# Multiple Electrolytes Solution Versus Saline as Bolus Fluid for Resuscitation in Pediatric Septic Shock: A Multicenter Randomized Clinical Trial*

Jhuma Sankar, MD[1]
Jayashree Muralidharan, MD[2]
A. V. Lalitha, MD[3]
Ramachandran Rameshkumar, MD, DM[4]
Mona Pathak, PhD[5]
Rashmi Ranjan Das, MD[6]
Vinay M. Nadkarni, MD[7]
Javed Ismail, MD[8]
Mahadevan Subramanian, MD[4]
Karthi Nallasamy, DM[2]
Nishanth Dev, MD[9]
U. Vijay Kumar, DM[1]
Kiran Kumar, MD[1]
Taniya Sharma, RN[1]
Kanika Jaravta, RN[1]
Neha Thakur, RN[2]
Praveen Aggarwal, MD[10]
Kana Ram Jat, MD[1]
S. K. Kabra, MD[1]
Rakesh Lodha, MD[1]

**OBJECTIVE:** To determine if initial fluid resuscitation with balanced crystalloid (e.g., multiple electrolytes solution [MES]) or 0.9% saline adversely affects kidney function in children with septic shock.

**DESIGN:** Parallel-group, blinded multicenter trial.

**SETTING:** PICUs of four tertiary care centers in India from 2017 to 2020.

**PATIENTS:** Children up to 15 years of age with septic shock.

**METHODS:** Children were randomized to receive fluid boluses of either MES (PlasmaLyte A) or 0.9% saline at the time of identification of shock. All children were managed as per standard protocols and monitored until discharge/death. The primary outcome was new and/or progressive acute kidney injury (AKI), at any time within the first 7 days of fluid resuscitation. Key secondary outcomes included hyperchloremia, any adverse event (AE), at 24, 48, and 72 hours, and all-cause ICU mortality.

**INTERVENTIONS:** MES solution ($n = 351$) versus 0.9% saline ($n = 357$) for bolus fluid resuscitation during the first 7 days.

**MEASUREMENTS AND MAIN RESULTS:** The median age was 5 years (interquartile range, 1.3–9); 302 (43%) were girls. The relative risk (RR) for meeting the criteria for new and/or progressive AKI was 0.62 (95% CI, 0.49–0.80; $p < 0.001$), favoring the MES (21%) versus the saline (33%) group. The proportions of children with hyperchloremia were lower in the MES versus the saline group at 24, 48, and 72 hours. There was no difference in the ICU mortality (33% in the MES vs 34% in the saline group). There was no difference with regard to infusion-related AEs such as fever, thrombophlebitis, or fluid overload between the groups.

**CONCLUSIONS:** Among children presenting with septic shock, fluid resuscitation with MES (balanced crystalloid) as compared with 0.9% saline resulted in a significantly lower incidence of new and/or progressive AKI during the first 7 days of hospitalization.

**KEY WORDS:** acute kidney injury; balanced crystalloids; children; hyperchloremia; multiple electrolyte solution; normal saline; saline; septic shock

Septic shock is a serious and concerning cause of morbidity and mortality in children (1–4). Fluid resuscitation is an important step in the early management of septic shock in children (4). Crystalloid solutions are recommended for initial fluid resuscitation; saline (0.9% sodium chloride) is commonly used, as it is inexpensive and readily available with an efficacy similar to colloids with respect to shock resolution and mortality (5, 6). Balanced crystalloids (BCs) have a composition resembling plasma (**eTable 1**, http://links.lww.com/CCM/H359) with a lower chloride concentration than saline. Some BCs

*See also p. 1587.



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## KEY POINTS

**Question:** Does the use of balanced crystalloid solution (e.g., multiple electrolytes solution [MES]), or normal saline (0.9% saline), for fluid resuscitation in children with septic shock adversely affect kidney functions?

**Findings:** In this blinded multicenter randomized clinical trial that included 708 patients, the risk of new and/or progressive acute kidney injury (AKI) within the first 7 days was significantly lower with MES as compared with 0.9% saline (21% vs 33%; relative risk: 0.62; 95% CI, 0.49–0.80; $p < 0.001$).

**Meaning:** Among children with septic shock, fluid resuscitation with MES (balanced crystalloid) as compared to 0.9% saline resulted in a significantly lower incidence of developing new and/or progressive AKI during the first 7 days of hospitalization.

(e.g., multiple electrolytes solution [MES] also known as PlasmaLyte A, lactated Ringer's, Ringer's acetate) have been reported to be associated with decreased risk of metabolic disturbances such as hyperchloremia and metabolic acidosis as compared with saline in children from diverse patient settings (7–13).

The Pediatric Surviving Sepsis Campaign (SSC) recently issued a recommendation to use BCs, rather than saline, for the initial resuscitation in septic shock (14). This suggestion; however, was based on evidence of limited quality, prompting the SSC committee (14) to comment in their report that the "type of fluid" to be used for resuscitation should be a research priority.

Our three-part rationale for conducting the present study was guided by equipoise from previous studies and systematic reviews (15, 16), including the SSC (14). First, adult data should not be extrapolated to pediatric populations; second, saline is the predominant resuscitation fluid used in the clinical management of children with shock (in India), and third, some of the BCs are more expensive than saline (particularly important in lower and middle-income countries such as India). We chose PlasmaLyte A over Ringer's because we wanted to use a fluid with a composition as close to plasma as possible (not hypotonic) and having lower chloride levels (98 mEq/L in MES vs 109 mEq/L in Ringer's lactate) as we wanted to evaluate the risk of AKI as our primary outcome.

Our study, designed with an adequate sample size in the pediatric emergency and PICUs chose as its primary outcome the development of new and/or progressive AKI in children presenting with septic shock when using BCs (MES) compared with saline for fluid resuscitation.

## MATERIALS AND METHODS

### Study Design

This parallel-group, randomized, blinded controlled trial was conducted over a 3-year period (April 10, 2017, to January 31, 2020) in the pediatric emergency and PICUs of four tertiary care centers in India. The trial protocol, available at ClinicalTrials.gov (NCT02835157) (**Appendix**, Clinical trials record), was approved by the institute ethics committee of All India Institute of Medical Sciences, New Delhi (IECPG-299/June 28, 2018, RT 11/August 30, 2018) and of the participating sites. We obtained written informed consent from the parent/guardian and followed procedures as per the ethical standards of the institute's ethics committee on human experimentation and according to the Declaration of Helsinki of 1975.

### Participants

All children were younger than or equal to 15 years old with a clinical diagnosis of septic shock (17, 18) at the participating centers (**eTable 2**, http://links.lww.com/CCM/H359) who were deemed by the treating clinicians to require a fluid bolus were screened for enrollment. Children were excluded from enrollment if they had received any fluid boluses before enrollment; met criteria for chronic kidney disease; had unrepaired cyanotic congenital heart disease; had severe malnutrition, had known metabolic disorders or parents declined consent. A patient was considered eligible only for their first episode of shock during the admission. If a patient developed additional episodes of shock after the first episode of shock had resolved or was discharged and readmitted with shock, he/she was not eligible for enrollment again. Both verbal and written informed consents were serially obtained from parents/guardians before enrollment **(eBox 1**, http://links.lww.com/CCM/H359).

## Randomization and Blinding

Participants were randomized to receive either MES (PlasmaLyte A) or saline. Block randomization was carried out by a statistician blinded to patient identity or status with the use of varying block sizes of 2–8 generated using a computer-based random number table generator (using STATA 13). Randomization was stratified by site. Serially numbered, sealed, opaque pouches containing 10 bags of 500 mL of either "MES" or "saline" each were kept at the study site. Each of the 500 mL bags was packed in sealed opaque covers inside the pouches as well (**eFigure 1**, http://links.lww.com/CCM/H359). The research staff picked the bag of fluids kept per allocation sequence and initiated the bolus in the given patient. The same fluid pouch containing the 500 mL bags was used when the given patient was transferred to the PICU and required further fluid boluses (through 7 d). The patient, the treating physician, and the outcome assessor were all blinded. The fluids were packed by the research assistants who had no role in patient randomization or enrollment.

## Procedure

Upon recognition of shock, all eligible patients for whom consent was obtained, received at least one fluid bolus of 20 mL/kg taken from the designated randomization pouch. Clinicians and staff, as well as family/patient, were blinded to fluid type. Subsequent boluses administered to each patient through 7 days were with the same blinded fluid type that they had been randomized to. The maintenance fluids administered to both groups were at the discretion of the treating team, as this was not part of the study intervention (**eBox 2**, http://links.lww.com/CCM/H359).

The data for the type of maintenance fluids, total input, and output were collected in the enrolled patients over the first 7 days. Preplanned per-protocol samples for serum electrolytes, lactate, blood gases, and serum creatinine were collected closest to the following time points: 6, 24, 48, and 72 hours, day 7, as well as at any time between these time points at the discretion of the treating team. If a patient recovered from AKI, no further sampling was done for study purposes for that given patient. Serum creatinine was measured by the modified Jaffe method (Roche modular P800 autoanalyzer, Germany).

During the study period, the framework provided for the management of septic shock in children in both groups adhered to recommendations of the SSC Guidelines 2012 and the American College of Critical Care Medicine guidelines 2017 (4). Data collection included demographics, clinical course, investigations, treatment received, and outcome variables. To establish infection as the etiology of shock, cultures were sent from various organs or body sites, depending upon specific localizing signs and symptoms.

## Outcomes

The primary outcome was the development of new or progressive AKI in the subsequent 7 days of hospitalization after enrollment. The definition of new or progressive AKI for the purpose of the study was adapted from the pediatric definitions in the 2012 Kidney Disease Improving Global Outcomes guidelines (19) as an absolute increase in serum creatinine greater than or equal to 0.3 mg/dL between any two measured values, or an increase in serum creatinine of greater than or equal to 1.5 times from the value preceding the abnormal value (age-based creatinine values are provided in **eTable 3**, http://links.lww.com/CCM/H359), or urine output less than or equal to 0.5 mL/kg per hour for any consecutive 6-hour period after the first hour of fluid resuscitation (for measuring urine output, all patients were catheterized until shock resolved or the patient died). Participants who met at least one of these criteria for new or progressive AKI within the first 7 days after study enrollment were considered to have met the primary outcome.

The secondary outcomes were all-cause ICU mortality and adverse events (AE) of hyperchloremia (chloride >108 mEq/L) and metabolic acidosis (pH < 7.35) at 24, 48, and 72 hours. The other outcomes were shock resolution, use of mechanical ventilation, vasoactive therapy, and renal replacement therapy (RRT) during the first 7 days. The pediatric-Sequential Organ Failure Assessment (pSOFA) scores on day 1 and day 2, Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score on day 1 and day 2, fluids received, transfusion of blood products; ventilator, vasopressor, ICU, and hospital-free days (calculated at day 28) were also compared between the groups (**study definitions:** eTable 2, http://links.lww.com/CCM/H359).

### Safety Outcomes and Adverse Events (AEs)

The principal safety outcomes were: acute kidney injury (AKI); requirement for RRT; hyperchloremia; metabolic acidosis; fluid overload and, mortality (**Appendix, supplementary methods**, http://links.lww.com/CCM/H359).

### Statistical Analysis

The incidence of AKI in critically ill children with severe sepsis ranges from 25% to 40% (20–23). We chose a 10% absolute risk reduction (using 25% baseline) as a clearly clinically meaningful difference. A total of 708 patients (354 in each group) were required to detect an absolute reduction in the incidence of AKI from 25% to 15% assuming a two-sided α level of 0.05 and a statistical power of 90% (calculated using Stata 13).

Data were entered into Microsoft Access 2013 and analyzed using STATA 15.1 (Stata Corp, College Station, TX). Following the initial data cleaning, initial analysis, and internal validation with source materials from each hospital, the data were additionally validated for Quality Control/Quality Assurance by an independent statistical team not involved in any aspect of the study. The data entry validation was executed by re-extraction of 10% of the hard copy source document proformas against electronically submitted data to the data coordinating center. The independent statisticians confirmed and certified that data were accurately entered with a mean error rate of less than 1%, and replicated the statistical findings independently.

Categorical data are presented as numbers (%), while continuous variables are presented as mean (SD), if normally distributed, and median (interquartile range), if skewed. There were no missing data for primary outcomes or protocol violations. As six patients refused written informed consent after verbal consent (four in MES group and two in saline group), they were withdrawn. Therefore no further protocolized study intervention or data gathering was conducted on those six patients. Due to these withdrawals, a modified intention-to-treat approach to analysis was carried out. We calculated the relative risk (RR)/mean difference (MD) with a 95% CI for primary outcome and all other outcomes except mortality (hazard ratio). A $p$ value of $< 0.05$ was considered significant, and the testing was two-sided. Because of the potential for type-1 error due to multiple comparisons, we did not perform any adjustment for this; therefore, the findings for analyses of secondary endpoints and subgroup analysis are interpreted as exploratory. The changes in statistical analysis plan and protocol are described in **eTables 11** and **12** (http://links.lww.com/CCM/H359).

As post hoc analysis the effect of treatment for AKI was also visualized using the "cumulative incidence competing risk (CICR)" method and estimated using Fine and Gray competing risk regression, considering death as a competing risk that was not planned in the original protocol (24). The incidence of AKI varies across different age categories and some have reported age to be an independent determinant of AKI. Any factors which increase the risk of renal injury may therefore manifest differently across different age groups (25–27). The effect of treatment on the primary outcome was therefore also explored for different age groups (0 to <5 yr, 5 to <10 yr, and 10 to 15 yr). Sensitivity analysis was also performed after excluding patients who had AKI at admission (Appendix, Supplementary methods, http://links.lww.com/CCM/H359).

## RESULTS

We screened 1080 patients; 366 were excluded and 714 were randomized. After randomization, 6 patients refused written consent after verbal consent and were withdrawn. Finally, 708 children were analyzed (MES group = 351, and saline group = 357 [**Fig. 1**]. The baseline characteristics of the study population are described in **Table 1** and **eTable 4** (http://links.lww.com/CCM/H359). The two study groups exhibited similar illness severity (PIM-3 and pSOFA scores) at enrollment.

The median volume of boluses received in the first hour was 30 (20, 40) mL/kg, in both groups. The groups were not significantly different in terms of fluid volumes received in the MES and saline groups in the first 6 hours (55 [45, 67] vs 52 [43, 70] mL/kg in the MES and saline groups, respectively) or the first 24 hours (105 [90, 130] vs 105 [90, 125] mL/kg in the MES and saline groups, respectively) (**eTable 5**, http://links.lww.com/CCM/H359). The median fluid volumes received declined gradually over the first 72 hours in both study arms. There was no difference between the groups with respect to the type of maintenance fluid or the proportion of maintenance fluid administered in the first 24, 48, or 72 hours.

### Primary Outcomes

Children receiving MES as bolus fluids had a significantly lower risk of meeting criteria for new and/or

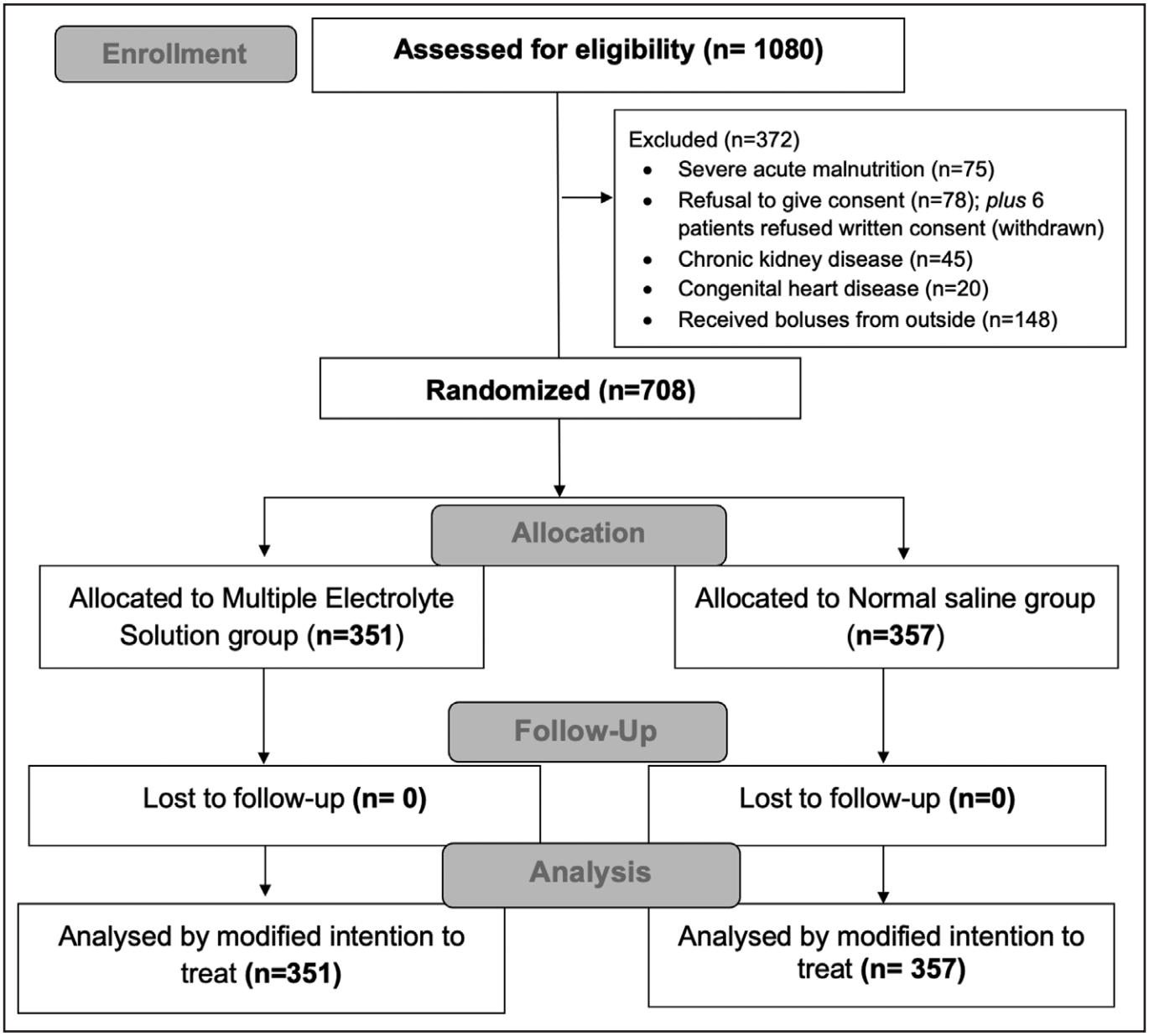


**Figure 1.** Consort study flow.

progressive AKI in the first 7 days (21%) as compared with those receiving saline (33%) (RR [95% CI], 0.62 (0.49–0.80); $p < 0.001$) (**Table 2**).

The demographic and laboratory features and clinical course of children with AKI at admission are provided in **eTable 6** (http://links.lww.com/CCM/H359).

## Secondary Outcomes

The secondary outcomes are provided in Table 2 and **eTable 7** (http://links.lww.com/CCM/H359). The number (%) of children developing hyperchloremia was lower at 24 hours (125/326 [38%] vs 168/325 [52%]), 48 hours (132/287 [46%] vs 180/297 [61%]) and 72 hours (102/229 [45%] vs 141/225 [63%]) in the MES and saline groups, respectively. The trend in the chloride, pH, and serum $HCO_3$ levels with time is provided in **eFigure 2** (http://links.lww.com/CCM/H359). The groups were not different with respect to the potassium levels at 24, 48, or 72 hours (**eTable 8**, http://links.lww.com/CCM/H359); ICU mortality (116/351 [33%] vs 121/357 [34%]); time to shock resolution (hr) (6 [6, 12] vs 8.5 [6, 16]), vasoactive drug therapy (241 [69%] vs 255 [71%]), PELOD score-24 hours (11 [3, 22] vs 13 [2, 22]), ventilator-free days (all patients) (27 [0, 28],

## TABLE 1.
### Baseline Characteristics of Participants According to Allocation

| Variables | MES Group (*n* = 351) | Saline Group (*n* = 357) |
|---|---|---|
| Gender | | |
| Male | 201 (57%) | 205 (58%) |
| Female | 150 (43%) | 152 (42%) |
| Age (yr) (median, IQR) | 4.0 (1.0–9.0) | 5.0 (1.5–9.0) |
| Age (stratified) | | |
| ≤ 5 yr | 177 (50%) | 167 (47%) |
| 5.1–10 yr | 93 (27%) | 117 (33%) |
| 10.1–15 yr | 81 (23%) | 73 (20%) |
| PIM-3 score (median, IQR) | 7.0 (2.0–31.0) | 7.0 (2.0–34.0) |
| pSOFA score (median, IQR) | 7.0 (4.0–10.0) | 7.0 (4.0–10.0) |
| Moderate undernutrition | 84 (24%) | 82 (23%) |
| Underlying comorbidities | 75 (21%) | 87 (24%) |
| Sources of infection (clinically suspected) | | |
| Pneumonia | 149 (42%) | 129 (36%) |
| Abdomen infection | 114 (32%) | 125 (35%) |
| Meningitis | 30 (8.6%) | 36 (10%) |
| Skin and soft tissue infection | 5 (1%) | 6 (2%) |
| Urinary tract infection | 7 (2%) | 10 (3%) |
| Hepatitis | 0 (0%) | 1 (0.3%) |
| Absence of focus of infection | 46 (13%) | 50 (14%) |
| Clinical findings | | |
| Mean heart rate (beats/min) | 144 (30) | 146 (30) |
| Tachycardia | 298 (85%) | 307 (86%) |
| Hypotension (systolic BP < 5th centile for age) | 141 (40%) | 149 (42%) |
| Mean arterial blood pressure (mm Hg) (mean, SD) | 69 (13) | 66 (11) |
| Mean capillary refill time (seconds) | 3 (1) | 3 (1) |
| Abnormal capillary refill time (>2 s) | 327 (94%) | 332 (94%) |
| Mean oxygen saturation ($Spo_2$) (mean, SD) | 93 (6) | 93 (5) |
| History of oliguria | 184 (53%) | 172 (49%) |
| Change in mental status | 288 (82%) | 284 (80%) |
| Acute kidney injury[a] | 17 (5.4%) | 20 (5.6%) |

AKI = acute kidney injury, BP = blood pressure, CRT = capillary refill time, MES = multiple electrolytes solution, PIM-3 = Pediatric Index of Mortality-3, pSOFA = pediatric-Sequential Organ Failure Assessment Score.

Values represent *n* (%) unless specified otherwise.

[a]For defining AKI at admission, we considered creatinine values > the upper limit of the range for each age group provided in the **electronic supplement** (http://links.lww.com/CCM/H359).

26 [0, 28]) or ICU-free days (21 [0, 24] vs 22 [0, 25]) in the MES and saline groups, respectively. However, the sodium levels differed between the groups (eTable 7, http://links.lww.com/CCM/H359). The Kaplan-Meier curve of the effect of the intervention on in-ICU mortality is provided in **eFigure 3** (http://links.lww.com/CCM/H359). The number (%) of children treated with RRT (AE) was 32 of 351 (9%) and 57 of 357 (16%) in the MES and saline groups, respectively (**eBox 3**, http://links.lww.com/CCM/H359).

**TABLE 2.**
**Primary and Secondary Outcomes of the Study Population**

| Variables | MES Group (351) | Saline Group ($n = 357$) | Relative Risk or Mean Difference | Risk Difference |
|---|---|---|---|---|
| Primary outcome | | | | |
| New and/or progressive AKI | 73 (21%) | 119 (33%) | 0.62 (0.49 to 0.80) | −12.5% (−19.0 to −6.06%) |
| Secondary outcomes | | | | |
| In ICU mortality | 116 (33%) | 121 (34%) | 0.97 (0.79 to 1.2) | −0.85% (−7.79 to 6.10%) |
| Chloride value (mEq/L) (mean, SD) at | | | | |
| 24 hr | 107 (8) | 110 (10) | −2.79 (−1.37 to −4.22) | – |
| 48 hr | 108 (9) | 111 (11) | −3.20 (−1.79 to −4.76) | – |
| 72 hr | 109 (10) | 112 (14) | −3.20 (−1.57 to −4.88) | – |
| Bicarbonate value (mEq/L) (Mean, SD) at | | | | |
| 6 hr | 16.50 (4.95) | 16.70 (4.67) | −0.26 (−0.99 to 0.47) | – |
| 24 hr | 18.24 (4.91) | 17.50 (4.36) | 0.74 (−0.02 to 1.50) | – |
| 48 hr | 19.67 (5.10) | 18.95 (4.50) | 0.72 (−0.20 to 1.64) | – |
| 72 hr | 19.0 (4.80) | 18.60 (3.70) | 0.37 (−0.65 to 1.40) | – |
| Vasoactive therapy | 257 (73%) | 267 (75%) | 0.96 (0.87 to 1.05) | −2.76% (−9.51 to 3.97%) |
| Vasoactive therapy in first 6 hr | 124 (35%) | 138 (39%) | 0.91 (0.75 to 1.1) | −3.32 (−10.44 to 3.78) |
| Resolution of shock during ICU stay | 255 (74%) | 249 (71%) | 1.04 (0.95 to 1.14) | 2.90% (−3.76% to 9.56%) |
| Mechanical ventilation | 189 (54%) | 198 (56%) | 1.02 (0.87 to 1.20) | 1.06% (−6.28% to 8.4%) |
| VFDs to day 28 (Intubated) (Median, IQR) | 0 (0, 22) ($n = 189$) | 0 (0, 22) ($n = 198$) | – | – |
| VFDs to day 28 (All patients) (Median, IQR) | 27 (0, 28) ($n = 351$) | 26 (0, 28) ($n = 357$) | | |
| IFDs to day 28 (those receiving inotropes) (Median, IQR) | 26 (0, 28) ($n = 257$) | 23 (0, 28) ($n = 267$) | – | – |
| IFDs to day 28 (All patients) (Median, IQR) | 28 (0, 28) ($n = 351$) | 28 (0, 28) ($n = 357$) | | |
| PICUFDs to day 28 (Median, IQR) | 21.0 (0.0 to 24.0) ($n = 351$) | 22.0 (0.0 to 25.0) ($n = 357$) | – | – |
| HFDs to day 28 (Median, IQR) | 19.0 (0.0 −22.0) ($n = 351$) | 18.0 (0.0 −22.0) ($n = 357$) | – | – |

HFD = hospital-free days, IFD = inotrope-free days, MES = multiple electrolytes solution, VFD = ventilator-free days.
Data are mean (SD), *n* (%), or parentheses with 95% CIs unless otherwise specified. Dashes indicate data is not applicable.

Among those with AKI, 43 of 351 (12%) and 55 of 357 (15%) children died in the MES and saline groups, respectively ($p > 0.05$). At the time of discharge from the hospital, 11 and 14 children in the MES and saline groups, respectively, had persistent renal dysfunction requiring dialysis intermittently. The incidence of other AEs such as febrile reactions, thrombophlebitis, extravasation, and hypervolemia/fluid overload was similar in the MES and saline groups respectively (**Table 3**). The causes of death were not attributed solely to the intervention in any of the groups (eTable 8, http://links.lww.com/CCM/H359).

### Post Hoc Analysis of Primary Outcome Measure

A post hoc analysis of the diagnosis of AKI by various criteria (urine output/creatinine/both) is provided in **eTable 9** (http://links.lww.com/CCM/H359). The CICR curve is provided in **eFigure 4** (http://links.lww.com/CCM/H359). MES was associated with a lower risk of AKI (subdistributional hazard ratio [sHR]) ([95% CI], 0.33 [0.21–0.53]) after adjusting for baseline creatinine. Sensitivity analysis excluding patients presenting with AKI at admission also provided the same results **(eTable 10**, http://links.lww.com/CCM/H359).

## DISCUSSION

The present study demonstrated a lower risk of new and/or progressive AKI in the first 7 days after fluid resuscitation with the use of BC (MES) as compared with saline in children with septic shock.

These findings contrast with data from prior trials in adults (28–32). Systematic reviews of such adult trials

## TABLE 3.
### Adverse Events and Serious Adverse Events in the Study Population

| Variables | MES Group ($n = 351$) | Saline Group ($n = 357$) | Relative Risk | $p$ | Risk Difference |
|---|---|---|---|---|---|
| Serious adverse events | | | | | |
| AKI requiring dialysis | 32 (9.1%) | 57 (16.0%) | 0.57 (0.38 to 0.86) | 0.006 | −6.85% (−11.7 to −2.0) |
| In-ICU mortality in patients with AKI | 43 (12%) | 55 (15%) | 0.79 (0.55 to 1.15) | 0.22 | −3.15% (−8.23% to 1.92%) |
| Adverse events (biochemical) | | | | | |
| Hyperchloremia at | | | | | |
| 24 hr | 125/326 (38%) | 168/325 (52%) | 0.74 (0.62 to 0.88) | 0.001 | −13.4% (−21.0% to −5.77%) |
| 48 hr | 132/287 (46%) | 180/297 (61%) | 0.76 (0.65 to 0.88) | <0.001 | −14.61% (−22.6% to −6.6%) |
| 72 hr | 102/229 (45%) | 141/225 (63%) | 0.71 (0.60 to 0.85) | <0.001 | −17.7% (−26.71% to −8.66%) |
| Metabolic acidosis at | | | | | |
| 6 hr | 279/326 (86%) | 290/331 (88%) | 0.98 (0.90 to 1.05) | 0.44 | −1.74% (−7.59% to 4.11%) |
| 24 hr | 226/317 (71%) | 256/323 (79%) | 0.90 (0.83 to 0.99) | 0.019 | −7.69% (−14.38 to −1.02%) |
| 48 hr | 161/291 (55%) | 192/297 (65%) | 0.86 (0.74 to 0.97) | 0.020 | −9.69% (−17.59% to −1.79%) |
| 72 hr | 98/141 (70%) | 124/158 (78%) | 0.88 (0.77 to 1.01) | 0.05 | −8.97% (−18.92% to 0.96%) |
| Adverse event (infusion-related) | | | | | |
| Thrombophlebitis at 24 hr | 116 (33%) | 121 (34%) | 0.97 (0.79 to 1.20) | 0.81 | −8.45% (−7.79% to 6.10%) |
| Fever | 91 (26%) | 106 (30%) | 0.87 (0.68 to 1.10) | 0.26 | −3.76% (−10.36% to 2.82) |
| Rash | 24 (7%) | 35 (10%) | 0.69 (0.42 to 1.14) | 0.15 | −2.96% (−7.02% to 1.09%) |
| Shortness of breath | 21 (6%) | 27 (8%) | 6.78 (5.13 to 8.89) | 0.40 | −1.58% (−5.28% to 2.12) |
| Extravasation | 114 (32%) | 127 (36%) | 0.91 (0.74 to 1.12) | 0.38 | −3.09% (−10.10% to 3.88%) |
| Hypervolemia/fluid overload after first hour | 34 (9.7%) | 31 (8.6%) | 1.11 (0.70 to 1.77) | 0.64 | 1.0% (−3.25% to 5.25%) |

AKI = acute kidney injury, MES = multiple electrolytes solution.
Data are *n* (%), or parentheses with 95% CIs.

demonstrated no difference in the incidence of new AKI, or in-ICU mortality between saline and BCs (15, 16, 32). However, among the subgroup of patients with sepsis or impaired renal function at baseline, BC resuscitation fared better than saline (29, 30).

The present study included children with septic shock requiring fluid resuscitation, and the results concur with the subgroup of adults with sepsis in the SMART trial and, with that of a recent meta-analysis of adults with sepsis (15, 31). Patients who received BC had a lower incidence of major adverse kidney events and a trend towards a lower incidence of new AKI.

In the present pediatric study, the reduction in the risk of new-onset or progressive AKI with MES was greater compared with the adult trials. These effects were observed despite the baseline characteristics being similar and were not explained by other potential confounding factors (volume of fluid boluses in the first 6 or 24 hours, fluid balance, or time to achieve therapeutic endpoints of shock). Despite constituting about one-third of the fluid volumes in the first 24 hours, there was an increased risk of renal injury in the saline group. The possible reason for this phenomenon could be 1) NS has 50 % greater chloride than serum (154 vs 100 mEq/L, respectively). In a study on adults who had severe sepsis and shock, the authors found a dose-response relationship between the change in serum chloride level and the development of AKI. Each 1 mEq/L increase in serum chloride was associated with 1.25 times the odds of developing AKI (statistically significant) without significantly increasing RRT (33). The authors also found that the AKI stages 1, 2, and 3 were all associated with a mean change in serum chloride level greater than or equal to 5 mEq/L. Similar relations were observed in other studies too (34, 35). In the present study, the difference in chloride volume was clinically relevant and to the tune of 30–10 mEq/L in the first 2 days. Thus, the present study findings concur with the studies that have shown adverse effects of hyperchloremia on physiologic variables 2) hyperchloremia has also been shown to decrease glomerular filtration rate, reduce blood flow velocity, increase inflammation (36–39), and 3) administration of higher amounts of chloride over a short period of time such as in a bolus may have greater impact and add to the injury as has been reported as a result of increased permeability, glycocalyx shedding, and, leukocyte adhesion, as compared to BCs such as RL (40, 41).

We observed hyperchloremia and metabolic acidosis to be present in the patients in MES group also throughout the study. It is possible that the high chloride content in the maintenance fluids contributed to hyperchloremia in the MES group. Among other electrolytes evaluated, there was no difference between the two groups with respect to $K^+$ despite MES containing potassium. However, the $Na^+$ values were higher over the first 3 days in the saline group in concurrence with the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) trial findings which could be attributed to the higher $Na^+$ content in saline (29).

In the present study, both preschool children and adolescents were at a higher risk of AKI as compared with children 5–10 years old. The age distribution of AKI is similar to previously reported studies (25–27). It appears that any factors predisposing children to AKI affect these age ranges more than the school-going children.

The present study did not observe differences in the time to shock resolution or proportion attaining shock resolution, organ dysfunction scores or ventilator-free days, inotrope-free days, or ICU-free days. These findings are similar to those reported in a recent Cochrane review (42). In our study, the difference in requirement of RRT between the groups did not translate into meaningful clinical outcomes such as length of stay or mortality. The possible explanation for this might be that majority who required dialysis in the saline group had metabolic acidosis (possibly due to the shock and hyperchloremia) and most received peritoneal dialysis for brief duration.

The present study has limitations. First, the effect of the intervention observed in the present trial may have been specific to the use of the MES, and we cannot assume that results would be similar to the use of other BCs. Second, the study was blinded; however, the electrolyte profile may have indicated the fluid type to the treating team, which might have resulted in subtle changes in the type of fluid prescribed for maintenance. However, such adjustment would have been expected to underestimate, rather than overestimate, the impact of the initial fluid boluses. Third, the higher cost of some of the MES as compared to saline. However, if MES (PlasmaLyte) were used more extensively, the cost would probably decrease substantially. Fourth, we had a staged process of consent owing to the nature of the intervention (emergency)

because of which a very small number of patients were withdrawn after verbal consent. Means to reduce such withdrawals would be desirable in future trials. Finally, we compared the fluids only for bolus and not maintenance, and therefore the effect of the fluid when used for total fluid therapy needs to be evaluated in future studies.

In conclusion, among children presenting with septic shock, fluid resuscitation with MES as compared with 0.9% saline resulted in a significantly lower incidence of new and or progressive AKI during the first 7 days of hospitalization.

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1 *Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.*

2 *Division of Pediatric Critical Care, Department of Pediatrics, PGIMER, Chandigarh, India.*

3 *Department of Pediatrics Intensive Care, St Johns' Medical College Bengaluru, India.*

4 *Division of Pediatric Critical Care, Department of Pediatrics, JIPMER, Puducherry, India.*

5 *Research and Development Department, Kalinga Institute of Medical Sciences, Bhubaneswar, India.*

6 *Department of Pediatrics, AIIMS, Bhubaneswar, India.*

7 *Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, The Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

8 *Pediatric Intensive Care Unit, NMC Royal Hospital Khalifa City, Abu Dhabi, United Arab Emirates.*

9 *Department of Medicine, VMMC and Safdarjung Hospital, New Delhi, India.*

10 *Department of Emergency Medicine, AIIMS, New Delhi, India.*

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*For information regarding this article, E-mail: jhumaji@gmail.com*

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*The protocol is available in https://www.clinicaltrials.gov/ and de-identified participant data set used for analysis will be shared on request to the corresponding author at email id: jhumasankar@aiims.edu. Additional related documents such as the study protocol, and statistical analysis plan will be available with the publication in the electronic supplement (http://links.lww.com/CCM/H359) from the time of publication.*

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