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Original Article

Difference in outcomes of pediatric septic shock after fluid resuscitation according to the ultrasound-guided fluid resuscitation (USFR) and *American College of Critical Care Medicine* (ACCM) protocols: A randomized clinical trial

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Abstract

Background Sepsis is a major cause of morbidity and mortality in children. *The American College of Critical Care Medicine* (ACCM) protocol currently in use in the management of septic shock carries a risk of fluid overload. With the use of ultrasonographic monitoring, the *ultrasound-guided fluid resuscitation* (USFR) protocol may reduce the incidence of fluid overload and mortality.

Objective To assess the difference in outcomes of fluid resuscitation in pediatric septic shock using the USFR *vs.* ACCM protocols.

Methods This randomized clinical trial involved 36 subjects randomized equally into the USFR and ACCM groups. After randomization, each subject was given fluid resuscitation starting at 20 mL/kg and repeated every 5-10 minutes as needed, according to the ACCM protocol. After fluid resuscitation was given, patients in the ACCM group were evaluated for clinical signs, liver span, and rhonchi, whereas those in the USFR group underwent USCOM examination for cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance index (SVRI). After 60 minutes, subjects in both groups were re-assessed for clinical signs, USCOM, pulmonary edema using lung ultrasound score (LUS), and liver span. Subjects were blinded as to the protocol they received. We compared 24-hour and 72-hour mortality rates, clinical improvement of shock at 60 minutes, cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance index (SVRI), as well as pulmonary edema and hepatomegaly, between the two groups.

Results At 60 minutes after resuscitation, there were significant differences between the ACCM and USFR groups in the proportion of clinical improvement (0/18 *vs.* 5/18, P=0.016), pulmonary edema (15/18 *vs.* 4/18, P<0.001), and hepatomegaly (16/18 *vs.* 5/18, P<0.001). Mortality rates at 24 hours and 72 hours in the ACCM *vs.* USFR groups were 17% *vs.* 12% (P=0.199) and 78% *vs.* 39% (P=0.009), respectively.

Conclusion The USFR protocol reduces the occurrence of fluid overload and leads to a lower mortality rate at 72 hours compared to the ACCM fluid resuscitation protocol. **[Paediatr Indones. 2023;63:49-56; DOI: https://doi.org/10.14238/pi63.1sup.2023.49-56].**

Keywords: *: paediatric septic shock; sepsis; fluid resuscitation; hemodynamic monitoring; USFR; ACCM*

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the immune system against infection. Septic shock is defined as sepsis with cardiovascular system dysfunction. The incidence of septic shock and severe sepsis has increased in the last 30-40 years.[1,2] *The American College of Critical Care Medicine* (ACCM) has devised an algorithm for the management of sepsis in children that has succeeded in reducing sepsis mortality in

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pediatric and neonatal intensive care units from 97% to 9%. Fluids are given in boluses of 20 mL/kg every 5-10 minutes to achieve the desired heart rate and blood pressure. The fluid bolus is continued until there is improvement in perfusion and stopped when there are signs of fluid overload: hepatomegaly, increased work of breathing, rhonchi, or gallop rhythm.[3] However, the risk of fluid overload is a concern associated with the ACCM fluid resuscitation protocol. The randomized controlled trial *Fluid Expansion as Supportive Therapy* (FEAST) showed a 3.3% increase in mortality at 48 hours in febrile children with volume depletion receiving fluid boluses group compared those receiving maintenance fluids only.[4] Determination of fluid overload according to the ACCM protocol is based only on clinical assessment, so there is a risk of delay in detecting fluid overload.

Hemodynamic monitoring using ultrasound/Doppler has the advantage of being non- invasive and can provide results quickly. Ultrasound, echocardiography, and *Ultrasonic Cardiac Output Monitor* (USCOM) have been widely used as hemodynamic monitoring tools in emergency and intensive care units. These devices are capable of assessing cardiac output (CO) and systemic vascular resistance index (SVRI) as resuscitation targets. In addition, it is also able to assess fluid responsiveness in the form of a >10% increase in stroke volume index (SVI) or cardiac index (CI), thereby preventing fluid overload.[5] The *Ultrasound-guided Fluid Resuscitation* (USFR) protocol incorporates such methods in monitoring for fluid overload. In this study, we aimed to compare the outcomes between the standard ACCM protocol and the *Ultrasound-Guided Fluid Resuscitation* (USFR) protocol.

Methods

This randomized controlled trial was conducted from July to November 2020 at the pediatric intensive care unit (PICU), high care unit (HCU), emergency room, and inpatient ward of Saiful Anwar General Hospital, Malang, Indonesia. Patients were included in the study if they were 1 month to 18 years of age and met septic shock criteria based on the presence of life-threatening organ dysfunction, as signified by a *Pediatric Logistic Organ Dysfunction-2* (PELOD-2) score score of ≥11.[1,2] Patients with congenital heart disease or who had received fluid resuscitation prior to admission were excluded. We calculated sample size using the formula for relative risk (RR) estimation in a clinical trial, with a predicted septic shock mortality from an epidemiologic studies of 0.71[6,7] and a relative risk of 1.75 considered clinically important. A P value of 0.05 was considered statistically significant. Using this formula, the minimum required sample size was 14 subjects. With a predicted drop-out rate of 20%, the minimum number of subjects was 17 in each group.

This study was approved by The Health and Medical Research Ethics Commission of Saiful Anwar Hospital. Patients were randomly assigned to either the USFR or ACCM group. Randomization was done using randomization table. Participants were unaware of the study group assignments. The residents who administered fluids were aware of the group assignments but did not assess outcomes or influence therapeutic decisions.

At the time of admission, all subjects underwent thorough physical examination and history taking. We recorded baseline demographic data (age, sex, body weight), comorbid diseases, nutritional state, clinical parameters, PELOD score, and Pediatric Index of Mortality-2 (PIM-2) score in all subjects in the first hour of assessment. The PIM-2 score is the predicted mortality considering various parameters including elective or emergency admission, mechanical ventilation, post-procedure recovery, cardiac bypass, pupillary light reaction, blood gases, and FiO_2/PaO2.[8,9] We also noted any occurrences of refractory shock and total fluid resuscitation received by the subject. The clinical parameters of shock recorded at baseline included heart rate, pulse strength, acral warmth, respiratory rate, axillary temperature, peripheral oxygen saturation by pulse oximetry, blood pressure, pulse pressure, capillary refill time, liver span, and presence of rhonchi on lung auscultation. Liver span was measured by percussion. Hepatomegaly was defined an increase of >1 cm in liver span post-resuscitation compared to the pre-resuscitation baseline.

Both the USFR and ACCM groups received 20 mL/kg of crystalloid bolus using a rapid pull-push and disconnect-reconnect technique. Before and after each fluid bolus, all subjects were evaluated for clinical parameters of heart rate, blood pressure,

acral warmth, and pulse strength. Age-specific heart rate and blood pressure reference values were used. The patient was considered to have hemodynamic improvement if there was a decrease in heart rate, increase in blood pressure, warm acrals, and stronger pulse. After the fluid bolus, all subjects also underwent liver span examination.

In the USFR group, *USCOM* (*USCOM Ltd*., Sydney, New South Wales) examinations were done prior to the fluid bolus and repeated after the bolus. If there was clinical hemodynamic improvement, no more fluid bolus was given. In the absence of clinical hemodynamic improvement, fluid bolus was repeated if ΔSVI/ΔCI on USCOM was 10%; if ΔSVI/ΔCI was >10, no more fluid bolus was given.

In the ACCM group, hemodynamic improvement was only assessed clinically. If there was clinical hemodynamic improvement after the fluid bolus, no more bolus was given. After the bolus, subjects were also assessed for clinical signs of fluid overload, i.e. hepatomegaly and rhonchi. If clinical hemodynamic improvement was not attained and no hepatomegaly or rhonchi was present, the fluid bolus was repeated. When there were signs of overload, no more fluid bolus was given.

At 60 minutes, subjects in both groups were reassessed for clinical hemodynamic parameters, USCOM, lung ultrasound score (LUS) to observe for pulmonary edema, and liver span. We noted mortality rates in both groups at 24 hours of observation. The treatment algorithm can be seen in **Figure 1**. The LUS is a score that represents aeration or filling of air in the lung parenchyma based on ultrasonographically measured air/fluid ratio. A LUS of >3 indicates the presence of pulmonary edema.10

We used *SPSS version 20* (*IBM*, Armonk, New York) for data analysis. The CI, SVI, and SVRI variables were expressed as mean (SD) or median (interquartile range/IQR). Mortality and presence of lung edema (yes or no) was shown as percentages. We analyzed the differences between the two groups using the unpaired T-test and Mann-Whitney test for normally distributed and non-normally distributed numerical variables, respectively. Categorical variables were analyzed using the chi-square and Fisher's exact tests. A P value of <0.05 was considered statistically significant. Whenever there were deviations from the intended fluid resuscitation protocol, we applied an intention-to-treat analysis. We also evaluated inter- and intra-observer variability of LUS, liver span, and USCOM using Cohen's kappa.

Results

We enrolled 36 participants with an age range of 6 months to 8 years. Eighteen subjects were randomized into each of the USFR and ACCM groups . Baseline demographic and clinical parameters were similar between both groups (**Table 1**). The study flowchart can be seen in **Figure 1**.

There was no difference in mortality rate at 24 hours (2/18 in USFR group and 3/18 in ACCM group; P=0.63). At 60 minutes, 5/18 subjects in the USFR group showed clinical improvement, while no subject in the ACCM group had improved clinically (P=0.016). Pulmonary edema was seen in 15/18 subjects in the ACCM group *vs.* 4/18 subjects in the USFR group (P<0.001). Hepatomegaly was found in 16/18 *vs.* 5/18 subjects in the ACCM *vs.* USFR groups, respectively (P<0.001). There was no difference in USCOM hemodynamic parameters (CI, SVI, and SVRI) at 60 minutes (**Table 2**). Kappa values for USCOM examination, LUS, and liver span determination were 0.645, 0.62, and 0.45, respectively.

Survival rate at 24 hours was 88% in the USFR group *vs.* 83% in the ACCM group (P=0.199). The USFR group had a lower mortality rate than the ACCM group throughout the first 24 hours (**Figure 2**), but the difference was not statistically significant (P=0.597). However, at 72 hours, this difference became significant, with a survival rate of 61% in the USFR group vs. 22% in the ACCM group (P=0.009) (**Figure 3**).

Violation of the fluid resuscitation protocol was found in one subject in the ACCM group. In accordance with the intention-to-treat analysis, the subject was analyzed in the ACCM group.

Discussion

We conducted this study comparing fluid resuscitation based on clinical monitoring alone (ACCM protocol) *vs.* USCOM-based hemodynamic monitoring (USFR protocol) because there is a risk of delay in assessing

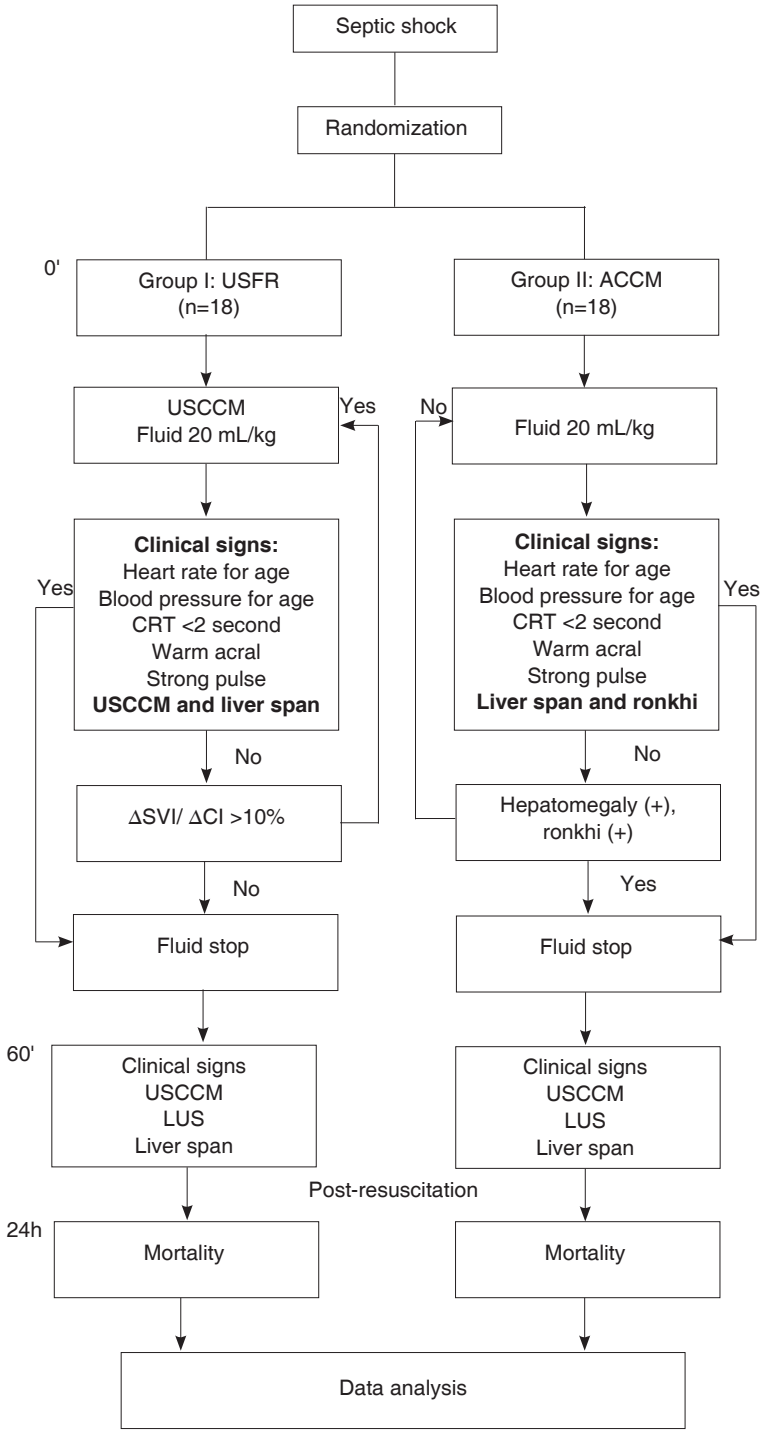

Figure 1. Treatment algorithm

Table 1. Subjects' characteristic

Characteristics	ACCM (n=18)	USFR (n=18)
Mean age (SD), years	8.8 (6.38)	6.8 (5.01)
Gender		
Female	9	9
Male	9	9
Mean body weight (SD), kg	27.85 (20.21)	21.91 (5.26)
Total fluid resuscitation, mL/kg	29.44 (11.09)	26.11 (8.49)
Predicted death rate (PIM2 score), %	33.5	24.7
Comorbid, n		
Pneumonia	2	2
Gastroenteritis	1	1
Meningitis	1	6
Malignancy	7	5
Post operation	4	1
Others	3	3
Malnutrition, n	6	6
Refracter shock, n	15	14

Table 2. Clinical and USCOM parameters at 60 minutes

Variables	ACCM (n=18)	USFR (n=18)	P value
Clinical parameters			
Clinical improvement,n	0	5	0.016
Pulmonary edema, n	15	4	<0.001
Hepatomegaly,n	16	5	<0.001
USCOM parameters			
Mean CI (SD)	4.73 (1.38)	5.03 (1.60)	0.552
Mean SVI (SD)	33.66 (9.64)	38.11 (10.43)	0.204
Mean SVRI (SD)	1,076 (443.9)	1,296 (653.0)	0.367

early fluid overload based on clinical monitoring alone. We found no differences between the two groups in hospital mortality at 24 hours and hemodynamic parameters (CI, SVI, SVRI) at 60 minutes. However, there were significant differences in favor of the USFR protocol in clinical improvement at 60 minutes, the incidence of pulmonary edema and hepatomegaly, and mortality rate at 72 hours.

Sepsis has a high prevalence in children; more than 8% of critically ill children experience severe sepsis. In Indonesia, the mortality rate of septic shock in the PICU is 88.2%.7 In this study, there was no significant difference in mortality rate between the ACCM and USFR groups at 24 hours, but at 72 hours, the mortality rate was significantly lower in the USFR group. Our findings were consistent with a previous study that reported a lower mortality rate at 7 days in ultrasound-guided fluid resuscitation compared to early goal-directed therapy, although ventilator use and length of stay did not differ significantly.[11] In our study, the lack of a significant difference in mortality rate at 24 hours could be due to the similar baseline PIM-2 score between the two groups.

The most common diseases underlying septic shock were malignancy and central nervous system infections. Malignancy and its treatments may lead to immunocompromised conditions, making it easier for patients to fall into severe sepsis and increasing mortality.[6]

Fluid overload is known to contribute to mortality. In this study, we found higher proportions of pulmonary edema (based on LUS) and hepatomegaly (based on increased liver span) in the ACCM group - the group with a higher overall mortality rate. Mean

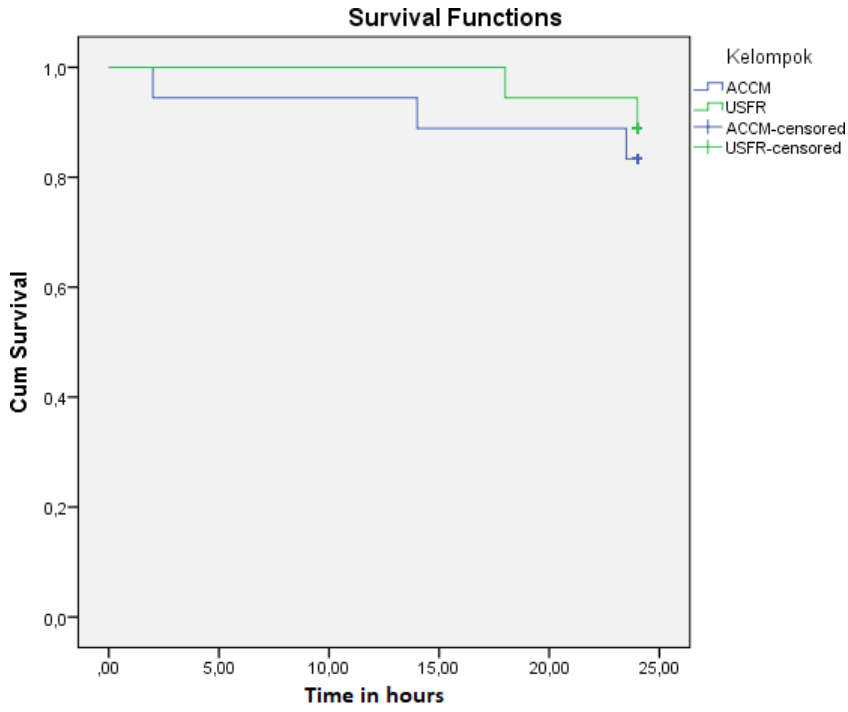

Figure 2. Kaplan-Meier analysis for mortality at 24 hours

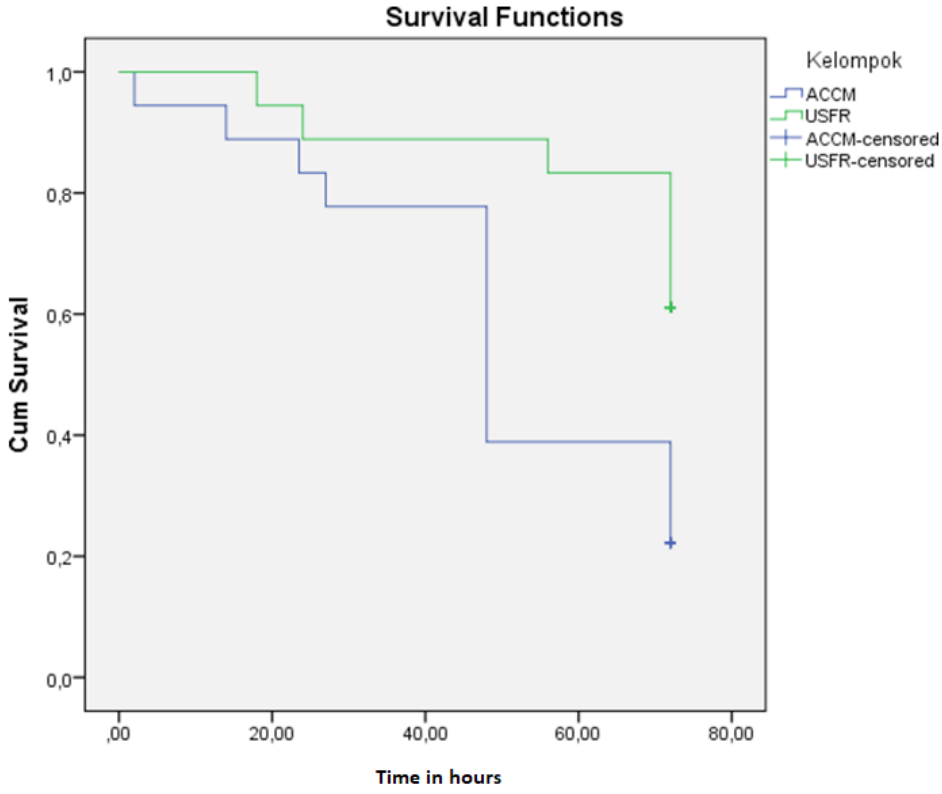

Figure 3. Kaplan-Meier analysis for mortality at 72 hours

total amount of fluid resuscitation was similar in both groups [29.44 (SD 11.09) mL/kg in the ACCM group vs. 26.11 (SD 8.49) mL/kg in the USFR group]. These findings support the utility of USFR in preventing fluid overload, thereby reducing the risk of death.

The most common cause of death reported in a previous study is refractory shock followed by secondary organ damage.[12] In our study, the proportion of refractory shock was similar between the two groups (15/18 in the ACCM group *vs.* 14/18 in the USFR group). Other factors that can contribute to the high mortality rate are pre-hospital factors such as delayed assessment and medical assistance, delayed transfer to a referral hospital, and other unidentified factors that were not evaluated in this study.[7]

The proportion of clinical improvement at 60 minutes was higher in the USFR group than in the ACCM group. This, accompanied by the higher proportion of signs of fluid overload (pulmonary edema, hepatomegaly) in the ACCM group, suggests that the superior results of the USFR protocol may be due to prevention of fluid overload.

In practice, blood pressure and pulse rate are the most frequently observed clinical parameters. However, non-invasive blood pressure tests tend to be unrepresentative. A study showed that non-invasive blood pressure had a positive predictive value of 58% for hypotension leading to a the tendency to overdo fluid resuscitation.[12]

In our study, there was no significant difference between CI, SVI, and SVRI between the ACCM and USFR groups 60 minutes after resuscitation. The effect of fluid resuscitation on CI and other cardiac parameters is still under investigation. However, several studies have shown that resuscitation fluids can temporarily increase CI, with a return to baseline within 40 to 60 minutes.[13] Another study that compared fluid resuscitation volumes of 10 mL/kg *vs.* 20 mL/kg also showed that the amount of resuscitation fluid did not correlate with changes in CI, although this study was limited in sample size.[13]

The ACCM recommends discontinuing resuscitation if there are signs of hepatomegaly, rales, or gallop rhythm.[3] In the present study, the ACCM group had a higher incidence of pulmonary edema than the USFR group. This result is consistent with a previous study that reported an increased incidence of hepatomegaly at 20 minutes after fast administration of 40 mL/kg of fluids within 15 minutes.[14] The high incidence of hepatomegaly and pulmonary edema in the ACCM group supports the assumption that fluid resuscitation based on clinical monitoring alone in this protocol may cause delays in the assessment of tissue edema.

Our study has several limitations. Firstly, compliance with administering fluid resuscitation according to the protocol is very important in this study. There is a tendency for clinicians to give less fluid than recommended and administering inotropic/vasopressor drugs before normovolemia is achieved. In our study, fluid resuscitation deviated from the protocol in one subject in the ACCM group. Secondly, LUS, USCOM, and liver span examinations were carried out by multiple observers. Kappa interobserver reliability values were good for USCOM and LUS, but only moderate for liver span. This could reduce the reliability of our outcome measurements.

In conclusion, the USFR protocol reduces the occurrence of fluid overload and leads to a lower mortality rate at 72 hours compared to the ACCM fluid resuscitation protocol. Further study should be directed at directly assessing the association between fluid overload and mortality between the two protocols.

Conflict of interest

None declared.

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