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Crystalloid fluid administration was associated with outcomes in pediatric patients with severe sepsis or septic shock

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Abstract

Intravenous fluid prescription plays an important role in sepsis management, which may be associated with patient prognosis. The objective of the present study was to determine if the administration of crystalloid fluids is associated with clinical outcome for patients with severe sepsis and septic shock.

The medical records of 79 patients with severe sepsis or septic shock at an academic tertiary care hospital between 2011 and 2016 were reviewed retrospectively. The patients were dichotomized based on the median 3-day amount of corrected crystalloid fluids as low (<193 mL/kg) versus high (>193 mL/kg). The primary outcome measure was mortality. Secondary outcome measures included length of stay in the pediatric intensive care unit (PICU), usage of mechanical ventilation, etc.

The most common bacterial pathogens were *Escherichia coli* and *Klebsiella* spp. with a strikingly high number of multidrug-resistant infections (10.1%). The most common site of infection was of abdominal origin. Patients who received larger amounts of crystalloids were more likely to have lower weight and underlying comorbidities (high PRISM score). Although fluid intake was different in the 2 groups, output volumes were almost the same; therefore, a positive fluid balance was present in the high crystalloid patients. The incidence of mortality increased as the accumulated 3-day amount of crystalloid fluids administered increased. The total length of stay in the PICU was longer for patients who received high volume crystalloid fluid (15.8 ± 7.8 days) than for patients who received the lower volume (9.7 ± 5.3 days, $P = .026$).

A higher amount of 3-day crystalloid administration was unfavorable for postoperative outcomes in children with sepsis and septic shock; these patients experienced higher PICU mortality, longer PICU stays, and more ventilator days. More study on the benefits and harms of fluid in children are needed to improve patient safety and the quality of care that would facilitate better outcomes.

Abbreviations: HR = heart rate, ICU = intensive care unit, MAP = mean arterial blood pressure, PICU = pediatric intensive care unit, PRISM = Pediatric Risk of Mortality.

Keywords: crystalloid administration, length of PICU stay, mortality, septic shock

1. Introduction

Sepsis or septic shock, the dysregulated inflammatory response to an infection, remains a leading cause of death among children[1,2] in the intensive care unit (ICU). Fluid resuscitation is integral to maintain intravascular circulating volume and electrolyte homeostasis because the major pathophysiologic changes in patients with septic shock are often associated with a deficit in effective blood volume, resulting from increased external losses, leakage to the interstitial space, and vasodilation.[3,4] Recent studies have demonstrated wide variations in fluid administration practices among patients and hospitals,[5,6] and strong evidence has shown that acute resuscitation among patients with severe sepsis and septic shock can seriously affect mortality and ICU length of stay.[7,8] In the ICU, the use of the Pediatric Risk of Mortality (PRISM) score is of great importance for evaluating the efficacy and efficiency of a particular ICU.

It has been suggested that both hyperchloremia[9] and the infusion of chloride-rich fluids[10,11] have detrimental effects on clinical outcomes in postoperative and critically ill patients. The usual fluid used in clinical practice is 0.9% saline. Unfortunately, hyperchloremic acidosis produced by large volumes of 0.9% saline has been associated with adverse physiological effects[12] because the concentration of chloride in 0.9% saline is supra-physiological. Furthermore, due to the limitations of monitoring techniques, signs of fluid responsiveness are not always easy to interpret; thus, guiding fluid therapy remains a complex issue, as cardiac filling pressures are not reliable.[13] Conflicting findings have raised questions about traditional fluid practices regarding the optimal type (administering large volumes of crystalloid), quantity, and timing of fluid administration. Not surprisingly, there is a scarcity of evidence and specific clinical guidelines to guide this practice.

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To better evaluate the association of fluid accumulation with clinical outcomes, the present study aimed to assess the variability in crystalloid administration, especially for 0.9% saline, among pediatric patients with severe sepsis and septic shock at a large, tertiary care hospital. Specifically, we studied the relationship between the cumulative 3-day crystalloid fluid amount and outcomes in a series of septic patients treated in our institution, in the belief that restrictive crystalloid fluid therapy would be associated with better clinical outcomes.

2. Methods

2.1. Population

This study is a retrospective analysis of patients who underwent treatment for severe sepsis or septic shock in an academic pediatric intensive care unit (PICU) between 2011 and 2016 at Children's Hospital of Chongqing Medical University. The Institutional Review Board of the Chongqing Children's Hospital approved the study, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Specific informed consent was not considered necessary because this was an observational study with no interventions other than routine care. The patients identified as having severe sepsis or septic shock were considered eligible for entry into the study. The exclusion criteria were a stay of <3 days in the PICU, fasting <3 days, age of <6 months or >12 years, unexpected discharge from the PICU or patients transferred from/to other facilities, and incomplete data on fluid balance. In our unit, severe sepsis and septic shock were defined using the criteria published by the Society of Critical Care Medicine Consensus Conference and modified by Hayden. The demographic, clinical, laboratory data and pathological details were collected on the day of admission. Clinical status as defined by illness severity, therapeutic interventions, and medication management, including antibiotics, inotropes/vasopressors, steroids, mechanical ventilation, diuretics, and renal replacement therapy (hemofiltration), and comorbidities were recorded daily until hospital discharge or death. During the study period, 108 children were admitted to the PICU with sepsis or shock. Of these 108 patients enrolled, 29 were excluded: 8 patients were younger than 6 months, 13 were unexpectedly discharged due to financial reasons, 3 had stays of <3 days in the PICU, and 5 had incomplete data on fluid balance. The remaining 79 patients made up the study cohort.

2.2. Fluid administration

Fluid administration was initially guided by a number of variables, including arterial pressure, heart rate (HR), cardiac filling pressures and volumes, cardiac output, central venous oxygen saturations, and blood lactate levels.[3] We computed the fluid balance by subtracting the total fluid output from the total intake. The daily fluid output was calculated as the sum of the volumes of urine output, ultrafiltration fluid, drain fluid, and estimated gastrointestinal losses (including stools only in the presence of profound diarrhea). Insensitive losses were not considered because they are difficult to assess reliably. Daily fluid intake was calculated as the sum of all intravenous fluids, including crystalloid and colloid fluids. Additionally, corrected crystalloid fluids were reported as a corrected metric: mL of fluid per 1 kg weight to adjust for the confounding effects of body mass. For the purposes of analyses, the patients were divided based on the median amount of corrected crystalloid fluids, which was defined as low (<193 mL/kg) versus high (>193 mL/kg). In some cases, biochemical parameters accounted for oxygen debt during operation, such as serum lactate level, central venous oxygen saturation ($ScvO_2$), arterial acid–base balance parameters, and intraoperative hemodynamic parameters; inotropes used were recorded and evaluated. The primary outcome measure was PICU mortality, defined as all-cause mortality occurring during the PICU stay, including deaths resulting from withdrawal of therapy. Death occurring in the PICU is more likely to be related to severe sepsis or septic shock, whereas mortality measured at later time points is increasingly contaminated by deaths unrelated to sepsis. The secondary clinical outcome was the length of stay in the PICU following sepsis recognition to the day of discharge.

2.3. Statistical analysis

All calculations were performed using SPSS 20.0 (IBM, Armonk, NY). Continuous data with normal distribution were tested with paired or unpaired *t* tests, and non-normally distributed data were assessed with the Mann–Whitney *U* test between the 2 groups; the Kruskal–Wallis *H* test was used to analyze differences among groups. Unless stated otherwise, normally distributed data are presented as the mean ± standard deviation and as median (interquartile ranges) where not normally distributed. The chi-squared test or Fisher exact test was used to compare differences in categorical variables between groups. To elucidate the association of fluid overload with clinical outcomes, univariate regression analysis was performed to calculate odds ratio with 95% confidence interval. We then used multivariable logistic regression (risk ratio) to assess potential confounding effects of select clinical variables on the association of delayed antimicrobial administration with mortality. A $P < .05$ was considered statistically significant for all tests.

3. Results

3.1. Description of the cohort

Our study comprised 108 patients, among which, there was a slight male preponderance (60.0%), as 45 cases were male, and the median PRISM III score on the day of sepsis diagnosis was 13.1 (8.0–17.0). Of the 79 children included, the median age was 3.1 years, with approximately 11% of the children being younger than 1 year. Severe sepsis was diagnosed in 33 patients on the first day after admission and in 2 (4.1%) patients on the second day after admission. There were 44 patients (55.7%) with septic shock. A significant proportion of the patients required mechanical ventilation (73.4%) and vasopressor support (38.0%) during their stay in the PICU.

Most infections were intra-abdominal in origin with/without bowel perforation (n = 26, 32.9%); additional infections included respiratory (n = 10, 12.6%), skin and soft tissue (n = 9, 11.4%), and others (Table 1). Antibiotics were administered during the first hour after presentation to 26 patients (32.9%). The microbiology feature and in vitro sensitivity data from both gram-positive and gram-negative isolates in the PICU are summarized in Table 2. Among all the patients, gram-positive bacteria were isolated from 16 (20.3%) patients, including from the blood (n = 11), the sputum (n = 3), pleural effusion (n = 2), etc. There was a preponderance of gram-negative microorganisms isolated from 41 (51.9%) patients, including from the blood (n = 35), the sputum (n = 3), the cerebrospinal fluid (n = 2), and from pleural effusion (n = 1). *Escherichia coli* (n = 12, 15.2%),

Table 1

Clinical sites of infection among the patients with severe sepsis or septic shock.

Site of infection value	n (%)
Respiratory	10 (12.6)
Pneumonia	8 (10.1)
Empyema	2 (2.5)
Abdominal	26 (32.9)
Intra-abdominal abscess	12 (15.2)
Pancreatitis	1 (1.3)
Cholecystitis	3 (3.8)
Bowel perforation	8 (10.1)
Clostridium difficile enterocolitis	2 (2.5)
Central nervous system	4 (5.1)
Skin and soft tissue	9 (11.4)
Cellulitis	5 (6.3)
Necrotizing soft tissue infections	4 (5.1)
Primary blood stream (bacteremia/fungemia without identifiable source)	6 (7.6)
Others	4 (5.1)

Table 2

Primary organisms among the patients with severe sepsis or septic shock.

Organism value	N (%)
Gram-positive cocci	16 (20.3)
Staphylococcus aureus	7 (8.9)
Staphylococcus epidermidis	5 (6.3)
Enterococcus spp.	1 (1.3)
Other gram-positive organisms	3 (3.8)
Gram-negative rods	41 (51.9)
Escherichia coli	12 (15.2)
Klebsiella spp.	11 (13.9)
Acinetobacter spp.	8 (10.1)
Pseudomonas aeruginosa	5 (6.3)
Proteus spp.	2 (2.5)
Other gram-negative organisms	3 (3.8)
Anaerobes	14 (17.7)
Clostridium difficile	6 (7.6)
Bacteroides fragilis	4 (5.1)
Other *Clostridium* species	2 (2.5)
Other anaerobes	2 (2.5)
Fungus	5 (6.3)
Cryptococcus	4 (5.1)
Monilia	1 (1.3)
Mycoplasmas	4 (5.1)
Total culture-positive	59 (74.7)
Total culture-negative	20 (25.3)
Multidrug-resistant	8 (10.1)
Methicillin-resistant *Staphylococcus aureus*	4 (5.1)
Carbapenem-resistant gram-negative bacteria	2 (2.5
ESBL-producing Enterobacteriaceae	2 (2.5)

ESBL = extended-spectrum β-lactamases.

Klebsiella species (n = 11, 13.9%), *Staphylococcus aureus* (n = 7, 8.9%), *Acinetobacter baumannii* (n = 8, 10.1%), and *Pseudomonas* species (n = 5, 6.3%) were predominant. There were 23 patients with 2 different positive cultures. Mycoplasmas were isolated from 4 (5.1%) patients, including from the blood in 2 patients and from sputum cultures in 2 patients. Culture-negative sepsis was diagnosed in 20 (25.3%) patients. In addition, among all the patients, viral DNA was isolated from the blood of 11 (13.9%) patients, and antivirus IgM antibodies were detected in 8 (10.1%) patients. Antibiotics administered included cephalosporins (52.9%), penicillin derivatives (41.4%), metronidazole (23.1%), quinolones (13.5%), vancomycin (10.3%), sulfa derivatives (7.9%), miscellaneous drugs (15.6%), antifungal agents (8.9%), and antiviral agents (9.8%). A high rate of multidrug-resistant organisms was found, including methicillin-resistant *S aureus* (n = 4, 5.1%), third/fourth-generation cephalosporin-resistant *Pseudomonas aeruginosa* (n = 2, 2.5%), extended-spectrum β-lactamases-producing enterobacteriaceae (n = 2, 2.5%).

3.2. Fluid administration

The total amount of fluid administered for the first 3 days of the PICU stay in all patients averaged 2989 mL. The median 3-day crystalloid volume administered among all patients was 2530 mL. After adjusting for patient weight, median corrected crystalloid among the entire cohort was an average of 193 mL/kg (standard deviation, 53.8) (Table 3). To explore clinical outcomes associated with crystalloid administration, corrected crystalloid volume was dichotomized as "high" or "low" based on the median amount of crystalloid fluids (Table 1). There were 39 patients (controls) in the high crystalloid group (>193 mL/kg) and 40 patients (cases) in the low crystalloid group (<193 mL/kg). Patients in both groups received a combination of 0.45% saline, lactated Ringer, and 0.9% saline. Not surprisingly, patients who received a greater volume of crystalloid proportionally had a greater median total amount of fluid ($P = .006$) and were more likely to receive a greater volume of colloidal fluid, although no statistical significance was attained ($P = .057$). Table 3 demonstrates the pattern of cumulative fluid balance between the 2 groups in the first 3 days in the PICU. Although daily fluid intake was higher in the high crystalloid group, the difference in fluid output was not significant. Overall, the daily fluid balance was more positive in the high crystalloid group from the second day because fluid intake decreased in the low crystalloid group. The cumulative fluid balance was negative for at least 1 day in 11 of 117 patients in the high crystalloid group (9.4%) but in only 25 of 120 (20.8%) patients in the low crystalloid group ($P = .011$) throughout the 3 days of PICU stay.

3.3. Association of high crystalloid with clinical characteristics and outcomes

Table 4 summarizes the comparisons between the 2 groups. There was no difference in some of the baseline laboratory values, including white blood cell count, procalcitonin, albumin, serum lactate, and blood culture before antimicrobials and procedure. The 2 patient groups also did not significantly differ with respect to degree of renal dysfunction. Significant differences were noted with respect to the reason for PICU admission, primary diagnosis and underlying comorbidities (PRISM score) ($P = .027$). Patients in the 2 groups were also different with respect to age ($P = .043$) and weight ($P = .019$).

PICU mortality was higher in the high crystalloid group (46.2% vs. 25.0%; $P = .041$) (Table 5), and this difference was statistically significant. Survivors in the high crystalloid group also showed a trend toward a longer PICU stay (15.8 ± 9.8 vs. 9.7 ± 5.3 days; $P = .026$) (Table 5). A concomitant decrease in base excess and serum bicarbonate from baseline to the end of 3 days stay was observed in both groups but normalized early in the low crystalloid group; no difference was found between the groups. A higher proportion of patients in the high crystalloid group required mechanical ventilation (84.6% vs. 62.5%; $P = .024$),

Table 3

Amount of crystalloid and fluids infused in the 2 groups (mean ± standard deviation).

	PICU day 1			PICU day 2			PICU day 3			3-day amount		
	High	Low	*P*	High	Low	*P*	High	Low	*P*	High	Low	*P*
IV 0.9% saline, mL/kg	57.3 ± 11.4	51.8 ± 11.4	.000	55.5 ± 12.8	48.9 ± 11.9	.001	52.9 ± 10.9	49.2 ± 12.1	.000	166.4 ± 18.7	138.6 ± 19.9	.000
IV crystalloids, mL/kg	69.1 ± 12.7	61.3 ± 11.8	.000	65.3 ± 13.4	59.2 ± 12.3	.000	66.2 ± 11.6	60.4 ± 12.6	.004	205.2 ± 21.4	182.6 ± 13.3	.000
IV colloids, mL/kg	16.8 ± 3.9	15.9 ± 5.2	.016	17.9 ± 4.8	16.8 ± 4.4	.037	16.4 ± 4.7	15.3 ± 4.9	.092	49.1 ± 9.3	46.8 ± 8.6	.057
Water intake, mL/kg	85.9 ± 13.6	77.3 ± 11.8	.000	83.2 ± 12.9	76.0 ± 11.5	.003	82.6 ± 12.6	75.7 ± 12.4	.006	252.8 ± 24.6	229.3 ± 22.3	.006
Water output, mL/kg	67.5 ± 11.7	69.1 ± 10.8	.16	67.0 ± 11.6	66.4 ± 11.7	.24	68.8 ± 12.9	66.9 ± 12.1	.19	211.3 ± 47.5	206.9 ± 39.2	.22
Fluid balance, mL/kg	21.4 ± 7.6	19.8 ± 5.1	.054	16.2 ± 6.7	10.6 ± 4.2	.013	13.8 ± 5.2	8.8 ± 3.9	.009	42.6 ± 11.2	24.8 ± 10.4	.000

IV = intravenous injection, PICU = pediatric intensive care unit.

Table 4

Baseline characteristics of eligible patients based on crystalloid fluid administration.

	High crystalloid (39)	Low crystalloid (40)	*P*
Age, y	2.75 ± 2.36	3.26 ± 2.48	.043
Male:female	21:18	24:16	.37
Weight, kg	12.72 ± 5.76	13.81 ± 4.66	.019
PRISM score	13.4 ± 6.12	12.7 ± 6.83	.027
Baseline laboratory values			
WBC count	17.9 ± 5.8	18.5 ± 6.9	.43
PCT, ng/mL (normal value: 0–0.5)	11.6 ± 5.3	9.4 ± 6.8	.18
CRP, mg/L (normal value: 0–8)	26.6 ± 11.2	25.8 ± 9.7	.11
Albumin, g/L (normal range: 35–50)	29.7 ± 5.8	29.4 ± 6.6	.27
Creatinine, mg/dL	29.5 ± 8.5	28.8 ± 7.5	.33
Serum lactate, mmol/L	0.74 ± 0.36	0.66 ± 0.29	.16
Serum bicarbonate, mmol/L	22.5 ± 3.3	21.6 ± 3.4	.22
Blood culture before antimicrobials, n (%)	31 (79.5)	28 (70.0)	.24
Procedure, n (%)	17 (43.6)	22 (55.0)	.22

CRP = C-reactive protein, PCT = procalcitonin, PRISM = Pediatric Risk of Mortality, WBC = white blood cell.

vasopressor support (43.6% vs. 32.5%; $P = .22$), and corticosteroid use (38.5% vs. 25.0%; $P = .15$). There was a trend toward maintaining higher diuresis during the study period in the high crystalloid administration group ($P = .19$). No incidence of hyperchloremic acidosis ($P = .30$), hypotensive events ($P = .41$), and renal failure ($P = .49$) were found between the 2 groups. No difference in mean arterial blood pressure (MAP), HR, and central venous pressure was observed between the groups at the end of the PICU stay, although in both groups a significant decrease of MAP against the baseline value was found (data not shown).

4. Discussion

This study evaluated a population of 79 patients with severe sepsis and septic shock, 78% of whom had septic shock, with an overall PICU mortality of 35.4%. We demonstrated a wide variation in the patterns of fluid administration among patients with severe sepsis and septic shock based on various patient and clinical characteristics. Perhaps of more importance, we found a large range of variability for crystalloid fluid administration. While providing a more practical weight-based approach to determine degree of fluid overload, it appears that the use of crystalloid in patients with severe sepsis and septic shock is associated with an increase in the risk of death, prolonged PICU stay, and an increased need for mechanical ventilation. This observational study provides further support for a possible signal of harm associated with crystalloid fluid (main component 0.9% saline), which may be avoided by the cautious usage of more physiological fluids.

Our study describes some of the unique features of septic shock in pediatric patients compared with adults.[14,15] *Escherichia coli* and *Klebsiella* spp. were the most common bacterial pathogens, and a strikingly high number of multidrug-resistant infections (9.3%) were found. The most common site of infection was of abdominal origin. The use of corticosteroids (31.6%) was relatively low compared with that in the general cohort of patients described. Here, we also noted significant differences in the practice of crystalloid administration among pediatric patients with severe sepsis and septic shock, with a consequence of illness severity, which is an important aspect of fluid management. The results of the present study reiterate the need for improvement regarding the traditional volume in relation to appropriately monitored hemodynamic changes.

The present study demonstrated that there was some association between higher total volume of crystalloid and patient-specific characteristics such as young ages, low weight,

Table 5

Patient outcomes according to the crystalloid fluids utilization.

	High crystalloid (39)	Low crystalloid (40)		
PICU mortality	18 (46.2)	10 (25.0)	0.041	2.57 (0.99–6.67)
PICU length of stay, d	15.8 ± 7.8	9.7 ± 5.3	0.026	
Renal failure, n (%)	2 (5.1)	1 (2.5)	0.49	
Hyperchloremic acidosis, n (%)	3 (7.7)	1 (2.5)	0.30	
Hypotensive events, n (%)	6 (15.4)	8 (20.0)	0.41	
Diuresis, n (%)	11 (28.2)	7 (17.5)	0.19	
Required mechanical ventilation, n (%)	33 (84.6)	25 (62.5)	0.024	3.30 (1.12–9.71)
Required vasoactive infusion, n (%)	17 (43.6)	13 (32.5)	0.22	
Required corticosteroid use	15 (38.5)	10 (25.0)	0.15	

PICU = pediatric intensive care unit.

and high PRISM score. Patient-level variation in fluid administration may be subject to some confounding and selection bias due to such factors. Thus, the residual differences we observed represent unexplained, and likely unwarranted, variation in clinical care. Recent evidence has demonstrated that other factors pertaining to structures and processes can be targeted as potential avenues to implement standardized fluid resuscitation therapies and, therefore, improve clinical outcomes.[16–18] Patients with a high PRISM score were prone to have high crystalloid fluid administration in our study. This raises the question of whether it is possible that the greater PRISM score and the greater numbers of patients with shock in the high crystalloid group signified much sicker patients, which may have led to increased mortality rather than mortality being directly related to crystalloid fluid administration. Because this is a retrospective study, it is not possible to distinguish whether high crystalloid administration is simply a marker of illness severity or a causative factor of outcome. However, our study does demonstrate that high crystalloid administration was independently associated with mortality even after controlling for severity of illness, as assessed by PRISM score, and other potential confounders, such as baseline laboratory values, serum lactate, and serum bicarbonate in multivariate models. Although some of the differences were explained by patient and operative factors, even after normalizing fluid administration by eliminating severity of illness, significant variation remained, suggesting that other nonmeasurable and potentially clinically irrelevant factors may account for variation in fluid practice. The therapy policy in our critical care unit might advocate for more fluid administration compared with other PICU settings. We also pursue with caution the use of diuretics and inotropes implementation in consideration of electrolyte disturbances. There is a real opportunity to standardize behavior at the hospital level if best practices can be identified and codified.

The debate about fluid administration has been ongoing. Early and aggressive fluid resuscitation is essential and lifesaving for critically ill patients with severe sepsis and septic shock.[19,20] At the same time, aggressive fluid resuscitation on admission to the ICU may lead to fluid overload and adverse outcomes.[21] It is critical for fluid management to reach a balance between insufficient fluid resuscitation with consequent hypovolemia and excessive fluid with resulting edema and certain risks including pulmonary and intestinal edema. Although current fluid administration practices may even encourage excessive fluid administration, a positive association between fluid balance and mortality is quite well established in general ICU populations. A negative fluid balance was independently associated with weaning success in mechanically ventilated patients as well as with improving survival.[22] Furthermore, a decrease in ventilator and ICU days was seen in patients treated with fluid restriction and increased diuresis compared with patients on a wedge pressure-guided fluid protocol.[23] The current study expanded previous work by examining fluid administration status in pediatric patients with severe sepsis and septic shock, among whom the topic of crystalloid administration is particularly relevant. The association between increasing crystalloid administration and worsening clinical outcomes found in our study is similar to findings from previous clinical studies conducted in adult patients with severe sepsis.[13,24] However, it is important to consider a time-related relationship, because fluid administration is dynamic, changing according to the patient's evolution. When analyzing PICU-acquired daily fluid administration, we studied a group of patients with at least 72 hours of PICU stay, who might have potentially benefited from appropriate early fluid management. We did not only focus on the initial, rescue phase of fluid resuscitation but, rather, evaluated the time course over 3 days.

In our study population, the fluid balance was initially quite similar in the 2 fluid administration groups, but the high crystalloid patients received more fluids; from the second day, the fluid balance was more positive in this cohort. After initial resuscitation, the fluid balance decreased steadily in the low crystalloid patients but not in the high crystalloid patients. The differences in fluid balance were due to greater fluid input in high crystalloid administration rather than to a lower fluid output. Patients with low crystalloid administration were more likely to have a negative fluid balance early in their ICU stay. It was indicated that a positive fluid balance was an independent prognostic factor for ICU mortality, regardless of whether diuretics were used. In our study, high crystalloid administration was associated with mortality, which might be associated with the related positive fluid balance. Intravenous fluid therapy is one of the most common inpatient interventions prescribed, and 0.9% saline is the most common fluid used worldwide.[25] Given the absence of evidence supporting the use of 0.9% saline, we believe its use should be limited to the few indications where it is likely of value (e.g., hypovolemic hypochloremic alkalosis). Therefore, additional randomized clinical trials to explore whether interventions aimed at reducing 0.9% saline administration/accumulation may be linked with improved outcomes are needed in children with severe sepsis.

Because of several potential limitations in the current study, care should be taken when interpreting the data. First, the relatively small sample of heterogeneous patients in 1 institution may limit the generalizability of the results. The positive correlation between age and high fluid administration in this study might have been due to the higher prevalence of severe underlying diseases or comorbidities, such as respiratory and intestinal problems, in younger children rather than because of a direct effect of age. Given the retrospective nature of this single-center study, selection bias was a possibility. There may be residual confounders that potentially have affected the variability in fluid administration. We were unable to assess interhospital variability in crystalloid administration; thus, the current result may not be generalizable to other hospitals. It is possible that the exclusion of patients who stayed in the PICU for <72 hours could have significantly weakened the power of the corresponding analyses. For example, hemodynamic parameters and end points affecting the quantum and type of fluid administered could not be assessed in this study, which may have influenced the quantity of fluids administered. To assess whether these results could inform future iterations of sepsis guidelines as to the safe volume for fluid resuscitation, further large multicenter prospective studies are needed to evaluate the effect of fluid balance on clinical outcomes in children with severe sepsis.

5. Conclusions

Our study indicates that a wide range and significant variability in crystalloid administration exists among pediatric patients with severe sepsis. The observed variability in crystalloid practice was multifaceted. The 3 days of high crystalloid administration significantly increased the PICU mortality and duration of hospital stay. Standardizing care will serve not only to improve patient safety and quality of care but also to reduce unwanted variability, thus facilitating better quality of care. Moving forward, randomized clinical studies are needed to implement

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Author contributions

Shan Zhang designed the study, analyzed the data, and evaluated the manuscript. Yuhua Deng performed the statistical measurements and analyzed the data. Chunbao Guo analyzed the data and wrote the paper.
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