Original Article

Positive Fluid Balance is Associated with Poor Clinical Outcomes in Paediatric Severe Sepsis and Septic Shock

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Abstract

Introduction: Growing evidence suggests there is potential harm associated with excess fluid in critically ill children. This study aimed to evaluate the association between percentage fluid overload (%FO) and paediatric intensive care unit (PICU) mortality in children with severe sepsis and septic shock. Materials and Methods: Patients with severe sepsis and septic shock admitted to the PICU were identified through discharge codes. Data on clinical characteristics, fluid input and output were collected. %FO was calculated as: (total daily input - total daily output [L]/admission body weight [kg]) × 100. The primary outcome was PICU mortality. Secondary outcomes were 28-day ventilator-free days (VFD), intensive care unit-free days (IFD) and inotrope-free days (InoFD). Multivariate analysis adjusting for presence of comorbidities, Pediatric Index of Mortality (PIM) 2 score and multiorgan dysfunction were used to determine the association between cumulative %FO over 5 days and outcomes. Results: A total of 116 patients were identified, with a mortality rate of 28.4% (33/116). Overall median age was 105.9 (23.1-157.2) months. Cumulative %FO over 5 days was higher in non-survivors compared to survivors (median [interquartile range], 15.1 [6.3-27.1] vs 3.6 [0.7-11.1]%; *P* <0.001). Cumulative %FO was associated with increased mortality (adjusted odds ratio 1.08, 95% confidence interval 1.03-1.13; *P* = 0.001) and decreased VFD, IFD and InoFD (adjusted mean difference -0.37 [-0.53 - -0.21] days, -0.34 [-0.49 - -0.20] days, and -0.31 [-0.48 - -0.14] days, respectively). Conclusion: Cumulative %FO within the first 5 days of PICU stay was consistently and independently associated with poor clinical outcomes in children with severe sepsis and septic shock. Future studies are needed to test the impact of restrictive fluid strategies in these children.

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Key words: Multiorgan dysfunction, Percentage fluid overload, Ventilator-free days

Introduction

For many years, the clinical dogma of early goal-directed therapy (EGDT) with fluid resuscitation was one of the cornerstones of treatment in sepsis.[1,2] Surviving Sepsis Campaign guidelines recommended fluid resuscitation to restore mean circulating filling pressure guided by bedside parameters for patients with sepsis.[3] However, recent studies have challenged this approach to fluid resuscitation, demonstrating that positive fluid balance was associated with poor clinical outcomes.[4,5] In light of the Fluid Expansion As Supportive Therapy (FEAST) trial in critically ill African children, where aggressive early fluid resuscitation in children with severe febrile illness was associated with relative risk of mortality of almost 1.5, recent World Health Organization (WHO) guidelines for fluid resuscitation in children with severe sepsis and septic shock now advocate for a more conservative approach to fluid resuscitation.[4,6]

Beyond the initial fluid resuscitation period, however, there is growing evidence on the potential harm of positive fluid balance in critically ill patients.[5] Adult sepsis studies

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demonstrated that positive cumulative fluid balance and volume overload lead to increased mortality, organ dysfunction, mechanical ventilation (MV) duration and need for renal replacement therapy.[5,7] Positive fluid balance over 7 days in adults with sepsis and septic shock was associated with mortality.[8] Other studies have demonstrated a "dose-dependent" relationship of cumulative fluid balance and mortality.[9] Fluid overload in other subgroups of patients such as adults with acute lung injury was associated with longer MV duration and intensive care unit (ICU) stay.[7]

With only a limited number of studies, the impact of fluid balance on septic children after admission to the paediatric intensive care unit (PICU) remains controversial.[10-12] In critically ill children with severe sepsis and septic shock, fluid overload—whether given within the first 24 hours or within 7 days of PICU admission—was shown to be associated with increased mortality.[11,12] Interestingly, a multicentre study reported that the effect of positive fluid balance on mortality was only present in those who had a low mortality risk from septic shock; whereas in the high mortality risk group, there was no association between fluid balance and worse clinical course.[10] Fluid overload in other groups of critically ill children including those with acute lung injury and those on continuous renal replacement therapy (CRRT) provides indirect evidence of its negative effects.[13-15] A recent meta-analysis of 3200 patients studying the association between fluid balance and a general cohort of critically ill children reported a 6% increase in odds of mortality for every 1% increase in percentage fluid overload (%FO).[16]

Therefore, there is equipoise on the impact of fluid balance in children with severe sepsis and septic shock. We postulated that a greater amount of positive fluid balance is associated with poor clinical outcomes. This study aimed to: 1) identify the risk factors for mortality in paediatric severe sepsis and septic shock; and 2) evaluate the relationship between %FO and PICU mortality in this group of patients.

Materials and Methods

This is a retrospective cohort study performed in a multidisciplinary PICU of the largest tertiary, university-affiliated paediatric hospital in Singapore. Intensivists treated patients with sepsis according to current sepsis guidelines though practice was not strictly protocolised. This study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2016/2171) and waiver of consent was granted.

Study Design

Patients were identified based on their discharge diagnosis from hospital-wide administrative-linked electronic databases. The study population was one with paediatric severe sepsis or septic shock as defined by the International Pediatric Sepsis Consensus Conference.[17] To ensure complete pick-up, we identified all patients discharged with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) after 12 January 2012 equivalent for codes A02.1, A31.2, A32.7, A39.1, A39.2, A40, A41, A48.3 and A49.9 or with the key words "bacteraemia", "sepsis", "severe sepsis" and "septic shock". Case records were examined to determine if the definition for severe sepsis or septic shock was fulfilled and thus eligible for inclusion in the study. Patients admitted to the PICU between 1 January 2010 and 31 October 2017 were included. Patients were 0 to 18 years of age and from any source of admission (whether from the ward or emergency room).

Data Collection

We extracted demographic, microbiological, clinical and detailed fluid input and output data from electronic medical records. Comorbidities were considered based on the "Complex Chronic Conditions" list of diseases.[18] The Pediatric Index of Mortality (PIM) 2 and Pediatric Logistic Organ Dysfunction (PELOD) scores were taken on PICU admission.[19,20] Data on the use of diuretics and renal replacement therapy were also collected. Organ dysfunction was defined according to the International Pediatric Sepsis Consensus Conference definitions.[7] Day 1 of sepsis was defined as the first day the patient fulfilled the criteria for severe sepsis or septic shock in the PICU.

Total daily input was calculated as the sum of all intravenous and oral fluids administered to the patient. Total daily output was calculated as the sum of all output volumes including urine, gastrointestinal aspirates, drains and fluid removal by renal replacement therapies. Insensible losses were not taken into account. For standardisation, fluid calculations were done based on 6 am input/output. This was done for the first 5 days of sepsis. The magnitude of positive fluid balance was expressed as %FO and was calculated using the following formula: Daily %FO = (total daily input - total daily output [L]/admission body weight [kg]) × 100.[16] Cumulative %FO was calculated as the sum of daily % FO over the first 5 days of sepsis.

Outcomes

Our primary outcome was PICU mortality. PICU mortality was treated as a binary variable with the categories of "survivors" and "non-survivors". Secondary outcomes were ventilator-free days (VFD), intensive care unit-free days (IFD) and inotrope-free days (InoFD), of up to 28 days. This was to account for mortality as a competing outcome. VFD was defined as days-free and alive from MV up to 28

days. Hence, if a patient was on MV for 28 days or more, or died at any time during PICU admission, his/her VFD was taken as zero. InoFD was defined as days-free and alive from inotropic support up to 28 days. IFD was defined as days alive and discharged from the PICU up to 28 days. VFD, IFD and InoFD were treated as continuous data.

Statistical Analysis

All demographic, clinical and microbiological data were summarised with respect to PICU mortality status. Categorical and continuous data were summarised as counts (percentages) and median (interquartile range [IQR]), respectively. Mortality groups were compared using Mann-Whitney U and chi-squared tests for continuous and categorical variables, respectively. Univariate and multivariate logistic regression was used to adjust for a priori determined covariates on the basis of previously established associations including %FO, presence of comorbidities, PIM 2 score and multiorgan dysfunction for the binary outcome of PICU mortality.[21-23] Association from logistic regression was expressed as odds ratio (OR) with 95% confidence interval (CI). Univariate and multivariate linear regression was used to estimate association between all secondary outcomes (i.e. VFD, InoFD, IFD and covariates).

Receiver operating characteristic (ROC) curve analysis was performed to examine the ability of %FO to discriminate between survivor and non-survivor patients. Sensitivity against (1− specificity) was plotted at each level and the area under the ROC curve (AUROC)—which reflects the probability of correctly identifying survivor and non-survivor patients—was calculated. The Youden index (sensitivity+ specificity−1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value to 1, the greater the diagnostic power.[24] %FO cut-offs were determined based on the best Youden Index. Univariate and multivariate models based on %FO as a continuous or categorical variable were also compared. %FO cut-offs were also used for all secondary outcomes.

All statistical tests were 2-sided and P values <0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, North Carolina, United States of America).

Results

There were 116 patients with severe sepsis or septic shock over the study period (Fig. 1). A total of 33/116 (28.4%) patients died with a median time to death of 4 (2-10) days. The overall median age was 105.9 (23.1-157.2) months (Table 1). Majority of patients (95/116 [81.9%]) were admitted to the PICU either directly from the emergency room or within 1 day of hospital admission. First-dose antibiotics were received within an hour of presentation

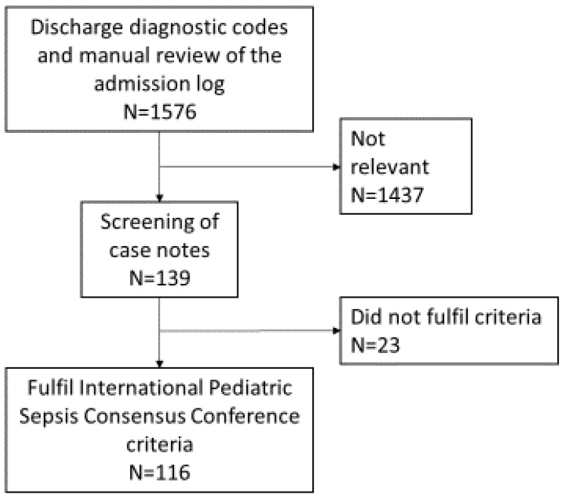

Fig. 1. Flowchart demonstrating the identification process of patients with severe sepsis and septic shock.

in 55/116 (47.4%) patients and the most common first-line antibiotic was a second-generation cephalosporin (45/55 [81.8%]). Fluid bolus and inotropes were received within an hour of presentation in 87/116 (75.0%) and 26/116 (22.4%) patients, respectively. Bacteraemia was present in 20/116 (17.2%) patients. The most common bacterial and viral aetiology of sepsis in our cohort was *Streptococcus species* (11/116 [9.5%]), influenzae (7/116 [6.0%]) and adenovirus (7/116 [6.0%]), respectively (Table 2).

Non-survivors had higher admission PIM 2 (5.0 [4.0-14.3]% vs 2.7 [1.1-6.4]%; P <0.001) and PELOD (22.0 [12.0-32.0] vs 11.0 [10.0-20.0]; P<0.001) scores compared to survivors. Non-survivors were also more likely to have underlying comorbidities (24/33 [72.7%] vs 35/83 [42.2%]; P = 0.004). Compared to survivors, there was a greater proportion of non-survivors with multiorgan dysfunction (33/33 [100%] vs 53/83 [63.9%]; P <0.001) and who required PICU support in the form of inotropes (33/33 [100%] vs 58/83 [69.9%]; P <0.001), MV (32/33 [97.0%] vs 42/83 [50.6%]; P ≤0.001) and CRRT (9/33 [27.3%] vs 4/83 [4.8%]; P = 0.002). The overall VFD, InoFD and IFD were 23 (0-28), 25 (0-28) and 21 (0-26) days, respectively.

Daily %FO on the first 5 days of sepsis was higher in non-survivors (Fig. 2). Non-survivors had persistently high daily %FO up to the 5th day of PICU admission. Cumulative %FO over 5 days was significantly higher in non-survivors compared to survivors (median [IQR], 15.1 [6.3-27.1] vs 3.6 [0.7-11.1]%; P <0.001) (Table 3).

In the multivariable logistic regression model, cumulative %FO was independently associated with mortality (adjusted OR, 1.08; 95% CI, 1.03-1.13; P = 0.001] (Table 4). Hence, for every 1% FO increase, there was an increase in mortality

Table 1. Clinical Characteristics of Patients with Severe Sepsis and Septic Shock

Characteristic	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Age, months	78.1 (28.4 – 1567.0)	112.8 (21.4 – 159.1)	105.9 (23.1 – 157.2)	0.951
Weight, kg	18.0 (12.0 – 30.9)	27.5 (11.0 – 45.0)	24.7 (11.4 – 40.0)	0.118
PIM 2	5.0 (4.0 – 14.3)	2.7 (1.1 – 6.4)	3.7 (1.3 – 9.6)	**<0.001**
PELOD	22.0 (1.02 – 32.0)	11.0 (10.0 – 20.0)	12.0 (10.0 – 22.0)	**<0.001**
Male gender	16 (48.5)	36 (43.4)	52 (44.8)	
Comorbidities	24 (72.7)	35 (42.2)	59 (50.9)	**0.004**
Multiorgan dysfunction	33 (100.0)	53 (63.9)	86 (74.1)	**<0.001**
Systemic corticosteroids	8 (24.2)	15 (18.1)	23 (19.8)	0.450
Mechanical ventilation	32 (97.0)	42 (50.6)	74 (63.8)	**<0.001**
Diuretics	11 (33.3)	28 (33.7)	11 (33.3)	1.000
CRRT	9 (27.3)	4 (4.8)	13 (11.2)	**0.002**
Duration of mechanical ventilation, days	3 (1 – 10)	2 (0 – 6)	2 (0 – 7.5)	**0.008**
Duration of PICU stay, days	4 (2 – 10)	4 (2 – 10)	4 (2 – 10)	0.973
Inotropes	33 (100.0)	58 (69.9)	91 (78.4)	**<0.001**
Dopamine	27 (81.8)	45 (54.2)	72 (62.1)	**0.006**
Adrenaline	31 (93.9)	20 (24.1)	51 (44.0)	**<0.001**
Noradrenaline	25 (75.8)	33 (39.8)	58 (50.0)	**<0.001**
Dobutamine	3 (9.1)	10 (12.0)	13 (11.2)	0.756
Vasopressin	12 (36.4)	3 (3.6)	15 (12.9)	**<0.001**
Milrinone	3 (9.1)	5 (6.0)	8 (6.9)	0.686
Duration of inotropes, days	2 (1 – 5)	1 (0 – 4)	2 (0 – 4)	**<0.001**
ECMO	4 (12.1)	4 (4.8)	8 (6.9)	0.221

CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; PELOD: Pediatric Logistic Organ Dysfunction; PICU: Paediatric intensive care unit; PIM 2: Pediatric Index of Mortality 2
Continuous and categorical data are presented as median (interquartile range) and counts (percentage), respectively.

Table 2. Microbiological Characteristics of Patients with Severe Sepsis and Septic Shock

Characteristic	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Bacterial sepsis	13 (39.4)	30 (36.1)	43 (37.1)	0.832
Viral sepsis	16 (48.5)	25 (30.1)	41 (35.3)	0.085
Fungal sepsis	4 (12.1)	2 (2.4)	6 (5.2)	0.054
No organism	7 (21.2)	33 (39.8)	40 (34.5)	0.083
Source of infection				
Lower respiratory tract	17 (51.5)	40 (48.2)	57 (49.1)	0.838
Genitourinary	2 (6.1)	3 (3.6)	5 (4.3)	0.622
Central nervous system	5 (15.2)	5 (6.0)	10 (8.6)	0.145
Soft tissue	1 (3.0)	5 (6.0)	6 (5.2)	0.673
Gastrointestinal	7 (21.2)	14 (16.9)	21 (18.1)	0.600
Others	1 (3.0)	14 (16.9)	15 (12.9)	0.064

Categorical data is presented as counts (percentage).
Values may not add up due to overlapping categories.

by 8%. The ROC curve analysis identified 2 cut-offs (2.3 and 14.6%FO) with the highest Youden index (data available from authors upon request). Patients with cumulative %FO in the range of 2.3-14.6% had 5-fold increased odds of mortality, whereas those with >14.6% had a nearly 20-fold increased odds of mortality (Table 5). Cumulative %FO was also independently associated with decreased VFD, InoFD and IFD (Table 4). Comparing the same %FO cut-offs, there was also a dose-dependent reduction in VFD, IFD and InoFD with increasing %FO.

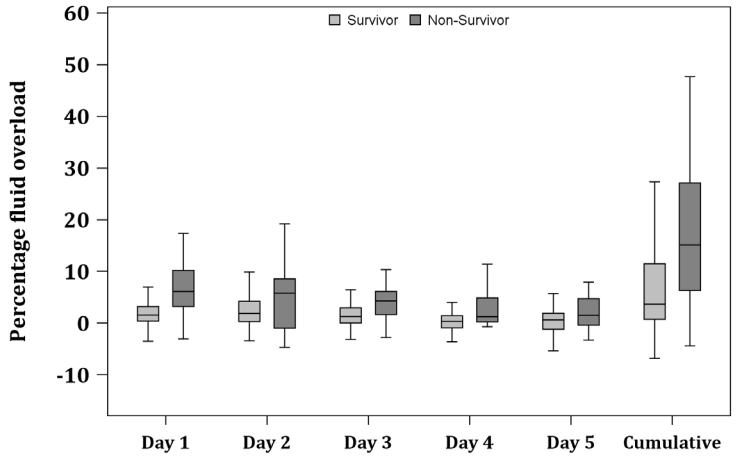

Fig. 2. Daily percentage fluid overload in survivors and non-survivors. The box spans the interquartile range. The median value is marked by the horizontal line within the box and the whiskers represent the minimum and maximum values.

Table 3. Percentage Fluid Overload in Survivors and Non-Survivors

Percentage Fluid Overload	Non-Survivor (n = 33)	Survivor (n = 83)	All (n = 116)	*P* Value
Day 1	6.1 (3.2 – 10.2)	1.5 (0.1 – 3.2)	2.3 (0.6 – 5.0)	**<0.001**
Day 2	5.8 (-1.0 – 8.5)	1.8 (0.2 – 4.1)	2.4 (0.2 – 5.8)	**0.046**
Day 3	4.3 (1.6 – 6.1)	1.0 (0.0 – 2.9)	1.6 (0.0 – 3.8)	**0.002**
Day 4	1.2 (0.2 – 4.8)	0.5 (-1.0 – 2.0)	0.7 (-0.5 – 2.2)	**0.035**
Day 5	1.5 (-0.5 – 4.7)	0.6 (-0.9 – 1.8)	0.9 (-0.7 – 2.1)	0.082
Cumulative	15.1 (6.3 – 27.1)	3.6 (0.7 – 11.1)	5.6 (1.2 – 14.3)	**<0.001**

Continuous data is presented as median (interquartile range).

Table 4. Multivariate Analysis for Primary and Secondary Outcomes

Outcome	Covariate	Unadjusted		Adjusted	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PICU mortality*	Comorbidities (ref: no)	3.66 (1.52 – 8.83)	0.0039	2.89 (1.04 – 7.99)	**0.041**
	PIM 2	1.02 (1.000 – 1.05)	0.0507	1.01 (0.98 – 1.03)	0.555
	Multiorgan dysfunction (ref: no)	38.22 (2.16 – 676.95)	0.0130	16.21 (0.9 – 292.34)	0.059
	% fluid overload	1.11 (1.06 – 1.16)	<0.0001	1.08 (1.03 – 1.13)	**0.001**
		β (95% CI)	*P* Value	β (95% CI)	*P* Value
VFD†	Comorbidities (ref: no)	-8.82 (-14.34 – -3.31)	0.0017	-3.97 (-8.68 – 0.73)	0.098
	PIM 2	-0.11 (-0.33 – 0.11)	0.3197	0.01 (-0.16 – 0.19)	0.881
	Multiorgan dysfunction (ref: no)	-14.39 (-20.15 – -8.64)	<0.0001	-8.45 (-14.14 – -2.76)	**0.004**
	% fluid overload	-0.50 (-0.66 – -0.33)	<0.0001	-0.37 (-0.53 – -0.21)	**<0.001**
IFD†	Comorbidities (ref: no)	-7.97 (-13.15 – -2.78)	0.0026	-3.51 (-7.73 – 0.71)	0.104
	PIM 2	-0.20 (-0.40 – 0.00)	0.0523	-0.08 (-0.23 – 0.07)	0.312
	Multiorgan dysfunction (ref: no)	-14.42 (-19.66 – -9.18)	<0.0001	-8.29 (-13.4 – -3.19)	**0.002**
	% fluid overload	-0.48 (-0.62 – -0.33)	<0.0001	-0.34 (-0.49 – -0.20)	**<0.001**
InoFD†	Comorbidities (ref: no)	-9.98 (-15.30 – -4.67)	0.0002	-5.97 (-10.88 – -1.05)	**0.018**
	PIM 2	-0.08 (-0.29 – 0.14)	0.4996	0.02 (-0.16 – 0.20)	0.817
	Multiorgan dysfunction (ref: no)	-12.67 (-18.55 – -6.80)	<0.0001	-6.85 (-12.80 – -0.91)	**0.024**
	% fluid overload	-0.43 (-0.60 – -0.26)	<0.0001	-0.31 (-0.48 – -0.14)	**<0.001**

CI: Confidence interval; IFD: 28-day intensive care unit-free days; InoFD: 28-day inotrope free-days; OR: Odds ratio; PICU: Paediatric intensive care unit; PIM 2: Pediatric Index of Mortality 2; Ref: Reference group; VFD: 28-day ventilator-free days

*Logistic regression.

†Linear regression.

Table 5. Association Between Categories of Cumulative Percentage Fluid Overload (Determined by Receiver Operating Curve Analysis) and Clinical Outcomes

Cumulative % Fluid Overload (Ref <2.3%)	Adjusted β Estimate (Days)	*P* Value
28-day ventilator-free days*		
2.3 – 14.6		
>14.6	-17.25 (-22.89 – -11.6)	**<0.001**
28-day intensive care unit days*		
2.3 – 14.6	-7.71 (-12.13 – -3.29)	**<0.001**
>14.6	-15.72 (-20.79 – -10.64)	**<0.001**
28-day inotrope-free days*		
2.3 – 14.6	-6.08 (-11.51 – -0.65)	**0.028**
>14.6	-13.49 (-19.72 – -7.26)	**<0.001**
	Adjusted OR (95% CI)	***P* Value**
Mortality†		
2.3 – 14.6	5.81 (1.29 – 26.25)	**0.022**
>14.6	19.10 (3.94 – 92.56)	**<0.001**

CI: Confidence interval; OR: Odds ratio; Ref: Reference group
*Linear regression.
†Logistic regression.
Covariates: Comorbidities, Pediatric Index of Mortality 2 and multiorgan dysfunction.

Discussion

The main overall finding of this study is that cumulative positive balance over the first 5 days of paediatric severe sepsis and septic shock is consistently, independently and in a dose-dependent manner associated with poor clinical outcomes including increased mortality, decreased VFD, IFD and InoFD. Other independent risk factors for mortality include the presence of comorbidities.

In adults with severe sepsis, there are conflicting data with regard to the impact of fluid balance and clinical outcomes. Retrospective studies in adults demonstrated that higher fluid balance was associated with increased mortality/organ dysfunction.[5,25,26] This association was supported in a single-centre prospective cohort of 173 adults with sepsis: positive fluid balance over 7 days was associated with mortality in all patients (adjusted hazard ratio [aHR], 1.01; 95% CI, 1.01-1.02 per ml/kg increase; P <0.001) and within the subgroup with septic shock (aHR, 1.01; 95% CI, 1.01-1.02; P <0.001).[8] A multicentre prospective observational study (n = 1808) involving 730 ICUs globally demonstrated a stepwise increased hazard ratio of mortality with higher quartiles of cumulative fluid balance on the 3rd day of admission in septic patients with and without septic shock.[9]

Nevertheless, there was also evidence of reduced mortality with higher fluid volumes in the subgroup of patients who remained in shock for longer periods.[27] When adults in septic shock from another prospective multicentre observational study were evaluated after day 3 of shock, 95/164 patients were deemed to be still in shock. Of these, the patients who received higher fluid volumes had lower 90-day mortality rates (40% vs 62%, P = 0.03) than those receiving lower volumes in spite of comparable simplified acute physiology score II and sequential organ failure assessment scores.[27]

Similar to critically ill adults, fluid management beyond the initial period of fluid resuscitation remains a controversial topic in children with severe sepsis. In these children, the impact of fluid balance after the initial resuscitation period was studied in 2 retrospective studies.[10,11] A single-centre study of 202 children with severe sepsis showed that fluid overload in the first 24 hours (aOR, 1.20; 95% CI, 1.08-1.33; P = 0.001) and PICU-acquired daily fluid overload for 7 days (aOR, 5.47 per log increase; 95% CI, 1.15-25.96; P = 0.032) were independent risk factors for mortality.[11] A multicentre retrospective cohort study involving 317 children with septic shock stratified patients into low-, intermediate- and high-risk categories using a validated biomarker-based stratification tool (the Pediatric Sepsis Biomarker Risk [PERSEVERE] model).[10,28] Cumulative positive fluid balance up to 7 days was associated with increased mortality in the low-risk category (OR, 1.04; 95% CI, 1.00-1.07) but not in the high-risk category (aOR, 0.93; 95% CI, 0.97-1.02; P = 0.536). Results from our study are contrary to the findings in this latter study. We still found an association between fluid balance and worse clinical outcomes after adjusting for severity of illness as measured by the PIM 2 score. However, our finding must be interpreted in the context that there is a possibility that severity of sepsis measured by the PIM 2 score is less robust compared to the PRESERVE biomarker model.

Taken together, findings from other paediatric studies and ours demonstrate that progressive fluid overload is associated with poorer clinical outcomes. This clinical observation is substantiated by cellular and pathophysiological studies. Due to increased capillary leak and protein extravasation, excessive fluid administration results in tissue oedema, impaired oxygen and metabolite diffusion, distorted tissue architecture and impaired lymphatic and capillary drainage which contribute to progressive organ dysfunction.[29,30] In the lung, the consequences of pulmonary oedema are evident by reduced compliance and impaired gas exchange.[31] Myocardial oedema causes impaired contractility and diastolic dysfunction.[32] Fluid accumulation also causes cerebral, hepatic, renal interstitial and gastrointestinal oedema and is associated with poor outcomes.[30] These adverse pathophysiologic changes correlate with our study findings which show an association between cumulative fluid balance and the need for MV and inotropic support as well as length of PICU stay. This is reinforced by our finding of association with poor clinical outcomes with higher cut-offs of cumulative %FO consistent with data from adult studies.[9] These thresholds may be considered for planning future randomised controlled trials.

Our study, however, has several limitations. Patients were identified by diagnostic codes and this may be incomplete as some patients may have been coded according to their original site of infection (e.g. pneumonia, urinary tract infection, etc.). The small sample size over a long period of time may have introduced confounders in treatment strategies over the years. Moreover, the retrospective design cannot exclude confounding by indication. Greater fluid administration and hence greater cumulative fluid balance may be due to greater illness severity associated with increased vascular leakage and third spacing of fluid, rather than a direct cause of increased mortality. The type of fluids received for resuscitation and maintenance were not protocolised and not investigated in this study. However, we did show that cumulative %FO was associated with poor clinical outcomes even after adjusting for severity of illness, comorbidities and multiorgan dysfunction. The retrospective design also precludes us from accounting for other unknown and unmeasurable confounders of disease severity and patient characteristics. However, given the challenge of performing a randomised controlled trial in this group of critically ill children, our study provides preliminary data that requires validation in future prospectively designed trials.

Conclusion

This retrospective study showed that cumulative fluid balance over the first few days of sepsis was associated with mortality, VFD, IFD and InoFD—with greater harm associated with a greater magnitude of positive balance. This association requires further validation and confirmation in future larger prospective studies. Specifically, future studies examining the impact of a liberal versus conservative fluid balance strategy in children with severe sepsis and septic shock need to inform on the impact of fluid balance in these critically ill children.

REFERENCES

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
2. Chong SL, Ong GY, Venkataraman A, Chan YH. The golden hours in paediatric septic shock – current updates and recommendations. Ann Acad Med Singapore 2014;43:267-74.
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.
4. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-95.
5. Brotfain E, Koyfman L, Toledano R, Borer A, Fucs L, Galante O, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. Am J Emerg Med 2016;34:2122-6.
6. World Health Organization. Paediatric Emergency Triage, Assessment and Treatment Care of Critically Ill Children. Geneva: World Health Organization; 2016.
7. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
8. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015;19:251.
9. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. Crit Care Med 2017;45:386-94.
10. Abulebda K, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, et al. Post-ICU admission fluid balance and pediatric septic shock outcomes: a risk-stratified analysis. Crit Care Med 2014;42:397-403.
11. Chen J, Li XZ, Bai ZJ, Fang F, Hua J, Li Y, et al. Association of fluid accumulation with clinical outcomes in critically ill children with severe sepsis. Plos One 2016;11:17.
12. Naveda OE, Naveda AF. Positive fluid balance and high mortality in paediatric patients with severe sepsis and septic shock. Pediatria 2016;49:71-7.
13. Hayes LW, Oster RA, Tofil NM, Tolwani AJ. Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care 2009;24:394-400.
14. Valentine SL, Sapru A, Higgerson RA, Spinella PC, Flori HR, Graham DA, et al. Fluid balance in critically ill children with acute lung injury. Crit Care Med 2012;40:2883-9.
15. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med 2012;13:253-8.

16. Alobaidi R, Morgan C, Basu RK, Stenson E, Featherstone R, Majumdar SR, et al. Association between fluid balance and outcomes in critically ill children: a systematic review and meta-analysis. JAMA Pediatr 2018;172:257-68.
17. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
18. Edwards JD, Houtrow AJ, Vasilevskis EE, Rehm RS, Markovitz BP, Graham RJ, et al. Chronic conditions among children admitted to US pediatric intensive care units: their prevalence and impact on risk for mortality and prolonged length of stay*. Crit Care Med 2012;40:2196-203.
19. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 2003;362:192-7.
20. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29:278-85.
21. Vila Perez D, Jordan I, Esteban E, Garcia-Soler P, Murga V, Bonil V, et al. Prognostic factors in pediatric sepsis study from the Spanish Society of Pediatric Intensive Care. Pediatr Infect Dis J 2014;33:152-7.
22. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes and therapies study. Am J Respir Crit Care Med 2015;191:1147-57.
23. Pedro Tda C, Morcillo AM, Baracat ECE. Etiology and prognostic factors of sepsis among children and adolescents admitted to the intensive care unit. Rev Bras Ter Intensiva 2015;27:240-6.
24. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J 2005;47:458-72.
25. Neyra JA, Li X, Canepa-Escaro F, Adams-Huet B, Toto RD, Yee J, et al. Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. Crit Care Med 2016;44:1891-900.
26. Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. Chest 2000;117:1749-54.
27. Smith SH, Perner A. Higher vs lower fluid volume for septic shock: clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort. Crit Care 2012;16:R76.
28. Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, et al. The pediatric sepsis biomarker risk model. Crit Care 2012;16:R174.
29. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol 2010;6:107-15.
30. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrology 2016;17:109.
31. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136:102-9.
32. Boyle A, Maurer MS, Sobotka PA. Myocellular and interstitial edema and circulating volume expansion as a cause of morbidity and mortality in heart failure. J Card Fail 2007;13:133-6.