The effect of fluid therapy during the first 12 hours after septic shock onset in pediatric patients

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Background: Initial fluid therapy is the cornerstone of hemodynamic resuscitation in pediatric patients with septic shock. This study investigated the association between fluid therapy during the first 12 hours after septic shock onset and the outcomes of pediatric patients.

Methods: This retrospective, observational study included consecutive pediatric patients with septic shock who were admitted to a multidisciplinary pediatric intensive care unit between January 2012 and December 2019. Data on total fluid administration within the first 12 hours of septic shock onset, patient characteristics, and outcome measurements were collected from validated electronic medical records.

Results: In total, 144 cases were included (overall 28-day mortality rate, 20.1%). Significant differences were found between survivors and non-survivors in the proportion of fluid received within the first 3 hours (36.9% vs. 25.4%, p=0.004) and within the last 3 hours (18.9% vs. 21.3%, p=0.031). The mortality rate was lower in patients who received a higher proportion of fluid within the first 3 hours (13.9% vs. 26.4%, p=0.048). Conversely, those with a higher proportion of fluid in the last 3 hours had a significantly higher mortality rate (29.6% vs. 14.4%, p=0.025). Multivariable logistic regression analysis revealed that a higher proportion of fluid within the first 3 hours was associated with decreased mortality (odds ratio [OR], 0.951; 95% confidence interval [CI], 0.918–0.986; p=0.028), while a higher proportion within the last 3 hours was associated with increased mortality (OR, 2.761; 95% CI, 1.175–6.495; p=0.020).

Conclusion: Higher fluid intake during the initial 3 hours after septic shock onset was linked to a reduction in 28-day mortality among pediatric patients; conversely, higher fluid volume during the final 3 hours of the 12-hour period post-onset was correlated with worse survival outcomes. Providing an adequate fluid volume within the first 3 hours, followed by a more conservative approach to fluid administration, may contribute to decreased mortality.

Keywords: Sepsis; Shock; Resuscitation; Fluid therapy; Critical illness
INTRODUCTION

Septic shock remains a leading cause of morbidity and mortality in children, with fatality rates reaching up to 60% [1]. In severe cases of sepsis and septic shock, the primary therapeutic treatment approaches include intravenous fluids, appropriate antibiotics, source control, vasopressors, and ventilator support [2]. A study by Carcillo et al. [3] in 1991 demonstrated that higher volumes of initial fluid resuscitation were associated with decreased mortality in pediatric septic shock. Specifically, patients who received a volume of resuscitation fluid equal to or greater than 40 mL/kg in the first hour after septic shock onset exhibited better survival rates than those who received smaller initial fluid amounts. Subsequent evidence led to a consensus statement in 2002, providing guidelines for hemodynamic support in pediatric and neonatal patients with septic shock [4]. These guidelines recommended aggressive fluid resuscitation with the aim of normalizing vital signs and evidence of perfusion within the first hour, followed by titration of inotropes and vasopressors along with ongoing volume resuscitation. The recommendations were updated in 2007 and 2017, maintaining the focus on early and aggressive normalization of perfusion through aggressive volume resuscitation, followed by the addition of vasopressors [5]. However, the 2020 Surviving Sepsis Campaign (SSC) guidelines recommended a bolus fluid of 40–60 mL/kg over the first hour if hypotension is present but did not provide distinct recommendations for subsequent fluid therapy [6].

It is now recognized that a positive fluid balance in the intensive care unit (ICU) is associated with an increased risk of mortality in adult septic shock patients [7-10]. This has challenged the idea that aggressive volume resuscitation is universally beneficial and has suggested potential harm in certain patient populations. As a result, the concept of optimal fluid resuscitation has gained attention as a critical component of clinical interventions and an essential factor in the initial management of sepsis. While the appropriate timing and quantity of fluid resuscitation in the ICU have been emphasized for improving survival, there is a scarcity of studies examining the relationship between fluid balance, timing of fluid resuscitation, and outcomes in pediatric patients with septic shock.

In our present study, we aimed to describe the characteristics of children experiencing septic shock and examine the potential association between the volume and distribution of resuscitation fluid administered during the initial 12 hours and the mortality rates in this patient population.

METHODS

This study received approval from the Institutional Review Board of Asan Medical Center (No. 2019-1269). Due to the retrospective and observational nature of the study, the requirement for informed consent was waived. Patients were treated following our institution’s pediatric septic shock management protocol.

Data were collected through a review of electronic patient records from January 2012 to December 2019 at the Asan Medical Center Children’s Hospital, a tertiary pediatric ICU in Seoul, Korea. We included consecutive admissions of patients under 18 years of age who were diagnosed with septic shock and required vasoactive agents.

The diagnosis of septic shock was based on the 2017 guidelines of the American College of Critical Care Medicine (ACCM) committee [3,5]. We identified patients who met the following criteria: (1) suspected infection accompanied by clinical signs of hypothermia or hyperthermia, (2) findings suggestive of inadequate tissue perfusion, such as altered mental status, prolonged capillary refill (> 2 seconds), diminished pulses, cool extremities, flush capillary refill, bounding peripheral pulses, wide pulse pressure, or urine output of less than 1 mL/kg/hr, and (3) the need for inotropics or vasopressors to maintain sufficient perfusion or blood pressure. We excluded patients who (1) were unable to receive fluid resuscitation according to the septic shock protocol due to severe pulmonary hypertension or increased intracerebral pressure and (2) had insufficient medical data available.

Data Collection

We carried out a retrospective analysis of electronic medical records to collect data on baseline demographics, Pediatric Risk of Mortality (PRISM) III score, duration of mechanical ventilation support, requirement for renal replacement therapy, length of ICU stay, 28-day mortality, and initial lactate concentration. The onset of septic shock was defined as the moment when fluid resuscitation or vasoactive drugs were first administered to enhance insufficient tissue perfusion.

Fluid intake and output volumes were obtained from electronic medical records to determine the amount of fluid administered during the first 3 hours, and then every 3 hours within the initial 12-hour period following the onset of septic shock. The intake volume encompassed all fluids given, including nutritional fluids, medications, resuscitation bolus fluids, and blood transfusions. The output volume was calculated based on urine, dialysis, drainage, stools, and vomitus.

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To evaluate the distribution of fluid intake during the initial 12 hours, the percentage of fluid administered every 3 hours was calculated and compared between survivors and non-survivors. The group with a higher proportion was defined as having a larger distribution than the median distribution of fluid administered for each 3-hour interval, while the group with a lower proportion was defined as having a smaller distribution. Following this, the 28-day mortality rates were compared between the higher-proportion group and the lower-proportion group within each time interval.

Statistical Analysis
Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp.). Categorical variables were represented as numbers and percentages and analyzed using either the Fisher exact test or the chi-square test. Continuous variables were expressed as medians (interquartile range). Two-tailed t-tests were employed for normally distributed continuous variables, while the Mann-Whitney U-test was utilized for non-parametric data. Multivariable logistic regression was performed to identify the variables associated with 28-day mortality rates. The variables incorporated into the multivariable models were chosen based on a priori clinical rationale and included age, sex, and the PRISM III score. A significance level of $p < 0.05$ (two-sided) was deemed statistically significant for all tests.

RESULTS

From the initial cohort of 167 children who met the inclusion criteria, 23 were subsequently excluded from the study. Of these, 15 patients had incomplete detailed data, while the remaining 8 patients were excluded due to contraindications for fluid resuscitation, specifically severe pulmonary hypertension and increased intracerebral pressure.

A total of 144 patients with septic shock were included in the study cohort. Table 1 displays the characteristics of these cases, as well as the results of the univariable analysis comparing survivors and non-survivors. The median age was 9.1 years, and the median weight was 20.6 kg. The overall 28-day mortality rate in the study population was 20.1%. Hematological/oncological disor-

### Table 1. Baseline characteristics of the enrolled pediatric patients with septic shock

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=144)</th>
<th>Survivor (n=115)</th>
<th>Non-survivor (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>9.1 (1.6–14.3)</td>
<td>9.8 (1.6–14.4)</td>
<td>4.1 (1.6–13.9)</td>
<td>0.222</td>
</tr>
<tr>
<td>Boy</td>
<td>89 (61.8)</td>
<td>61 (61.7)</td>
<td>18 (62.1)</td>
<td>0.576</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>20.6 (7.7–43.0)</td>
<td>24.6 (7.4–44.0)</td>
<td>14.4 (9.2–42.8)</td>
<td>0.274</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td>0.323</td>
</tr>
<tr>
<td>Hematology-oncology</td>
<td>61 (42.4)</td>
<td>47 (40.9)</td>
<td>14 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td>23 (16.0)</td>
<td>21 (18.3)</td>
<td>2 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>18 (12.5)</td>
<td>14 (12.2)</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>16 (11.1)</td>
<td>14 (12.2)</td>
<td>2 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>12 (8.3)</td>
<td>8 (7.0)</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>14 (9.7)</td>
<td>11 (9.6)</td>
<td>3 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Microorganism</td>
<td></td>
<td></td>
<td></td>
<td>0.138</td>
</tr>
<tr>
<td>Fungus</td>
<td>10 (6.9)</td>
<td>6 (5.3)</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>36 (39.6)</td>
<td>31 (38.6)</td>
<td>5 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative</td>
<td>57 (25.0)</td>
<td>44 (27.2)</td>
<td>13 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>1 (0.7)</td>
<td>1 (0.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unproven</td>
<td>40 (27.8)</td>
<td>33 (28.9)</td>
<td>7 (24.1)</td>
<td></td>
</tr>
<tr>
<td>PRISM III score</td>
<td>11.0 (8.0–17.0)</td>
<td>11.0 (8.0–15.0)</td>
<td>14.0 (11.0–20.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>VIS at 24 hours</td>
<td>10.0 (0.0–25.0)</td>
<td>10.0 (0.0–20.4)</td>
<td>20.0 (3.5–63.4)</td>
<td>0.024</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>10.0 (2.8–18.3)</td>
<td>9.9 (3.2–18.7)</td>
<td>10.0 (2.4–16.7)</td>
<td>0.673</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>2.1 (1.0–4.5)</td>
<td>2.0 (1.0–4.2)</td>
<td>3.8 (1.4–8.5)</td>
<td>0.052</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>79 (54.9)</td>
<td>53 (46.1)</td>
<td>26 (89.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>CRRT</td>
<td>29 (20.1)</td>
<td>14 (12.2)</td>
<td>15 (51.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>ECMO</td>
<td>7 (4.9)</td>
<td>2 (1.7)</td>
<td>5 (17.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
PRISM, Pediatric Risk of Mortality; VIS, vasoactive inotropic score; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.
ders were the most common underlying diseases, while patients with gastrointestinal diseases experienced the highest mortality rate at 33.3%. Significant differences were observed in the PRISM III score on the day of onset and the vasoactive inotropic score at 24 hours between survivors and non-survivors.

Table 2 demonstrates that similar amounts of fluid were administered to both survivors and non-survivors within the initial 12-hour period. However, when divided into 3-hour intervals, survivors received a significantly smaller volume of fluids during the last 3 hours than non-survivors (9.4 vs. 13.1 mL/kg, p = 0.014). Additionally, although the difference was not statistically significant, a higher volume of fluid was administered to survivors during the initial 3 hours compared to non-survivors (21.9 vs. 16.1 mL/kg, p = 0.239). There was no significant difference in overall net fluid balance between survivors and non-survivors during the initial 12-hour period. Fig. 1 displays the distribution of fluid administered every 3 hours over the course of 12 hours. Among survivors, the largest proportion of fluid was given during the first 3 hours, followed by a gradual decline. In contrast, non-survivors exhibited a consistent distribution of fluid administration throughout the entire 12-hour period. As illustrated in Fig. 2, when comparing the distribution of fluid within each 3-hour interval to the total amount administered within the initial 12 hours, the group with a higher proportion of fluid during the first 3-hour interval had a significantly lower 28-day mortality rate. However, the group with a higher proportion of fluid administered during the last 3-hour interval experienced a significantly higher 28-day mortality rate.

Table 3 displays the results of a multivariable logistic regression
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Table 3. Multivariable logistic regression analysis of 28-day mortality risk factors in the critically ill study children with septic shock

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM III score</td>
<td>1.069</td>
<td>1.012–1.130</td>
<td>0.017</td>
</tr>
<tr>
<td>Group with a higher proportion of fluid intake during the first 3-hour period</td>
<td>0.951</td>
<td>0.918–0.986</td>
<td>0.028</td>
</tr>
<tr>
<td>Group with a higher proportion of fluid intake during the 9–12 hour period</td>
<td>2.761</td>
<td>1.175–6.495</td>
<td>0.020</td>
</tr>
</tbody>
</table>

PRISM. Pediatric Risk of Mortality.

analysis that investigates potential risk factors, such as the PRISM III score, the group with a higher proportion of fluid intake during the initial 3 hours, and the group with a higher proportion of fluid intake during hours 9–12. The group with a higher proportion of fluid intake during the first 3 hours demonstrated a significant association with a reduced risk of 28-day mortality (odds ratio [OR], 0.951; 95% confidence interval [CI], 0.918–0.986; p = 0.028). In contrast, the group with a higher proportion of fluid intake during hours 9–12 had a significantly elevated risk of 28-day mortality (OR, 2.761; 95% CI, 1.175–6.495; p = 0.020).

DISCUSSION

The aim of this study was to investigate the effect of fluid management within the first 12 hours following the onset of septic shock in pediatric patients on clinical outcomes. Our results show that the total volume of fluid administered during the initial 12 hours was similar between survivors and non-survivors, with no significant differences in net fluid balance between the two groups. However, the distribution of fluid administration within the first 12 hours served as a distinguishing factor. Survivors received approximately 40% of the total fluid volume within the first 3 hours, followed by a gradual decrease. In contrast, non-survivors displayed a more consistent distribution of fluid administration throughout the entire 12-hour period. Notably, among the subgroup receiving a relatively higher proportion of fluid during the first 3 hours, there was a significant reduction in 28-day mortality. Conversely, during the last 3 hours of the initial 12-hour period, the higher-proportion group exhibited a significant association with increased mortality rates.

The ACCM guidelines emphasize the importance of initiating aggressive fluid resuscitation, up to 60 mL/kg, within the first hour following the diagnosis of severe septic shock. This is followed by adjusting vasoactive medications based on the specific shock phenotype and potentially administering additional fluids if necessary [4,5,11]. The most recent update of the SSC guidelines did not introduce any changes to this recommended fluid therapy [6]. However, recent research has drawn increased attention to the potentially harmful effects of excessive volume overload beyond the initial resuscitation period [7,8,12]. Fluid resuscitation is a crucial aspect of septic shock management, and the importance of early initiation of fluid resuscitation in the initial phases of septic shock is widely acknowledged and supported by numerous previous studies [2-4,13-15]. In our study, the survival rate was higher among patients who received a greater amount of fluid within the first 3 hours than among those who did not, highlighting the significance of optimizing blood pressure during the early stages of septic shock management. However, determining the appropriate fluid volumes and optimal hemodynamic targets in pediatric patients remains challenging. Fluid responsiveness is a crucial factor guiding fluid resuscitation strategies, yet accurately estimating this parameter remains difficult, and no consensus currently exists on assessment tools specifically tailored for pediatric patients [16-19]. In the present study, a smaller volume of resuscitation fluid was administered than the recommended amount by the ACCM guidelines (i.e., approximately 25 mL/kg within the first 3 hours). Notably, however, the mortality rate was not higher than that reported in other studies. While our institute adheres to ACCM or SSC guidelines, fluid resuscitation strategies in septic shock cases are determined by the treating physicians, who take into account various factors influencing fluid responsiveness and potential adverse effects on cardiac, respiratory, and renal function.

To minimize adverse reactions associated with fluid resuscitation, we implemented a comprehensive evaluation of organ function, including cardiac echocardiography, a chest X-ray examination, and various blood tests (e.g., B-type natriuretic peptide), while administering fluid therapy. For these reasons, adherence to the guideline-recommended fluid volumes in all septic shock patients was not achievable. The primary objective of fluid resuscitation is to raise the mean circulating pressure and stroke volume, leading to an improvement in tissue perfusion pressure. However, crystalloids have a limited capability to expand the intravascular volume, as shown by previous studies where less than 5% of a crystalloid bolus was found to remain in the intravascular space 1 hour after an infusion was completed [20,21]. Macrocirculatory parameters, such as blood pressure or central venous pressure, are currently recognized as poor indicators of microcir-
culation, especially in patients with sepsis and septic shock. Instead, the microvasculature plays an independent role in tissue perfusion and oxygenation that may not be influenced by macrovascular alterations [22,23]. Hence, fluid therapy aimed at macrocirculatory indicators can lead to fluid overload, which has been consistently associated with harm in critically ill children.

In our study, we discovered that even though the administered fluid volumes did not meet the levels recommended by the guidelines, there was a significant difference in fluid distribution between the survival and non-survival groups. Both groups received comparable total fluid volumes over a 12-hour period; however, the survival group received a larger volume of fluid during the initial 3 hours. In contrast, the non-survival group received a consistent amount of fluid throughout the entire 12-hour period. These findings indicate that the distribution pattern of fluid administration is important, not only the total volume of administered fluid. Aggressive fluid administration during the early phase, followed by a more conservative approach in later hours, seems to be crucial for optimal fluid management.

The Fluid Expansion as Supportive Therapy study, a randomized controlled trial involving over 3,000 acutely ill African children with sepsis and impaired perfusion, has played a crucial role in highlighting concerns about the potential harm associated with fluid bolus therapy. This study showed that children who received fluid boluses in response to impaired perfusion experienced higher early mortality rates (within 48 hours) as well as higher late mortality rates (4 weeks) compared to those who did not receive fluid [9]. Notably, a post hoc analysis revealed that although fluid boluses initially offered short-term benefits by resolving the state of shock, children who received fluid boluses faced increased mortality due to the worsening of cardiovascular dysfunction following the initial improvement [24,25].

Abulebda et al. [26] discussed the influence of volume balance on the clinical course of pediatric septic shock patients during the post-ICU admission period. The authors conducted a stratified analysis based on mortality risk using their risk stratification tool and discovered that increased fluid intake and positive fluid balance after ICU admission were linked to worse outcomes in pediatric septic patients with a low initial mortality risk. However, these associations were not observed in patients with moderate or high mortality risk. The findings of that study somewhat diverge from previous reports in adult septic shock patients [7,8,27-29]. The authors attributed this discrepancy to the absence of pre-ICU admission fluid balance data, which made it challenging to predict the overall impact on their results if such data were available. In contrast, our study boasts a significant strength in that the total fluid intake was estimated from the onset of shock, irrespective of the patient’s location (emergency room or general ward). This approach has enabled a more transparent illustration of the effects of early fluid therapy in our study.

Existing literature reviews have consistently shown that a positive fluid balance, identified at various time points within the first 24 hours of ICU admission and culminating in a cumulative positive balance at discharge, is associated with higher mortality rates [10,12,30-34]. It is also important to emphasize that our current findings, in line with previous studies, show that an increase in fluid intake volumes starting 3 hours after the onset of septic shock is associated with increased mortality. Notably, our present data reveal that a high intake volume between 9 and 12 hours post-onset is strongly linked to higher mortality in children with septic shock. These findings suggest that a positive fluid balance beginning 3 hours after the onset of septic shock may have detrimental effects.

Our study had several significant limitations. First, it was conducted at a single center, potentially limiting the generalizability of our findings. Second, our observational design covered a brief period of only 12 hours, and our sample size was relatively small compared to other studies on fluid therapy. As a result, our capacity to determine a definitive relationship between fluid resuscitation and patient outcomes was limited. Furthermore, other factors, such as antibiotic therapy, source control, and unmeasured clinical parameters, may have impacted our results.

We found that a higher fluid intake during the initial 3 hours of septic shock onset is associated with a reduced 28-day mortality rate. Conversely, an increased fluid intake in the last 3 hours of the first 12-hour period following onset is linked to poorer outcomes. As a result, we cautiously propose that administering an adequate amount of fluid within the first 3 hours, followed by a more conservative approach to fluid administration, may help decrease mortality. However, given the absence of consensus on these strategies, future high-quality studies involving specific patient populations will be of vital importance.

**CONFLICT OF INTEREST**

Won Kyoung Jhang is an Editor-in-Chief, and Seong Jong Park is an editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.
REFERENCES


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