

# Fluid Overload in Children with Severe Sepsis and Septic Shock

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**Abstract:** Fluid therapy is one pillar of the treatment of septic shock, however, a hydric  $\geq 10\%$  of the weight or Fluid Overload (FO  $> 10\%$ ) is associated with poor hospital outcomes. The present study aims to determine the FO in patients with septic shock, and its main associations in terms of mortality and morbidity. An observational and descriptive study was conducted in 49 hospitalized children with septic shock in the PICU of the Manuel Ascencio Villarroel Children's Hospital (MAVCH); The patients were divided into two groups according to the FO  $> 10\%$  (22 patients) and  $< 10\%$  (18 patients), for their descriptive analysis we included comparison of means and calculation of the OR. Regarding the water requirements, we observed that the group with FO  $> 10\%$  a mean of 5681ml; while in the group with ISCH  $< 10\%$  the mean was 3297.8ml ( $p=0.19$ ) during first 72 hours, showing greater overload with the administration of colloids and blood products ( $p=0.02$ ,  $p=0.004$ ). Regarding hospital outcomes, was found morbidity associated with FO  $> 10\%$  (respiratory dysfunction, vasopressor requirement and renal replacement therapy); The length of hospitalization and FO were not different in groups ( $p=0.60$ ), but there was higher mortality of patients with FO  $> 10\%$  ( $p=0.01$ , OR: 5.57 IC95% 1.4-21.8). Fluids therapy of in the patient with septic shock constitutes one of the first-line hemodynamic treatments, however in limited resources settings, overload should be avoided, mainly due to associated morbidity during the first 72 hours.

**Keywords:** Fluid Overload, Sepsis, Septic Shock, Fluid Therapy

## 1. Introduction

The incidence of severe sepsis and septic shock varies between 20 and 30% in most pediatric intensive care units (PICU) and is one of the leading causes of mortality. [1]

One of the pillars of septic shock treatment is fluid therapy to increase systolic volume and, thus, the patient's cardiac output as an initial resuscitation measure. [2-4] However, the balance of fluids provided  $\geq 10\%$  of body weight or Fluid Overload (FO) is associated with organic dysfunction, mortality, stay in PICU, duration of Mechanical Ventilation (MV) and use of Renal Replacement Therapy (RRT). [5-8]

This research will provide knowledge regarding fluid therapy in children with septic shock, filling the void that exists regarding FO and its possible negative effects present

in our patients. Therefore, the present study sought to determine the FO in patients with septic shock admitted to the PICU of the Manuel Ascencio Villarroel Children's Hospital (MAVCH), and its main associations based on mortality and hospital stay.

## 2. Methods

An observational and descriptive study was conducted in 49 children hospitalized with septic shock in the MAVCH PICU, using a randomized sampling of all admissions, a sample size of 50 patients was calculated for this purpose; excluding those with congenital heart disease, known kidney or liver disease, those resuscitated with fluids or vasopressor therapy outside the hospital and those who died before 72 hours of admission. The patients were divided into 2 groups

according to the FO>10% or<10% for later analysis.

The FO was established according to the following formula: Fluid overload index=((total of liquids administrated - total of eliminated liquid) / body weight of entry x 100), assuming as a cut-off point the FO>10% registered until the third day of hospitalization in the FO. The score of the Pediatric Logistic Organic Dysfunction Score (PELODS) was determined according to pre-established values. It was established on the 3rd day of the study, which was compared with the water overload index, to see the relationship of organic dysfunction.

In the statistical analysis, version 23.0 of the SPSS Statistics® program was used. The descriptive analysis

included a comparison of means for the quantitative variables and percentages for the qualitative variables with the Chi square test and the Mann-Whitney U test. Determination of the normality of the sample using a t-student test.

### 3. Results

In 2016, 254 patients were admitted to PICU, 49 of them with septic shock, 9 were excluded due to the criteria of this study, with 40 remaining for the study, they were divided into 2 groups: FO>10% 22 patients and 18 patients in FO<10% group, which were groups with comparable characteristics. See Table 1.

**Table 1.** Distribution by age, sex, infectious focus, comorbidities of the study groups Fluid overload<and>10%.

		Fluid Overload Index	
		FO>10%	FO<10%
Gender	Male	12 (54,5%)	10 (55,6%)
	Female	10 (45,5%)	8 (44,4%)
Ege	<1 year	5 (22,7%)	9 (50%)
	1 to 5 years	9 (40,9%)	9 (50%)
	6 to 9 years	3 (13,6%)	0 (0%)
	10 to 15 years	5 (22,7%)	0 (0%)
	Respiratory	14 (63,6%)	11 (61,1%)
Infectious source	Soft tissues	2 (9,1%)	0 (0%)
	Abdominal	1 (4,5%)	4 (22,2%)
	Without focus	5 (22,7%)	1 (5,6%)
	Nervous system	0 (0%)	2 (11,1%)
	None	12 (54,5%)	15 (83,3%)
Comorbidities	Malnourishment	5 (22,7%)	3 (16,7%)
	Oncohematologic	4 (18,2%)	0 (0%)
	Prematurity	1 (4,5%)	0 (0%)

Regarding the administration of crystalloid, colloid and blood products solutions, they were administered (additional to basal requirements) a total volume of 1610ml to 7700ml (80 to 385 ml/kg/24hours) with a mean of 2121ml (106 ml/kg/24hours) in the FO>10% group and a volume of 312ml to 2949ml (16 to 147 ml/kg/24hours) with a mean of 499ml (25ml/kg/24hour) in the FO<10% group. Being able to determine a significant relationship between the administration of crystalloid, colloid and blood products and FO (p=0.004).

The 0.9% saline solution was administered in 85% (n=34) of the total patients and ringer lactate in 45% (n=18). A

mean bolus of 891ml (45 ml/kg) of 0.9% saline were administered in FO>10% group and 366ml (19 ml/kg) in the FO<10% group. From ringer lactate, an average of 381.4ml in patients with FO>10% group, and 161ml in patients with FO<10%, in relation to FO there is no statistically significant difference between both crystalloid solutions (p=0.28). See table No 2. Colloid administration is observed in 65% (n=26) of patients; The albumin being 5% used in 25 patients and the jellies in 4. In patients with FO>10%, an average of 390.5ml of colloids was administered, while in the FO group<10% 159.6ml; having a significant difference in relation to FO (p=0.02). See tables 2-3.

**Table 2.** Cristaloid solution administration and Fluid Overload.

Fluid Overload Index	Saline Solution 0,9% (Vol. ml)	Ringer Lactato Solution (Vol. ml)	Cristaloid total Volume Total (Vol. ml)
FO>10% (Mediana)	891	381,4	1272,5
FO<10% (Mediana)	366,6	161,1	527,8

p=0,28.

**Table 3.** Colloid solution administration and Fluid Overload.

Fluid Overload Index	Albumin 5% (Vol. ml)	Scratch (Vol. ml)	Colloid total volume (Vol. ml)
FO>10% (Mediana y rangos)	372,3 (0,0–1200)	18,1 (0,0–400)	390,5 (0,0–1600)
FO<10% (Mediana y rangos)	119,6 (0,0–860)	40 (0,0–430)	159,6 (0,0–1290)

p=0.02.

The administration of blood products (transfusion of red blood cells and fresh frozen plasma) administered in 80%

(n=32) of the patients; The red blood cells transfusion (RBCT) was performed in 75% (n=30) of the cases and

frozen fresh plasma (FFP) in 52.5% (n=21). In patients with FO>10% they received an average of 325.7ml of RBCT and 289.84ml of FFP; while patients with FO<10% averaged

89.86ml of RBCT and 57.7ml of FFP, both groups showing statistically significant differences (p=0.002 for RBCT and p=0.09 for FFP). See table 4.

**Table 4.** Hemoderivated transfusion and fluid overload.

Fluid Overload Index	Red Cell Transfusion (Vol. ml)	Fresh Frozen Plasma Transfusion (Vol. ml)	Total hemoderivated volume (Vol. ml)
FO>10% (Median and range)	325,7 (0.0–1400)	289,8 (0.0–1050)	615,5 (0.0 2450)
FO<10% (Median and range)	89,8 (0.0–264)	57,7 (0.0–350)	147,6 (0.0 -528)

p=0,002 CGR; p=0,09 PFC.

Regarding the clinical criteria used to guide the administration of fluids during resuscitation, it is observed that: Blood pressure (77% of cases), heart rate (77%), hourly diuresis (60%), of the which, based on blood pressure and

heart rate, did not show significant differences in the study groups (p=0.1 for blood pressure; p=0.6 for heart rate); however, being guided according to hourly urine output was associated with an FO>10% (p=0.01). See table 5.

**Table 5.** Arterial pressure, Cardiac frequency and diuresis oriented fluid administration an Fluid Overload.

Clinical criteria used to oriented fluid therapy			Fluid Overload Index		% percentage (Chi square test)
			FO>10%	FO<10%	
Starting fluid therapy according to low systolic blood pressure of the 50th percentile	Yes	Count	19	12	31
		%	86,4%	66,7%	77,5% (p=0.1)
	No	Count	3	6	9
		%	13,6%	33,3%	22,5%
Starting fluid therapy according to cardiac frequency above of the 95th percentile	Yes	Count	17	14	31
		%	77,3%	77,8%	77,5% (p=0.6)
	No	Count	5	4	9
		%	22,7%	22,2%	22,5%
Starting fluid therapy according to low diuresis rate below to 1ml/kg/hr	Yes	Count	17	7	24
		%	77,3%	38,9%	60,0% (p=0.01)
	No	Count	5	11	16
		%	22,7%	61,1%	40,0%

Regarding the morbidity and mortality associated with FO>10%, those associated with the deterioration of the most frequent organ function and the most frequent metabolic disorder are mentioned, of which renal function and hyperchloremic acidosis showed no differences as regards FO>10% (p=0.35 for impaired renal function and p=0.12 for hyperchloremic acidosis), however, there is an important difference in respiratory function, PaFiO<sub>2</sub> in

FO>10% (p=0.001). See table 6. The length of hospital stay (LOS) shows no difference in FO>10% and FO<10% group (p=0.60), in the same way with the PICU stay is observed a mean of 9.4 and 7.2 days in the ISCH groups>10% and<10% respectively (p=0.6). Mortality in the FO>10% group was 75% vs. 25% in the FO<10% group (p=0.01 and an OR: 5.57 95% CI 1.4-21.8). See table 7.

**Table 6.** Relationship between complication and Fluid Overload>10%.

Complications within the first 72 hours of resuscitation		Values
FO>10%	Respiratory function (PaO <sub>2</sub> /Fio <sub>2</sub> <200)	148,42 media (p=0.001)
	Renal function (Creatinine>1mg/dl)	50% (p=0,35)
	Hiperchloremic acidosis (Delta chloro>2)	72.7% (p=0,12)
	PaO <sub>2</sub> /Fio <sub>2</sub>	238,6 media
ISCH<10%	Renal fuction	38%
	Hiperchloremic acidosis	50%

**Table 7.** Relationship between hospitalary outcomes and Fluid Overload>10%.

Fluid Overload Index	Lenght of PICU (Days)	Lenght of Stay (Días)	Mortality
FO>10% (Media)	9.4 (3–23)	17 (3–80)	15 (75%) OR=5.57 (IC95 1.4-21.8)
FO<10% (Media)	7.2 (3–21)	17 (7–41)	7 (25%)

p=0.6 for LOS; p=0.42 for Lenght of PICU stay; p=0.01 for mortality.

Regarding vasopressor requirements, dopamine was administered in 77% (n=31), norepinephrine in 67.5% (n=27), dobutamine in 45% (n=18), adrenaline in 25% (n=10) of the cases. It was found that there is no relationship between the administration of dopamine, dobutamine and adrenaline with

FO, but it was found association with the administration of norepinephrine (p=0.031). Regarding the administration of diuretics, this was carried out in 65% (n=26) of the total study subjects (n=40), with patients with FO>10% in 59% (n=13).), and patients with FO<10% in 72.2% (p=0.40). In

addition, it is worth mentioning that 4 patients with  $FO > 10\%$  were medicated with continuous infusion furosemide, and 2 patients with  $ISCH < 10\%$ . It was also observed that 18% ( $n=4$ ) of patients with  $FO > 10\%$  received renal replacement therapy ( $p=0.012$ ). To finalize the analysis of the results of the present study, the determination of the pediatric logistic organ dysfunction (PELOD) is performed, where values of 14 to 25 can be observed in patients with  $FO > 10\%$  with a mean of 22, while patients with  $FO < 10\%$  values between 10 and 13 with an average of 11.5 ( $p=0.00$ ).

## 4. Discussion

The observed results suggest that an  $FO > 10\%$  is associated with a high probability of mortality, very similar to studies conducted by Naveda E. Omar and collaborators where an association between mortality and  $FO > 10\%$  was found ( $p=0.002$ ); Boyd and colleagues demonstrated that a positive balance is associated with higher mortality in children and adults. Vasst and colleagues also indicated that a positive fluid balance at 12 hours and 96 hours was associated with higher mortality in critically ill patients. In the SOAP study, positive balance on the third day after the onset of infection was associated with higher mortality in the PICU in the subgroup of patients with sepsis, among which 40% had septic shock. [9-16]

The mechanisms by which the increase in FO influence the prognosis of patients with septic shock are still under debate, it is considered that a positive accumulated fluid balance is associated with the development of systemic hypoperfusion, tissue edema, respiratory and renal system failure; Studies carried out by Flori and collaborators concluded that persistently positive balance is deleterious in pediatric patients with acute lung injury, since it causes more days in mechanical ventilation and greater mortality, regardless of the magnitude of the oxygenation failure or severity of organic dysfunction. Along the same lines, Arikan and collaborators demonstrated similar findings, although in this study the time of ventilatory assistance was not considered. [17-20]

In our study, no significant association was observed between renal function impairment and  $FO > 10\%$ , but a relationship was observed regarding the use of RRT; similar to findings described by Goldstein and colleagues who observed an association between renal lesion and  $FO > 10\%$  and the onset of continuous renal replacement therapy (CRRT); Gillespie et al, showed that an  $FO > 10\%$  at the onset of CRRT is independently associated with mortality. These data suggest a survival benefit when CRRT is started early to prevent water overload, in patients with septic shock, renal function impairment and  $FO > 10\%$ . Situation that don't be easily allowed in limited resources settings [20-24].

In our study, as in other studies on the administration of crystalloid and colloid solutions in the critical patient (SAFE, CHEST, VISEP, ALBIOS), they have shown that the use of colloids is associated with mortality, coagulopathies and renal failure; unlike Rivers and collaborators on the use of blood products (RBCT, FFP), our study observed in patients

transfused a higher mortality and association to  $FO > 10\%$  ( $p=0.009$ ), with the mention that the transfusion strategy used in our study protocol was liberal and not objective oriented. [25-35] The FEAST study is undoubtedly the most important in that it is the only RCT performed in a population with limited resources, similar to our facilities, and the results suggest a higher mortality in children who received bowling fluids and with positive balance; mainly in view of the associated respiratory and renal morbidity. [36]

## 5. Conclusion

We conclude that the judicious administration of liquids (crystalloids, colloids and blood products) in patients with severe sepsis and septic shock is one of the most useful and first-line hemodynamic treatments; but, if administered liberally, they could produce a water overload with the aforementioned complications, and in a resource limited settings hospital that's means use resources that are scarce, such as assisted ventilation, renal replacement therapy and use of vasoactive drugs.

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