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Original Article

Mortality rates in pediatric septic shock

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Abstract

Background Septic shock remain a major cause of morbidity and mortality in children admitted to intensive care unit. Recent investigations from developed countries have reported mortality rates of 20-30%. Few studies had reported mortality rate for pediatric septic shock in intensive care setting from developing countries with limited resources.

Objective To determine the current mortality rate for pediatric patients with septic shock in developing country.

Methods A retrospective study was conducted in Pediatric Intensive Care Unit (PICU) in DR. Sardjito General Hospital. Medical record and chart were reviewed and recorded for diagnosis of septic shock, from November 1st, 2011 to June 30th, 2014.

Results A database of all PICU admissions and cases with diagnoses of septic shock were reviewed. The final data consisted of 136 patients diagnosed with septic shock. Septic shock was defined as a clinical suspicious of sepsis, manifested by hyperthermia or hypothermia, and accompanied by hypoperfusion The overall mortality rate for the study cohort was 88.2%. The median age of patients was 16 months, with 52.2% male. Median initial PRISM III and PELOD scores were 10 and 22, respectively. The median length of PICU stay was 4 days. A total of 48.5% of the subjects were in need of crystalloid and colloid fluid in a median amount of 40 mL/kg. The median time required to complete the initial resuscitation was 60 minutes. Mechanical ventilator support in the first 24 hours was required in 79.4% of the cases. Fluid overload of > 10% (FO>10%) was found in 58.8% of the subjects.

Conclusion The mortality rate in pediatric septic shock in our unit is very high. There is a higher incidence of fluid overload in non-survival group. **[Paediatr Indones. 2016;56:304-10. doi: 10.14238/pi56.5.2016.304-10]**.

Keywords: *septic shock; mortality rate; children; developing country*

Septic shock is still a major cause of morbidity and mortality in children in the scope of intensive care.[1-6] The incidence reached 1.5% of all pediatric patients admitted to hospital, in a study from India with a mortality rate of more than 50%.4 A US study report mortality rate of 13.5%, in a multidisciplinary PICU setting.[7] Several studies conducted in the 1980s and 1990s reported mortality rates >50% in children with septic shock.[7] More recent investigations from developed countries have reported mortality rates of 20-30%.[8] This decrease in mortality has been associated with many aspects of intervention, include progress in all areas of intensive care medicine. Five to 30% of pediatric patients with sepsis develop septic shock.[7]

The diagnosis of septic shock is quite difficult because of the wide spectrum etiology and physical findings, especially in pediatric patients. Unique features of septic shock and its dynamic clinical course further complicate the diagnosis of septic shock.[3] The clinical diagnosis of septic shock is made in children who: 1) have a suspected infection

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manifested by hypothermia or hyperthermia; and 2) have clinical signs of inadequate tissue perfusion including any of the following; decreased or altered mental status, prolonged capillary refill >2 secs (cold shock), diminished pulses (cold shock) mottled cool extremities (cold shock) or flash capillary refill (warm shock), bounding peripheral pulses, and wide pulse pressure (warm shock) or decreased urine output <1 mL/kg/h. Hypotension is not necessary for the clinical diagnosis of pediatric septic shock; however, its presence in a child with clinical suspicion of infection is confirmatory.[9]

Treatment of septic shock requires administration of antimicrobials, aggressive fluid rescucitation, and titration of appropriate inotropic and/or vasopressor agents. Our management in PICU followed the algorithm for pediatric septic shock from Carcillo *et al*.[10] Initial resuscitation include management of airway-breathing-circulation and initial fluid rescucitation with push boluses of 20 mL/kg body weight (BW) at the soonest possible time, of isotonic saline or colloid up to and over 60 mL/kg BW, until perfusion improve unless rales or hepatomegaly develop. Correction of hypoglycemia and hypocalcemia was done if necessary and antibiotics started within 1 hour of management. Shock episode which did not reverse after fluid boluses was defined as fluid refractory shock, inotrope agent was started in this case.[10]

We retrospectively examined the medical records of children admitted to a multidiscplinary PICU, had septic shock at the time of admisssion, or who developed septic shock during their hospitalization in our PICU. The objective of this study is to determine the mortality rate for pediatric patients with septic shock in our setting.

Methods

This study was conducted in a multidisciplinary PICU in university hospital in Yogyakarta, Indonesia. Our PICU had 10 beds with 8 ventilators. Patient management was done by 1 pediatric intensivist, 2 general pediatricians, and residents. All pediatricians and residents had completed the *Pediatrics Advanced Life Support* (PALS) course. The Institutional Review Board at University of Indonesia approved this retrospective study. A computerized database and the raw data sheets of all PICU admission from November 1, 2011 though June 30, 2014 were reviewed to identify patients with septic shock. Demographic and clinical data from medical record were collected. Data included patients' age, gender, underlying diagnoses, pediatric risk of mortality score (PRISM) III, P*ediatric Logistic Organ Dysfunction* (PELOD) score,7 type of initial and supportive treatment given, incidence of fluid overload (FO), PICU length of stay (LoS), and mortality.

Percentage of fluid overload (FO%) was calculated based on the total fluid input (in mL) minus total fluid output (in mL) divided by body weight (in kg, body weight at admission) and multiplied by 100% per day for the first 7 days after PICU admission or until PICU mortality outcome status was achieved.[11] We also recorded data for the types of initial treatment include the modality of oxygen therapy, time of antibiotic administration, episode of hypoglycemia, type of resuscitation fluid, as well as the amount and duration of administration. The supportive treatment include the need for mechanical ventilator in the first 24 hour after diagnosis of septic shock was established, inotrope agents, steroids, red blood cell transfusion, administration of insulin and/or 10% dextrose solution to maintain blood sugar levels, and results of blood culture. Septic shock was defined by definition from Goldstein *et al*.[6] We used the clinical parameters for septic shock diagnosis from Carcillo *et al*.[10] All of these parameters must clearly written in the medical records in order to meet the inclusion criteria.[6,9]

Descriptive data such as the subject characteristics by group mortality outcomes are presented in the form of tables. Assessment of the differences in the dependent variables based on mortality outcomes were done by independent T-test, for normal distribution data. Non-parametric Mann-Whitney test was performed for abnormal distribution data.

Results

A total of 239 shock cases from all types were observed, representing 20.3%from all PICU admissions between November 1, 2011 to June 30, 2014. From 239 cases, there were 55 cases related to dengue shock syndrome; 38 cases who failed to meet the criteria for septic shock, and 1 case of obstructive shock. Nine cases

were initially considered to be septic shock cases, but were excluded because the medical records were unavailable for review. Of these 9 cases, 8 were died

This study included 136 cases with septic shock. The patient's ranged in age from 1 month to 17 years and 6 months. Ages, sex, PICU length of stay, PRISM III score, and PELOD score are presented in **Table 1**.

infections (17 cases), and sepsis (10 cases). Malignancy included acute lymphoblastic leukemia (10 cases), lymphoma (3 cases), and teratoma (2 cases). Chronic diseases included chronic kidney disease (7 cases) and SLE (4 cases).

Blood cultures were positive in 41 cases (30.1%). Of these, 8 cases had cultures from which one bacterial species grew (7 Gram-negative and

Table 1. Characteristics of subjects, based on demographics, length of stay, scores of PRISM III, PELOD, and F0 >10%

Variables	Total (N=136)	Surviving (n=16)	Non-surviving (n=120)	P value
Median age (range), months	16 (1-210)	12.5 (2-134)	16 (1-210_	0.94[a]
Males, n(%)	71 (52.2)	8	63 (52.5)	0.85
Median LoS (range), days	4 (1-590	7.5 (2-45)	3 (1-59)	0.001[a]
Median PRISM III (range)	10 (0-250	5.5 (0-25)	10 (0-19)	0.006[a]
Median PELOD (range)	22 (9-58)	12 (9-58)	22 (10-32)	0.003[a]
FO>10%, n(%)	80 (58.8)	4	76 (63.3)	0.003

ER=emergency room; PICU=pediatric intensive care unit; PRISM III=pediatric risk of mortality score III; PELOD=pediatric

In all subjects , the median age of patients was 16 months, 12.5 months in the surviving group and 16 months in the non-survival group. Male comprised 50% (or 8 subjects) of the survival group and 52.2% (or 63 subjects) of the non-survival group. The median PICU length of stay (LoS) were significant different, with 7.5 days in the survival group and 3 days in non-surviving group ($P<0.05$). Initial PRISM III and PELOD in the surviving group had median score of 5.5 and 12, respectively, while in the non-survival group were 10 and 22, respectively. These differences in PRISM III and PELOD were also found to be significant different between the two groups ($P <0.05$), as seen in **Table 2**.

Of the 136 cases, 74 (54.4%) were infections, 34 cases (25%) were post-surgery, 15 cases (11.1%) was malignancy, 11 cases (8.1%) were chronic disease, and 2 cases were Guillain-Barre syndrome. Infections diagnosed included pneumonia (47 cases), intracranial

1 Gram-positive). Twenty-three patients had cultures from which 2 bacterial species grew (15 cases with 2 different Gram-negative species, 6 cases with 1 Gram-negative and 1 Gram-positive species, and 2 cases with 2 different Gram-positive species). Ten patients had cultures from which multiple organisms grew, and 1 patient culture from which 1 fungus grew (Candida sp). *Pseudomonas aeroginosa* and K*lebsiella pneumoniae* were the common Gram-negative bacteria found, and coagulase-negative staphylococci were the most common Gram-positive bacteria found.

The most common early clinical sign of septic shock was diminished peripheral pulse, found in 97.8% cases. Other early clinical signs were tachycardia in 97.3% cases, capillary refill time more than 2 seconds in 94.6% cases, altered mental status in 86.6% cases, and decreased urine output less than 1 mL/kgbw/hour in 44.6% cases. The least common early clinical sign was low blood pressure in 32.6% cases. All signs were

Table 1. Type of initial management given

Variables	Total (N=136)	Surviving (n=16)	Non-surviving (n=120)	P value
Endotracheal tube (%)	99 (72.8)	7	92 (76.7)	0.009*
Hypoglycemia correction, n(%)	15 (11)	0	15 (12.5)	0.137*
Antibiotic within 1 hour, n(%)	129 (94.9)	16	113 (94.2)	0.402*
Electrolyte correction, n(%)	13 (9.6)	1	12 (10)	0.532*

*Fischer's exact test

written in the medical records.

The distribution of initial management modalities between group is shown in **Table 2**. Fluid therapy management are shown in **Table 3.** Ringer's lactate was used as the first crystalloid rescucitation fluid in all patients, while 6% hydroxyethyl starch (HES) was the most common colloid used. Total amount of fluid rescucitation given, reason for discontinuation of fluid rescucitation, and the time needed to complete the initial fluid resuscitation, showed no statistically significant differences between the two groups.

PELOD and PRISM scores. The 15 surviving patients consisted of 8 patients with post-abdominal surgery and 7 patients with infections who were previously healthy. No bacteria were grown from blood cultures from the survival group.

Eighty (58.8%) patients had FO% more than 10%. There was a higher incidence of FO% in non-survival group (63.3%) compared to survival group (25%). We also recorded the clinical signs of overload status associated with this high incidence of FO% >10% in those 80 patients. The most common clinical

Table 3. Management of septic shock

Variables	Total (N=136)	Surviving (n=16)	Non-surviving (n=120)	P value
Median total fluid (range), mL/kg	40 (10-80)	40 (20-80)	40 (10-80)	0.613**
Reason to terminate fluid rescucitation, n(%)#				
Shock overcome	16 (11.8)	3	13 (10.9)	
Guideline	41 (30.1)	4	37 (31.1)	0.298***
Overload signs	17 (12.5)	0	17 (14.3)	
No response	61 (44.8)	9	52 (43.7)	
Median duration of fluid therapy (range),## minutes	60 (1-960)	45 (15-180)	60 (1-960)	0.745**
10% dextrose, n(%)	48 (35.3)	8	40 (33.3)	0.190
Insulin, n(%)	17 (12.5)	0	17 (14.2)	0.103
Steroid, n(%)	11 (8.1)	0	11 (9.2)	0.238
PRC, n(%)	43 (31.6)	7	36 (30)	0.267
MV within 24 hours, n(%)	108 (79.4)	5	103 (85.9)	0.000
>1 inotrope, n(%)	47 (34.5)	1	46 (38.3)	0.011

**Mann-Whitney test; ***Pearson's Chi-square; #reason to terminate fluid rescucitation=condition in the medical records to discontinue initial fluid resuscitation; ##duration of fluid therapy=period of time needed to give initial fluid rescucitation; PRC: transfusion of packed red cells; MV in 24hrs: mechanical ventilator support in the first 24 hours after diagnosis of septic shock was established; >1 inotrope: more than 1 inotrope used

Table 3 also shows the variable distribution of supportive treatment given after fluid therapy in the two groups. There were statistically significant difference in the need for a mechanical ventilator in the first 24 hours and usage of more than 1 inotrope agent between the two groups. Dobutamin was the most common inotropic agent used.

The overall mortality rate was 88.2% (120 of 136 cases) which was higher than predicted by the

sign was liver enlargement in 48 (60%) patients, followed by lung rales in 29 (36.25%) patients, gallop sound in 2 (2.5%) patients, and increase jugular venous pressure in 1 (1.25%) patient. These data were also written in the medical records.

Multivariate analysis was done using conditional logistic regression test stepwise method. Variables included in the multivariate test was a variable of P <0.25, did not have empty cells, and have complete

Table 3. Multivariate logistic regression analysis on clinical variables

Clinical variables	coefficient	P value	OR (95% CI)
FO>10%	1.901	0.020	6.69 (1.35 to 33.21)
MV in 24 hours	2.796	0.002	16.38 (2.69 to 99.66)
>1 inotrope	0.403	0.743	1.49 (0.13 to 16.62)
PRISM III	-0.661	0.436	0.52 (0.09 to 2.73)
PELOD	-0.165	0.849	0.85 (0.15 to 4.65)
PICU LoS	2.024	0.209	7.57 (0.31 to 178.32)

data on bivariate test. The final result of the analysis stated that degree of FO > 10% and the need for mechanical ventilator for the first 24 hours after PICU admission increased mortality (P <0.05) (**Table 4**).

Discussion

Mortality rate in pediatric septic shock have declined steadily over the past several decades, but most reports came from developed countries. Few study reported mortality rate and factors that contribute in pediatric septic shock from developing countries. Here we report the mortality rate of pediatric septic shock from our unit, in Yogyakarta, Indonesia from 2011-2014. In a developing country, we face more complicated problems than do developed countries, such as limited access to health care, lack of PICU facilities, and health insurance matters. There are a large numbers of factors that determine the outcome of pediatric shock septic in our setting. We believe some factors relate to the pre-hospital period, such delay in seeking medical attention, delay in detection of critically ill condition, and delay in transport to referral hospital. Unfortunately, we did not evaluate these factors in this study.

We found mortality rate was 88.2% in a cohort of patients with septic shock admitted to our PICU, reflecting data collected in a case-by-case medical record review. This was very high compared to data from developed countries that reported mostly lower rates range from 20-30%. Similiar study from Rohtak District, Haryana, India also reported high mortality rate of 93.1% in pediatric septic shock, and the authors concluded that mortality was not predictable by any individual factor, including time lag to PICU transfer, duration of PICU stay, presence of multiorgan dysfunction, or PRISM score at admission.[12]

Regarding supportive treatment, two variables showed significant differences between the two groups: the use of inotrope agent more than 1 and mechanical ventilator support in the first 24 hours after diagnosis of septic shock was established. The mechanical ventilatitor support was given when patients showed clinical signs of respiratory distress. In this study, the use and selection of inotrope agent as supportive therapy was only based on clinical findings and simple hemodynamic monitoring tools.

Another important finding was high incidence of fluid overload. In our setting, we gave initial fluid rescucitation for septic shock start from 20 mL/kgbw until 60 mL/kg BW, unless rales or hepatomegaly develop, according to the guidelines used. We also aggressively perform fluid challenge test by giving 10 mL/kg BW in patients who developed tachycardia, to exclude the shock condition or in condition which we not sure of preload status in our patients. In other words, many patients still received large intravenous fluid volumes after initial rescucitation. Another reason for this was that we do not have any renal replacement therapy modalities for unstable hemodynamic patients in our unit.

Early studies revealed that the influence of fluid overload (FO) on population mortality begin in critically ill pediatric patients who require renal replacement therapy (RRT). An observational study done by Goldstein involving 21 critically ill pediatric patients who require continuous venovenous hemofiltration (CVVH) concluded that the only variable that showed significant differences between survival and non-survival groups was the degree of FO. The study also calculated the initial PRISM scores of all patients and FO in the surviving group had a lower degree than the non-surviving group.11 Gillespie et al. conducted a retrospective study in pediatric patients requiring continuous renal replacement therapy (CRRT) and showed the subjects with FO> 10% at the start of CRRT had 3.02 times higher risk of death than subjects without FO or FO <10%.[13] We used the same cut-off point of fluid overload as reference in our study. Foland et al. conducted a retrospective study on 113 critically ill pediatric patients requiring CRRT with the same aim as the two previous studies and found comparable results. The study observed that FO and multiple organ dysfunction syndrome (MODS) of more than 3 were predictors of mortality. Median FO percentage in the survival group was 7.8% (2-16.7%), while in non-survival group was 15.1% (4.9-25.9%).[14] The first study which revealed the influence of FO on critically ill children who do not require RRT was done by Arikan et al. in 2012. The study suggested that FO% ≥ 15% was associated with the use of a ventilator and a long length of stay in the PICU.[15]

Excessive fluid administration may cause acute lung injury (ALI), abdominal compartment syndrome, coagulopathy, and cerebral edema, affecting the

outcome of patients with septic shock. The pattern of therapy to achieve adequate perfusion with resuscitation fluids should be modified to targeted fluid administration therapy in maintaining euvolemia condition after achieving a stable hemodynamic state.[15] A study in adult populations also found that the FO is one of the risk factor for mortality in septic shock.[16]

This high mortality rate in our study might be influenced by the disease severity of patient, as characterized by high initial PRISM III and PELOD scores, and the incidence of FO. The FO% was found to be significantly higher in the non-survival group and this might be rationalized by the lack of available hemodynamic monitoring tools in our setting, which could be utilized to guide fluid therapy and administration of inotrope agent.

A limitation of this study is its retrospective method, performed with medical record data. As such, the data fully depend on the completeness of existing medical records. In addition, careful interpretation was required when performing data extraction. Also, this study was conducted at only a single center, which may not representative for epidemiology data of septic shock in Indonesian pediatric population. We also did not include data prior PICU admission. A multicenter study is imperative to develop more comprehensive epidemiology data in Indonesia.

This study was conducted with no preceding, comparable Indonesian study, as this was the first study aimed to assess the mortality rate of septic shock in pediatric population in Indonesia. Therefore, since we aspired to include as many variables in the analysis for possible risk factors of mortality in patients, there were several variables that had not been previously analyzed in other studies from other countries. It is also plausible that there might be other variables that should be considered in the analysis to account for various distinctive features of Indonesia.

In conclusion, the mortality rate in pediatric septic shock in developing country is still very high compared to developed country. There is a higher incidence of FO% in non-survival group. However, large multicenter prospective studies should be done to evaluate the true burden and outcome of pediatric septic shock in developing country

Conflict of Interest

None declared.

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