failure	43/4224 (1.0)	47/4236 (1.1)
Pulmonary hypertension	28/4224 (0.7)	30/4236 (0.7)
Kidney disease	193/4224 (4.6)	175/4236 (4.1)
Neurologic dysfunction causing severe developmental delay	1182/4224 (28.0)	1182/4236 (27.9)
Sickle cell disease	61/4224 (1.4)	59/4236 (1.4)
Chronic ventilator dependence	247/4224 (5.8)	219/4236 (5.2)
Indwelling central catheter	745/4224 (17.6)	742/4236 (17.5)
Median time from emergency department arrival to first antibiotic administration (IQR) — min‡	94 (50–183)	90 (48–183)
Median time from emergency department arrival to trial enrollment (IQR) — min§	103 (50–191)	101 (49–188)
Median volume of crystalloid fluid received before enrollment (IQR) — ml/kg		
0.9% Saline	18 (0–20)	17 (0–20)
Balanced fluid	0 (0–0)	0 (0–0)
Median initial blood lactate level (IQR) — mmol/liter¶	1.9 (1.3–3.0)	1.9 (1.3–3.0)
Median baseline serum creatinine level (IQR) — mg/dl‖	0.30 (0.25–0.50)	0.30 (0.25–0.47)
Acute kidney injury stage at enrollment — no. (%)**		
Stage 1	560 (13.2)	612 (14.4)
Stage 2	201 (4.7)	214 (5.0)
Stage 3	204 (4.8)	228 (5.4)

* IQR denotes interquartile range.

† Patients who were found to be 18 years of age after enrollment (17 patients in the balanced-fluid group and 9 in the 0.9%-saline group) were retained in the primary analysis to avoid bias from differential assessment of eligibility. Data were missing for 3 patients in the balanced-fluid group and for 5 patients in the 0.9%-saline group.

‡ Included is a subpopulation of 8157 patients (4065 in the balanced-fluid group and 4092 in the 0.9%-saline group) who did not receive the first antibiotic dose before arrival at the trial-site emergency department.

§ A total of 31 patients (16 in the balanced-fluid group and 15 in the 0.9%-saline group) with invalid time intervals because of erroneous time stamps were excluded.

¶ The initial blood lactate level was the value measured closest to trial enrollment, between 6 hours before through 2 hours after randomization, and was not measured in 1634 patients in the balanced-fluid group and in 1652 patients in the 0.9%-saline group.

‖ The serum creatinine level was measured as the lowest creatinine level available between 12 months and 24 hours before trial enrollment in 5044 patients (59.5%; 2515 in the balanced-fluid group and 2529 in the 0.9%-saline group) and was imputed with the use of established median values for age and sex in 3431 patients (40.5%; 1717 in the balanced-fluid group and 1714 in the 0.9%-saline group). Data were missing for 3 patients in the balanced-fluid group and for 4 patients in the 0.9%-saline group because data regarding age, sex, or both were also missing.

** The stage of acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria.

in 5.2% of the patients, including in 194 (4.6%) in the balanced-fluid group and 249 (5.9%) in the 0.9%-saline group.

FLUID ADMINISTRATION

The total volume of crystalloid fluids administered, the volume administered as a bolus, and the volume administered for maintenance hydration were similar in the treatment groups before randomization and during the intervention phase (Fig. 1). The median total crystalloid volume, including both the volume administered before randomization and that administered during the intervention phase, was 85 ml per kilogram (interquartile range, 55 to 119) in the balanced-fluid group and 88 ml per kilogram (interquartile range, 57 to 123) in the 0.9%-saline group (difference in medians, −2 ml per kilogram; 95% confidence interval [CI], −4 to 0) (Table S10 and Fig. S5).

Overall, 80% of the patients in the balanced-fluid group and 88% of those in the 0.9%-saline group received at least 75% of the total crystalloid fluid as their randomized fluid type. The median volume of 0.9% saline administered was 20 ml per kilogram (interquartile range, 6 to 32) in the balanced-fluid group, as compared with 79 ml per kilogram (interquartile range, 49 to 113) in the 0.9%-saline group, whereas the median volume of balanced fluid was 58 ml per kilogram (interquartile range, 31 to 92) and 0 ml per kilogram (interquartile range, 0 to 0), respectively.

PRIMARY OUTCOME

A primary-outcome event occurred in 137 of 4073 patients (3.4%) in the balanced-fluid group and in 124 of 4068 patients (3.0%) in the 0.9%-saline group (absolute difference, 0.4 percentage points [95% CI, −0.5 to 1.3]; risk ratio, 1.10 [95% CI, 0.88 to 1.40]; P=0.85) (Table 2 and Fig. S6). The results were similar in a prespecified sensitivity analysis of patients without missing components of the primary outcome and in the per-protocol analysis (Table S11). The results of a post hoc analysis did not show effect modification when 0.9% saline was administered before randomization (Table S12). Results of the tipping-point analysis showed that the findings with respect to the primary outcome remained robust to all but extreme departures from the missing-at-random assumption (Fig. S7).

SECONDARY OUTCOMES

Results for the secondary effectiveness and safety outcomes are shown in Table 2. The median number of hospital-free days during 28 days was 23 (interquartile range, 19 to 25) in both treatment groups. The incidence of death before hospital discharge was 1.1% in both treatment groups, and the incidence of death within 90 days was 2.3% in the balanced-fluid group and 2.1% in the 0.9%-saline group (Table 2 and Fig. S8).

Among patients with follow-up laboratory values measured within 4 days after enrollment, hyperchloremia and hypernatremia occurred less often, and hyperlactatemia more often, with balanced fluid than with 0.9% saline (Table 2, Table S13, and Fig. S9). The lower incidence of hyperchloremia with balanced fluid remained significant across sensitivity analyses (Table S14 and Fig. S10). Differences in follow-up blood chloride, bicarbonate, and creatinine levels appeared to be more pronounced between the groups as crystalloid volume increased (Figs. S11, S12, and S13). The incidence of thrombosis and cerebral edema did not differ between the groups (Table 2), nor did the incidence of other adverse events (Table S15).

SUBGROUP ANALYSES

The percentage of patients who had a primary-outcome event did not appear to differ between the balanced-fluid group and the 0.9%-saline group in analyses with stratification according to prespecified subgroups (Fig. 2) or in post hoc analyses with stratification according to measured or imputed creatinine levels at baseline (Fig. S14) or according to initial bicarbonate or lactate levels (Fig. S15). A post hoc analysis comparing the incidence of a primary-outcome event across increasing total volumes of crystalloid fluid also did not show apparent differences between the treatment groups (Fig. S16).

DISCUSSION

In this trial involving children treated for suspected septic shock in an emergency department, the use of balanced fluid for up to 48 hours did not result in a lower incidence of a major adverse kidney event within 30 days. There was no apparent difference between the groups in the number of hospital-free days or the incidence of death. Adequate difference in treatment between the two groups was evident in the distribution of fluid

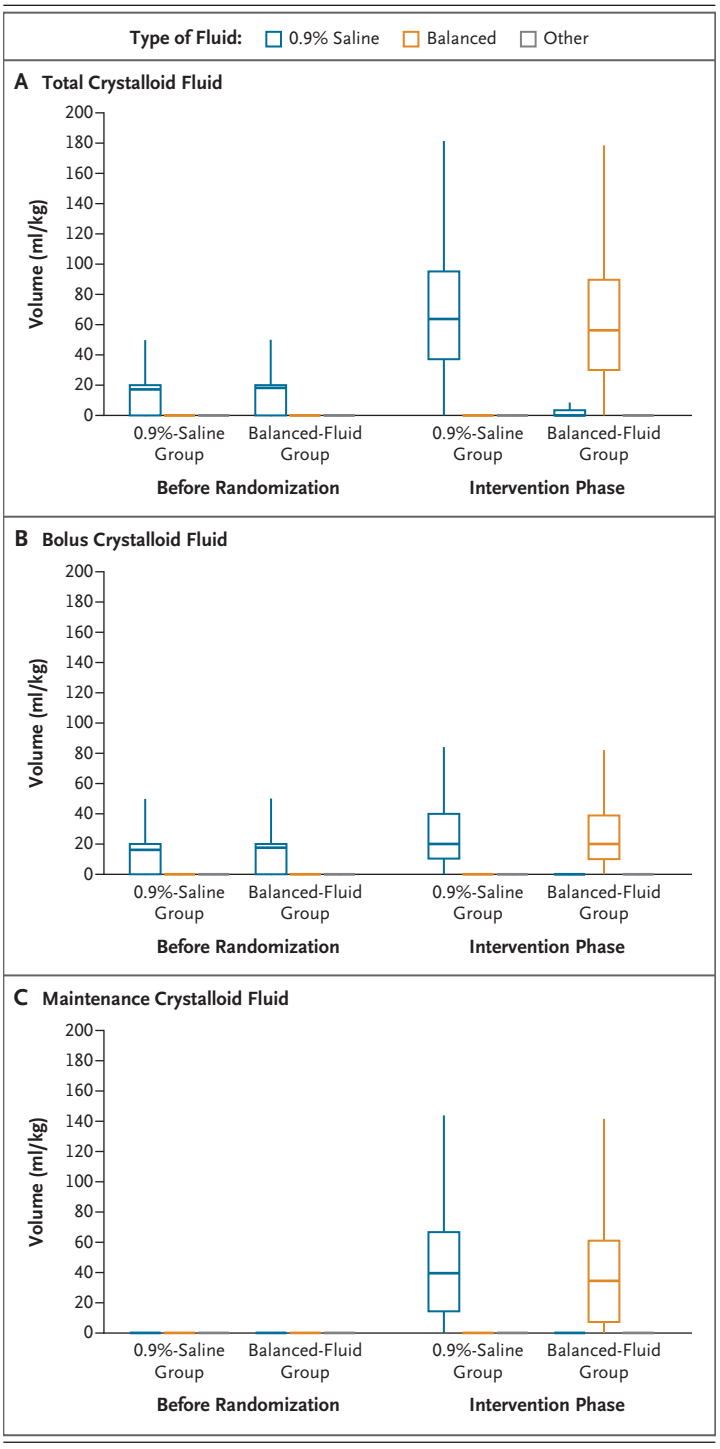

Figure 1. Type and Volume of Fluid Administration.
Shown are box plots of the total volume of crystalloid fluid (Panel A), the volume of bolus crystalloid fluid (Panel B), and the volume of maintenance crystalloid fluid (Panel C) administered to patients from presentation at the emergency department until 11:59 p.m. on the calendar day after the day of randomization, with stratification according to assigned treatment group (balanced fluid or 0.9% saline). Maintenance fluids were defined as the base fluid administered regardless of additives (e.g., dextrose or potassium). In the box plots, the horizontal line within the box indicates the median; the bottom and the top of the boxes indicate the 25th and 75th percentiles, respectively; and the whiskers indicate the lowest and highest values within 1.5 times the interquartile range (outliers beyond these thresholds are not shown).

type, as well as in the lower incidence of hyperchloremia and hypernatremia in the balanced-fluid group than in the 0.9%-saline group. In addition, hyperlactatemia was more frequent with balanced fluids, but the incidence of thrombosis, cerebral edema, or other adverse events did not differ between the two groups.

Our data do not show a benefit with the routine use of balanced fluid over 0.9% saline in children with suspected septic shock. As seen in previous trials, treatment with balanced fluid resulted in a lower incidence of hyperchloremia and hypernatremia than treatment with 0.9% saline,[6,16] but these biochemical effects did not translate to improved patient-centered outcomes. Notably, our findings differ from those of the trial by Sankar et al.,[16] which showed a 38% relative reduction in the incidence of new or progressive acute kidney injury with balanced fluid among 708 children with septic shock. However, in that trial, the outcome was monitored for only 7 days and included any increase in serum creatinine levels of at least 0.3 mg per deciliter, whereas a major adverse kidney event within 30 days in our trial required at least a 200% increase in creatinine levels above the baseline value. Despite these differences, neither the trial by Sankar et al.[16] nor our trial showed differences in the incidence of death or the number of hospital-free days.

A meta-analysis of six clinical trials involving adult patients estimated an 89.5% probability that balanced fluids reduce mortality as compared with 0.9% saline.[37] However, a recent cluster-randomized trial involving 43,626 patients did not find a beneficial effect of hospital-wide use of lactated Ringer's solution.[19] Two previous trials involving adults showed small, but significant, reductions in major adverse kidney events within 30 days with balanced fluids as compared with

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome*	Balanced Fluid	0.9% Saline	Risk Difference (95% CI)†	Effect Measure (95% CI)‡	P Value§
Primary outcome					
Major adverse kidney event within 30 days — no./total no. (%)¶	137/4073 (3.4)	124/4068 (3.0)	0.004 (–0.005 to 0.013)	1.10 (0.88 to 1.40)	0.85
Secondary effectiveness outcomes					
Death within 30 days — no./total no. (%)	41/4214 (1.0)	39/4226 (0.9)	0.001 (–0.004 to 0.005)	1.07 (0.70 to 1.64)	
New renal-replacement therapy — no./total no. (%)	26/4214 (0.6)	31/4226 (0.7)	–0.001 (–0.005 to 0.002)	0.84 (0.50 to 1.42)	
Persistent kidney dysfunction at hospital discharge — no./total no. (%)	93/4085 (2.3)	78/4079 (1.9)	0.004 (–0.004 to 0.012)	1.15 (0.88 to 1.49)	
Death before hospital discharge — no. /total no. (%)	48/4216 (1.1)	47/4230 (1.1)	0.001 (–0.005 to 0.005)	1.02 (0.69 to 1.51)	
Death within 90 days — no./total no. (%)‖	90/3857 (2.3)	83/3867 (2.1)	0.002 (–0.005 to 0.008)	1.07 (0.80 to 1.42)	
Median length of hospital stay (IQR) — days**	5.0 (3.0 to 9.0)	5.0 (3.0 to 9.0)		0 (0 to 0)	
Median no. of hospital-free days during 28 days (IQR)††	23 (19 to 25)	23 (19 to 25)		0 (0 to 0)	
Safety outcomes — no./total no. (%)‡‡					
Thrombosis	55/4216 (1.3)	55/4230 (1.3)	0 (–0.005 to 0.005)	1.00 (0.69 to 1.45)	0.91
Cerebral edema	18/4216 (0.4)	17/4230 (0.4)	0.001 (–0.003 to 0.003)	1.09 (0.55 to 2.13)	0.57
Sodium >155 mmol/liter	52/2830 (1.8)	89/2882 (3.1)	–0.013 (–0.021 to –0.004)§§	0.60 (0.43 to 0.84)§§	0.003
Sodium <128 mmol/liter	2/2830 (0.1)	0/2882 (0)	—	—	—
Chloride >110 mmol/liter	868/2765 (31.4)	1383/2823 (49.0)	–0.176 (–0.201 to –0.151)§§	0.64 (0.60 to 0.69)§§	<0.001
Potassium >6 mmol/liter	63/2798 (2.3)	74/2853 (2.6)	–0.003 (–0.011 to 0.005)§§	0.87 (0.62 to 1.20)§§	0.39
Total calcium level >12 mg/dl or ionized calcium level >1.35 mmol/liter	127/926 (13.7)	140/1005 (13.9)	–0.002 (–0.033 to 0.029)§§	0.95 (0.76 to 1.18)§§	0.62
Lactate level >4 mmol/liter	260/1314 (19.8)	228/1363 (16.7)	0.031 (0.001 to 0.060)§§	1.18 (1.01 to 1.39)§§	0.04

* Outcomes are reported according to the number of patients with observed (i.e., not missing) data.
† The risk difference is reported as the difference in percentages and is combined across multiple imputed datasets using Rubin's rules.
‡ The effect measure is reported as the site-adjusted risk ratio with 95% confidence interval estimated with the Mantel–Haenszel method or as the median difference with 95% confidence interval estimated with the Hodges–Lehmann estimator.
§ P values are calculated from the Cochran–Mantel–Haenszel test for binary outcomes, with stratification according to trial site, and from the Van Elteren test for continuous outcomes, with stratification according to trial site, without adjustment for multiple comparisons for the primary and safety outcomes.
¶ A major adverse kidney event was defined as a composite of death, new renal-replacement therapy, or persistent kidney dysfunction.
‖ Data were considered to be missing if not available in the trial-site medical record.
** Data were available for 4211 patients in the balanced-fluid group and for 4226 patients in the 0.9%-saline group.
†† Data were available for 4209 patients in the balanced-fluid group and for 4222 patients in the 0.9%-saline group.
‡‡ Safety outcomes must have occurred within 4 calendar days after randomization, except for thrombosis, which must have occurred within 7 days after randomization.
§§ The risk difference and risk ratio are reported only for patients who had values measured from 2 hours after randomization on trial day 0 through trial day 3.

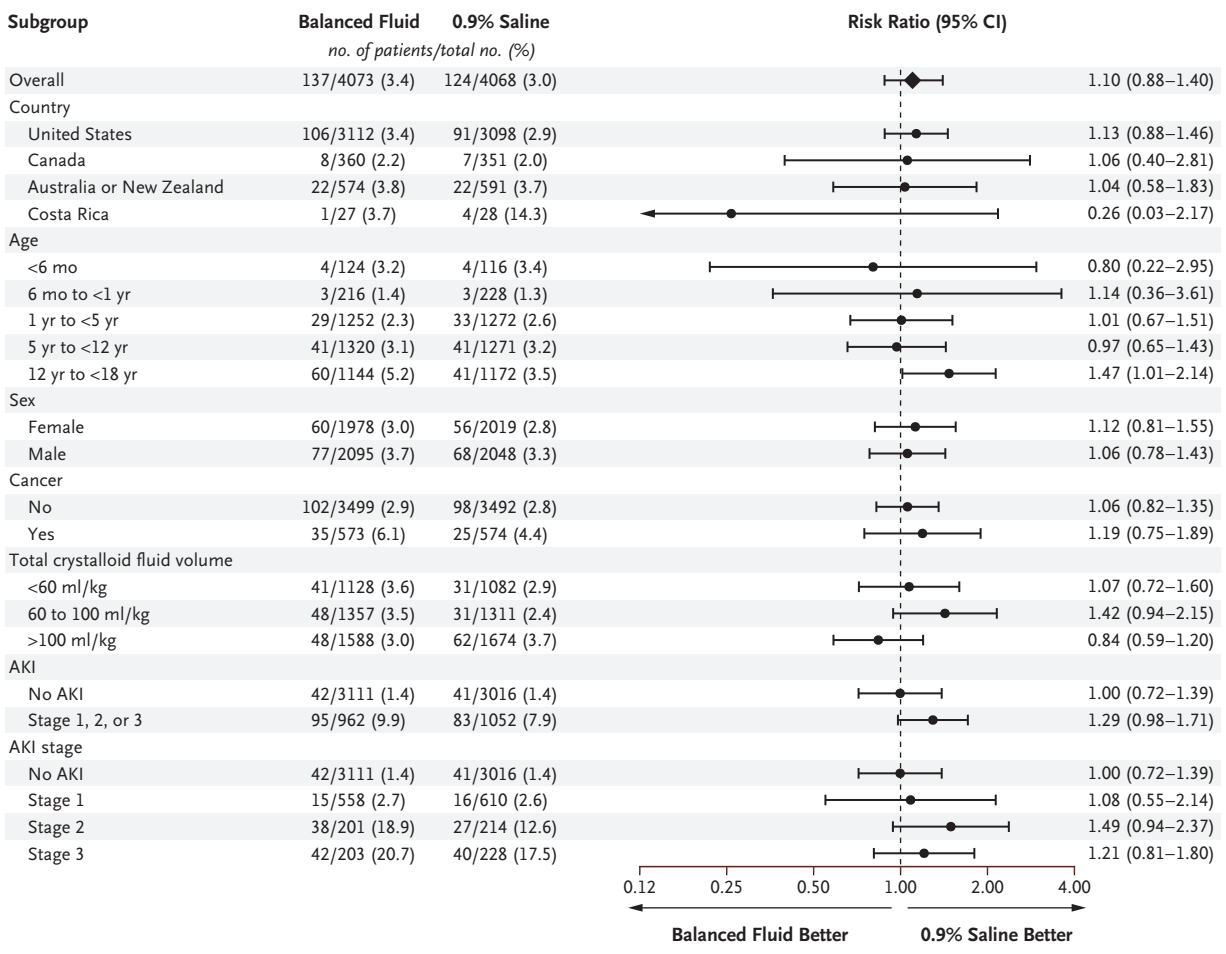

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the subgroup analyses of the percentage of patients in the balanced-fluid group and in the 0.9%-saline group who met the criteria for a major adverse kidney event (defined as a composite of death from any cause, new renal-replacement therapy, or persistent kidney dysfunction) within 30 days after enrollment or hospital discharge, whichever occurred first. Cancer was considered to be present if the patient was being treated or monitored for a blood or solid-tissue cancer before trial enrollment or started treatment during the trial-related hospitalization; previous cancer diagnoses that were considered to be cured or resolved were not included. Total crystalloid fluid volume refers to the total volume of crystalloid fluid administered either as a bolus or as maintenance hydration during the combined prerandomization and intervention phases. Acute kidney injury (AKI) stage was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria (see the Supplementary Appendix).

saline, but neither trial showed differences in hospital-free days between treatment groups.[13,14]

Strengths of our trial included a large sample size, which was needed to detect small differences in patient outcomes. In addition, we enrolled patients before they had undergone large-volume fluid resuscitation because previous trials have suggested that this population would be most likely to benefit from balanced fluid.[14,21]

Our trial also had several limitations. First, whether our results are generalizable to low-resource contexts or hospital-acquired sepsis is not certain. Second, we defined septic shock using immediately accessible clinical signs of abnormal perfusion to capture patient data near the onset of fluid therapy rather than waiting for abnormal laboratory results, which are often not available at presentation. Although this approach aligns with clinical practice and the trial population was representative of children treated for septic shock in an emergency department (Table S16), the low incidence of a primary-outcome event di-

minished statistical power to detect planned differences between groups. Moreover, although we did not observe heterogeneity of treatment effect in subgroup analyses, point estimates favored balanced fluid among patients who received the highest fluid volumes and presented with more extreme acidosis and hyperlactatemia; thus, we cannot exclude a benefit of balanced fluid in children with the most severe illness. Third, although previous trials have shown that most crystalloid fluid is administered within the initial 48 hours of sepsis treatment,[6,14,16,21] unmeasured fluid administration after the intervention phase may have altered the outcomes. Fourth, our analysis could not distinguish patients who had been enrolled more than once. Fifth, a higher percentage of patients than expected withdrew before ascertainment of the primary outcome. However, withdrawal was unlikely to be related to the intervention, and the results were robust to all but unplausible conditions among patients with missing data. Sixth, a major adverse kidney event within 30 days was defined by a composite of outcomes that may not be of equivalent acceptability to patients; however, the incidence of the subcomponents or other secondary effectiveness outcomes did not differ between the treatment groups.

In this pragmatic, randomized clinical trial involving approximately 9000 children with suspected septic shock treated with fluid resuscitation for abnormal perfusion in an emergency department, the incidence of death, new renal-replacement therapy, or persistent kidney dysfunction (the composite primary outcome) was not significantly different between treatment with balanced fluid and treatment with 0.9% saline.

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