Resuscitation With Balanced Fluids Is Associated With Improved Survival in Pediatric Severe Sepsis*

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Objective: To evaluate outcomes in patients receiving balanced fluids for resuscitation in pediatric severe sepsis.

Design: Observational cohort review of prospectively collected data from a large administrative database.

Setting: PICUs from 43 children's hospitals.

Patients: PICU patients diagnosed with severe sepsis.

Interventions: None.

Measurements and Main Results: We reviewed data from the Pediatric Health Information System database from 2004 to 2012. Children with pediatric severe sepsis receiving balanced fluids for resuscitation in the first 24 and 72 hours of treatment were compared to those receiving unbalanced fluids. Thirty-six thousand nine hundred eight patients met entry criteria for analysis. Two thousand three hundred ninety-eight patients received exclusively balanced fluids at 24 hours and 1,641 at 72 hours. After propensity matching, the 72-hour balanced fluids group had lower mortality (12.5% vs 15.9%; $p = 0.007$; odds ratio, 0.76; 95% CI, 0.62–0.93), lower prevalence of acute kidney injury (16.0% vs 19.2%; $p = 0.028$; odds ratio, 0.82; 95% CI, 0.68–0.98), and fewer vasoactive infusion days (3.0 vs 3.3 d; $p < 0.001$) when compared with the unbalanced fluids group.

Conclusions: In this retrospective analysis carried out by propensity matching, exclusive use of balanced fluids in pediatric severe sepsis patients for the first 72 hours of resuscitation was associated with improved survival, decreased prevalence of acute kidney injury, and shorter duration of vasoactive infusions when compared with exclusive use of unbalanced fluids. (*Crit Care Med* 2017; 45:1177–1183)

Key Words: fluid therapy; isotonic solutions; mortality; pediatric; severe sepsis

Severe sepsis remains an important cause of morbidity and mortality in children. A recent study found a prevalence of pediatric severe sepsis (PSS) of 7.7% with a mortality rate of 14.4% (1). Fluid resuscitation remains integral to the management of severe sepsis, with crystalloids being used most frequently.

Crystalloids can be delineated as balanced or unbalanced in composition, based on the fluid's strong ion difference (SID), or the net charge of the solution's cations and anions (2–4). Decreases in SID below normal plasma SID (40 mEq/L) lead to a metabolic acidosis. Balanced fluids (BFs) are isotonic solutions having an SID closer to plasma SID and causing minimal acid base disturbances. An unbalanced fluid (UF) is one that causes a reduction in the plasma SID leading to a metabolic acidosis (3, 4).

Current standard treatment guidelines do not make specific recommendations for either BFs or UFs in the initial treatment of severe sepsis (5, 6). However, recent studies in adults have suggested that the use of BFs could confer outcome benefits (7, 8). No studies to date have evaluated the effect of crystalloid composition on outcomes in children with severe sepsis. The primary objective of this study was to evaluate associated outcomes in patients receiving BFs or UFs using a large administrative children's hospital database. We hypothesized that the exclusive use of BF for initial fluid resuscitation in PSS was associated with improved survival when compared with the use of UFs.

METHODS

Data Collection

This study was an observational cohort review of prospectively collected data in the Pediatric Health Information

***See also p. 1246.**

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System (PHIS) database. This database, maintained by the Children's Hospital Association (CHA), incorporates demographic, outcome, and resource utilization data from 43 different freestanding children's hospitals in the United States (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C484). As previously described, the CHA and participating hospitals assure data quality for the database (9). This study was approved by institutional review boards from both the CHA and Children's Healthcare of Atlanta.

Patient Identification

Patients from 0 to 18 years old who were admitted to a PICU from January 2004 to December 2012 and had a diagnosis of PSS were included for analysis.

Definitions

Patients were identified as having PSS based on the presence of one of the following *International Classification of Diseases*, 9th Revision (ICD-9) codes: severe sepsis (995.92), septic shock (785.52), or an ICD-9 code for infection plus at least one code of organ dysfunction (as previously described by Angus et al [10]). As defined by Weiss et al (11) in 2012, we used a modified approach to the criteria by Angus et al (10) with an updated set of ICD-9 codes, and codes specific for septicemia, sepsis with acute organ dysfunction, and septic shock were also included (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/C485).

The definition of a pediatric complex chronic condition, as outlined by Feudtner et al (12) (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/C486), was used to identify comorbidities. Length of ICU and hospital stays were reported as medians with the interquartile range being 25th and 75th percentiles. Type of infection was identified by ICD-9 codes. No culture results were available for further classification. Acute kidney injury (AKI) was defined by ICD-9 codes for acute kidney failure, as clinical variables such as serum creatinine and urine output were not available in this database.

Identification of Resuscitation Fluids

BFs were defined as solutions having an SID close to plasma, and they were identified in the PHIS database as multiple electrolyte solutions. UFs were defined as having an SID equal to 0 and included only 0.9% saline. We defined a fluid bolus as any recorded volume greater than 90 mL to differentiate fluid used for resuscitation from fluid used for carrier solutions or maintenance fluids. Time of administration for first fluid bolus was considered the beginning of the resuscitation period, and 72 hours after the first-reported bolus was defined as the end of the resuscitation. Patients were selected for comparative analysis if they had either exclusively received BFs or UFs for fluid boluses during the resuscitation period. Patients with missing or invalid data were excluded from analysis.

Outcomes

The primary outcome measure was in-hospital mortality. Secondary outcomes included presence of AKI, use of continuous renal replacement therapy (CRRT), hospital length of stay (total LOS), PICU LOS, and vasoactive infusion days.

Statistical Analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Statistical significance was assessed at the 0.05 level unless otherwise noted. Chi-square tests were used to compare categorical variables, and two-sample *t* tests or Wilcoxon rank-sum tests were used to compare continuous variables. Propensity score matching was performed to balance fluid groups on baseline characteristics. Briefly, multivariable logistic regression was used to predict receipt of BFs. All significant characteristics identified in univariate analysis were considered for the propensity model with the model that maximized model fit ultimately being used. The ability of the model to predict BF use was assessed using the area under the receiver operating characteristic curve (AUROC). For each patient, the multivariable model was used to obtain their predicted probability, or propensity, of receiving BFs. A 1:6 greedy matching algorithm was used to match patients with and without BFs based on their propensity scores. After propensity matching was completed, the matched cohort was then assessed to ensure balanced distribution of covariates between groups using similar methods as described above. Outcomes of interest were compared in the balanced propensity-matched cohorts utilizing generalized linear mixed models with random intercepts and slopes to account for variation among hospitals. The identity link function assuming a normal distribution was used to model log-transformed values of total LOS and PICU LOS. Logistic distributions with logit links were used to model mortality, and Poisson distributions with log links were used to model the number of vasoactive infusion days. A sensitivity analysis of propensity score methods was performed by utilizing the inverse probability of treatment weighting (IPTW) method, truncating extreme weights to the first and 99th percentiles. The same models as described previously were performed using the IPTW method. Results from using IPTW were compared to the 1:6 matched propensity score results to ensure there was no bias resulting from the statistical method applied to the propensity scores.

RESULTS

Of 636,842 PICU admissions, 49,153 patients met criteria for PSS. Of those patients who met PSS criteria, 36,908 were identified for analysis of fluid resuscitation.

Clinical Characteristics

In the overall cohort, mortality decreased from 21% in 2004 to 12% in 2012 ($p < 0.001$). Prevalence of AKI did not change over the period (24–23%; $p = 0.453$), but CRRT use decreased (12–7%; $p < 0.001$). Patients with exclusive use of BFs in the 72-hour resuscitation group decreased from 10.9% in 2004 to 3.4% in 2012 ($p < 0.001$). Twenty-four percent of patients (n = 8,935) received any amount of BFs during the first 24

TABLE 1. Twenty-Four–Hour Fluid Groups Demographics

Clinical Characteristics	Balanced Fluids Only ($n = 2,398$)	Unbalanced Fluids Only ($n = 30,166$)	p
Gender, *n* (%)			
Male	1,308 (54.5)	15,891 (52.7)	0.079
Female	1,090 (45.5)	14,271 (47.3)	
Age at admission			< 0.001
Mean years ± SD	6.0 ± 6.1	7.4 ± 6.3	
Median years (25–75th percentile)	3.2 (0.6–11.6)	5.8 (1.2–13.5)	
Median year of visit (25–75th percentile)	2007 (2005–2009)	2008 (2006–2010)	< 0.001
Comorbidities, *n* (%)			
Any condition	1,845 (76.9)	22,332 (74.0)	0.002
Neurologic	663 (27.7)	7,580 (25.1)	0.006
Cardiovascular	790 (32.9)	7,748 (25.7)	< 0.001
Respiratory	199 (8.1)	2,020 (6.7)	0.003
Renal	92 (3.8)	1,884 (6.3)	< 0.001
Gastroenterology	150 (6.3)	1,625 (5.4)	0.071
Hematology/immunology	153 (6.4)	2,257 (7.5)	0.047
Metabolic disorder	238 (9.9)	4,252 (14.1)	< 0.001
Malignancy	356 (14.9)	5,766 (19.1)	< 0.001
Other	377 (15.7)	3,804 (12.6)	< 0.001
Type of infection, *n* (%)			
Bacterial	1,937 (80.8)	24,069 (79.8)	
Fungal	12 (0.5)	218 (0.7)	
Both	415 (17.3)	5,280 (17.5)	0.135
None	34 (1.4)	599 (2.0)	

Demographic characteristics of PICU patients meeting pediatric severe sepsis criteria receiving either exclusive unbalanced fluids or exclusive balanced fluids in the first 24 hr of resuscitation.

hours; 2,398 patients received exclusively BFs at 24 hours and 1,641 at 72 hours. In the 24-hour (**Table 1**) and 72-hour fluid groups (**Table 2**), patients receiving BFs were younger at admission and more likely to have neurologic, cardiovascular, or respiratory comorbidities. General type of infection did not differ between BFs and UFs groups in either the 24- or 72-hour fluid cohorts. Unadjusted patient outcomes for the 24- and 72-hour groups are noted in **Table 3**. Hospital mortality was significantly lower in the 24-hour exclusive BFs group compared with the UFs group (14.3% vs 15.8%; $p = 0.048$), as was AKI prevalence (17.2% vs 23.2%; $p < 0.001$) and CRRT use (6.1% vs 9.0%; $p < 0.001$). In the 72-hour fluid groups, mortality did not significantly differ between exclusive BFs and UFs patients. However, AKI (16.2% vs 23.1%; $p < 0.001$) and CRRT use (6.2% vs 8.9%; $p < 0.001$) were significantly less common in the BFs group. Patients receiving BFs for the first 24 hours had longer PICU LOS (10 vs 8 d; $p < 0.001$) and total LOS (23 vs 19 d; $p < 0.001$). Patients receiving BFs for 72 hours also had longer PICU LOS (9 vs 8 d; $p < 0.001$) and total LOS (23 vs 19 d; $p < 0.001$). Of note, LOS in nonsurvivors was significantly shorter in those who received UFs compared with those who received BFs at both 24 and 72 hours (Table 3).

Propensity-Matched Analysis

Patients who exclusively received BFs were matched in a 1:6 ratio with those who received only UFs at both 24 and 72 hours. Propensity models for both 24 and 72 hours resulted in good model fit (AUROC, 0.795 and 0.823, respectively). Variables in the propensity model included hospital, year, gender, age, use of therapeutic plasmapheresis, septic shock, acute organ dysfunction, and neurologic, cardiovascular, respiratory, renal, metabolic, malignancy, or other comorbidities. In the 24-hour fluid group (**Table 4**), 10,318 patients were matched (8,844 UFs and 1,474 BFs). Total LOS and PICU LOS were significantly longer for patients who received exclusively BFs. Total LOS among survivors and nonsurvivors was also longer

TABLE 2. Seventy-Two–Hour Fluid Groups Demographics

Clinical Characteristics	Balanced Fluids Only (*n* = 1,641)	Unbalanced Fluids Only (*n* = 27,973)	*p*
Gender, *n* (%)			
Male	910 (55.5)	14,721 (52.6)	0.026
Female	731 (44.5)	13,248 (47.4)	
Age at admission			
Mean years ± SD	5.5 ± 6.3	7.4 ± 6.3	< 0.001
Median years (25–75th percentile)	2.5 (0.5–10.5)	5.8 (1.1–13.5)	
Median year of visit (25–75th percentile)	2007 (2005–2009)	2008 (2006–2010)	< 0.001
Comorbidities, *n* (%)			
Any condition	1,271 (77.5)	20,802 (74.4)	0.005
Neurologic	469 (28.6)	7,091 (25.4)	0.004
Cardiovascular	562 (34.3)	7,224 (25.8)	< 0.001
Respiratory	152 (9.3)	1,895 (6.8)	< 0.001
Renal	61 (3.7)	1,770 (6.3)	< 0.001
Gastroenterology	103 (6.3)	1,508 (5.4)	0.124
Hematology/immunology	103 (6.3)	2,122 (7.6)	0.051
Metabolic disorder	165 (10.1)	3,960 (14.2)	< 0.001
Malignancy	209 (12.7)	5,351 (19.1)	< 0.001
Other	264 (16.1)	3,552 (12.7)	< 0.001
Type of infection, *n* (%)			
Bacterial	1,331 (81.1)	22,339 (79.9)	
Fungal	10 (0.6)	195 (0.7)	0.490
Both	274 (16.7)	4,874 (17.4)	
None	26 (1.6)	565 (2.0)	

Demographic characteristics of PICU patients meeting pediatric severe sepsis criteria receiving either exclusive unbalanced fluids or exclusive balanced fluids in the first 72 hr of resuscitation.

in the BFs group. There were no significant differences in vasoactive infusion days, presence of AKI, or CRRT use between the two groups. Although mortality was lower in the group who received exclusively BFs, this difference was not statistically significant (13.4% vs 15.5%; $p = 0.051$; odds ratio [OR], 0.85; 95% CI, 0.72–1.00). In the 72-hour fluid group (**Table 5**), 7,000 patients were matched (1,000 patients in the BFs group and 6,000 patients in the UFs group). Mortality was significantly lower in the group receiving BFs (12.5% vs 15.9%; $p = 0.007$; OR, 0.76; 95% CI, 0.62–0.93), as was AKI prevalence (16.0% vs 19.2%; $p = 0.028$; OR, 0.82; 95% CI, 0.68–0.98), and vasoactive infusion days (3.0 vs 3.3 d; $p \leq 0.001$). Total LOS was longer in the BFs group, but PICU LOS was not significantly different. Again, total LOS in survivors and nonsurvivors was longer among the BFs group. The use of CRRT was lower in the BF group, but this difference was not significant (5.4% vs 7.2%; $p = 0.054$; OR, 0.75; 95% CI, 0.56–1.01). Additional analysis of outcomes by age (**Supplemental Table 4**, Supplemental Digital Content 4, http://links.lww.com/CCM/C487; and **Supplemental Table 5**, Supplemental Digital Content 5, http://links.lww.com/CCM/C488) found significantly better survival in the cohorts of children 1–4 years old who received exclusively BFs when compared with those who received exclusively UFs at both 24 (10.3% vs 15.0%; $p = 0.02$; OR, 0.66; 95% CI, 0.46–0.93) and 72 hours (9.4% vs 16.3%; $p = 0.005$; OR, 0.54; 95% CI, 0.35–0.83). Mortality was not significantly different for all other age groups. Sensitivity analyses using IPTW methods showed similar results to the matched analysis in both 24- and 72-hour fluid groups (**Supplemental Table 6**, Supplemental Digital Content 6, http://links.lww.com/CCM/C489; and Supplemental Table 7, **Supplemental Digital Content 7**, http://links.lww.com/CCM/C490). Because of the increased sample size by using the entire sample when using the IPTW method, we had greater power to detect differences between BFs and UFs groups. Therefore, our sensitivity analysis found significant differences between BFs and UFs for all outcomes except the number of vasoactive infusion days in the 24-hour group. Mean estimates of total and PICU LOS were within 3% of the

TABLE 3. Unadjusted Outcomes for 24- and 72-Hour Fluid Groups

24-hr Fluid Group Outcomes	Balanced Fluids Only (*n* = 2,398)	Unbalanced Fluids Only (*n* = 30,166)	*p*
Mortality, *n* (%)	343 (14.3)	4,776 (15.8)	0.048
Acute kidney injury, *n* (%)	413 (17.2)	7,001 (23.2)	< 0.001
Continuous renal replacement therapy use, *n* (%)	147 (6.1)	2,710 (9.0)	< 0.001
Median total LOS in days (25–75th percentile)	23 (11–45)	19 (9–39)	< 0.001
Median total LOS in nonsurvivors in days (25–75th percentile)	25 (7–57)	19 (5–49)	0.001
Median total PICU LOS in days (25–75th percentile)	10 (4–22)	8 (3–19)	< 0.001
72-hr Fluid Group Outcomes	**Balanced Fluids Only (*n* = 1,641)**	**Unbalanced Fluids Only (*n* = 27,973)**	***p***
Mortality, *n* (%)	234 (14.3)	4,449 (15.9)	0.076
Acute kidney injury, *n* (%)	266 (16.2)	6,471 (23.1)	< 0.001
Continuous renal replacement therapy use, *n* (%)	101 (6.2)	2,486 (8.9)	< 0.001
Median total LOS in days (25–75th percentile)	23 (11–48)	19 (9–39)	< 0.001
Median total LOS in nonsurvivors in days (25–75th percentile)	28 (7–67)	19 (5–50)	0.001
Median total PICU LOS in days (25–75th percentile)	9 (3–22)	8 (3–19)	< 0.001

LOS = length of stay.

Outcomes including mortality, acute kidney injury, use of continuous renal replacement therapy, and length of stay for patients receiving exclusively balanced fluids or exclusively unbalanced fluids at 24 and 72 hr of resuscitation.

TABLE 4. Propensity-Matched Outcomes for 24-Hour Fluid Groups

Outcome	Only Balanced Fluids (*n* = 1,474), Mean (95% CI) or *n* (%)	Only Unbalanced Fluids (*n* = 8,844), Mean (95% CI) or *n* (%)	Adjusted OR	*p*
Total length of stay in days[a]	22.0 (20.2–24.0)	18.6 (17.4–19.9)	–	< 0.001
Total length of stay in survivors in days[a]	22.2 (20.4–24.2)	19.5 (18.2–20.9)	–	< 0.001
Total length of stay in nonsurvivors in days[a]	21.3 (16.8–26.9)	14.7 (12.0–16.8)	–	0.001
PICU length of stay in days[a]	8.4 (7.6–9.4)	7.5 (6.9–8.3)	–	0.001
Vasoactive infusion days[b]	3.4 (3.1–3.9)	3.4 (3.1–3.8)	–	0.897
Mortality[c]	198 (13.4)	1,370 (15.5)	0.85 (0.72–1.00)	0.051
Acute kidney injury[c]	289 (19.6)	1,702 (19.2)	1.05 (0.91–1.21)	0.492
Continuous renal replacement therapy use[c]	90 (6.1)	621 (7.0)	0.88 (0.70–1.11)	0.289

OR = odds ratio.

[a]Linear regression on log-transformed values.

[b]Poisson regression.

[c]Logistic regression.

Propensity-matched outcomes (1:6) of patients receiving exclusive balanced fluids compared with exclusive unbalanced fluids in the first 24 hr of resuscitation (*n* = 10,318).

matched results. All OR estimates were within 18% of the matched results, with only AKI and CRRT ORs in the 24-hour fluid group differing by more than 12%.

DISCUSSION

This study represents the first large comparison of balanced and unbalanced crystalloids in PSS patients. We found that the use of BFs for the first 72 hours of resuscitation was associated with improved survival when compared with the use of UFs. The survival difference, although suggestive, was not appreciated over the 24-hour resuscitation period. Overall mortality improved over the decade evaluated. However, the percent of cohort exclusively using BFs decreased over time. Recommendations for fluid choice have not changed over this period (5, 13). These findings make it difficult to ascribe mortality changes with BF use alone.

TABLE 5. Propensity-Matched Outcomes for 72-Hour Fluid Groups

Outcome	Only Balanced Fluids ($n = 1,000$), Mean (95% CI) or n (%)	Only Unbalanced Fluids ($n = 6,000$), Mean (95% CI) or n (%)	Adjusted OR	p
Total length of stay[a]	21.0 (19.1–23.0)	18.1 (16.0–19.3)	–	< 0.001
Total length of stay in survivors in days[a]	21.5 (19.6–23.5)	19.0 (17.7–20.3)	–	0.001
Total length of stay in nonsurvivors in days[a]	18.9 (14.0–25.4)	14.2 (12.0–16.8)	–	0.050
PICU length of stay[a]	7.8 (6.8–8.9)	7.4 (6.6–8.2)	–	0.202
Vasoactive infusion days[b]	3.0 (2.6–3.4)	3.3 (2.9–3.8)	–	< 0.001
Mortality[c]	125 (12.5)	954 (15.9)	0.76 (0.62–0.93)	0.007
Acute kidney injury[c]	160 (16.0)	1,153 (19.2)	0.82 (0.68–0.98)	0.028
Continuous renal replacement therapy use[c]	54 (5.4)	433 (7.2)	0.75 (0.56–1.01)	0.054

OR = odds ratio.

[a]Linear regression on log-transformed values.

[b]Poisson regression.

[c]Logistic regression.

Propensity-matched outcomes (1:6) of patients receiving exclusive balanced fluids compared with exclusive unbalanced fluids in the first 72 hr of resuscitation ($n = 7,000$).

The impact of crystalloid composition on survival in adults has been variable, with only retrospective studies showing a mortality benefit with the use of BFs. In a retrospective cohort study of septic adults (7), patients receiving BFs had lower in-hospital mortality (19.6% vs 22.8%; relative risk, 0.86; 95% CI, 0.78–0.94). In a propensity-matched cohort review, adults with systemic inflammatory response syndrome (SIRS) receiving BFs had increased survival compared with those receiving UFs (8). However, in a more recent double-blind, cluster randomized, double-crossover trial of adult ICU patients, randomization to UFs or BFs showed no difference in survival (14).

Differences in pathophysiologic mechanisms of pediatric and adult sepsis could affect the ability to apply results of adult studies to outcomes in children. Adult sepsis is associated with vasoplegia and high cardiac output dysfunction (15, 16). Myocardial dysfunction and low cardiac output are more prevalent in pediatric sepsis (6, 16, 17). Additionally, ongoing maturation of pediatric organ systems has necessitated pediatric-specific definitions for clinical entities such as sepsis and septic shock (18). Management of pediatric sepsis is therefore directed in light of these differences (5). In our analysis, associated survival benefit in 24- and 72-hour BFs patients was seen among children 1–4 years old. No significant survival benefit was seen among older children and adolescents. Lack of survival difference could reflect relatively small numbers for subgroup analysis, or it could reflect a differential impact of BFs in pediatric sepsis which is less prominent with transition to adulthood.

Patients who received BFs for 24 or 72 hours had increased total LOS compared with those who received UFs. Further analysis showed LOS was significantly shorter in both survivors and nonsurvivors receiving UFs, although it was still greater than 14 days in both groups. This suggests either a relative reduction in LOS in patients receiving UFs or prolongation of LOS with BFs. This difference could be due to some unmeasured confounder not accounted for in the propensity model resulting in greater severity of illness in the UFs group.

AKI was decreased in patients receiving BFs for the first 72 hours of resuscitation. Some adult studies have also suggested increased propensity for development of AKI with the use of UFs (19, 20). In a prospective adult trial, the use of chloride-restricted fluids was associated with lower incidence of injury and failure class AKI and decreased use of CRRT (19). However, randomization to UFs or BFs in the SPLIT trial did not result in a difference in AKI prevalence (14).

The proposed mechanisms for the harmful effects of UFs remain uncertain. The most frequently cited hypothesis is the impact of chloride on development of metabolic acidosis, altered immune function, and kidney function (21). A retrospective cohort study of adult sepsis patients found higher mortality in patients with hyperchloremia at admission and at 72 hours (22). In a retrospective analysis of adult SIRS patients, higher chloride loads were associated with increased mortality (23). Although hyperchloremic metabolic acidosis has been recognized in children as a consequence of fluid resuscitation, associated harm has not been established (24). Our findings of associations between outcomes and fluid choice did not address mechanisms of harm.

There are several limitations to this study. Use of an administrative database is retrospective and lacks clinical detail. The PHIS database does not differentiate sepsis on admission from hospital-acquired sepsis, creating difficulties confirming timing of fluid resuscitation in relation to timing of the septic episode. However, 90% of the cohort had their initial day of resuscitation on the first hospital day. It was also not possible to determine patient fluid balance. Since fluid overload has been associated with worse outcomes (25, 26), inability to account for this variable is a limitation. Previous adult studies were also able to evaluate the impact of BFs in a dose-response fashion (7).

The inability to calculate patient fluid amounts precluded a similar dose-response measurement in the current study.

The use of ICD-9 codes to define patients with severe sepsis has been established as problematic, as PSS may be underrepresented (11). Recently, updated consensus adult sepsis definitions have been created that could help better define sepsis (27). However, these definitions have not been validated in pediatric patients. Until revised pediatric sepsis definitions are confirmed, dependence on ICD-9 codes remains a standard approach. Additionally, using database codes to define kidney injury may underrepresent true AKI prevalence (28–30).

We used propensity matching analysis to help correct for possible confounding characteristics; however, this analysis still has the potential for introducing bias (31). Therefore, we performed a sensitivity analysis using IPTW methods and found similar results to our propensity-matched analysis.

In conclusion, in this propensity-matched analysis of PSS patients, exclusive use of BFs for the first 72 hours of resuscitation was associated with improved survival, decreased prevalence of AKI, and shorter duration of vasoactive infusion use when compared with those receiving UFs for resuscitation. These findings warrant further prospective studies comparing outcomes with BFs in PSS.

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