

Corticosteroids for pediatric septic shock patients

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Abstract

Background Septic shock remains a major cause of mortality and admission to the pediatric intensive care unit (PICU) in children. Management includes adequate fluid resuscitation, followed by catecholamine infusion, if needed. Corticosteroid therapy is advised for catecholamine-refractory shock, although this practice is controversial, as it was not beneficial in other studies.

Objective To assess corticosteroid use in pediatric septic shock patients in Cipto Mangunkusumo Hospital.

Methods This cross-sectional study included all patients aged 1 month-18 years with a diagnosis of septic shock during the study period of January 2014 to July 2018 admitted in PICU Dr. Cipto Mangunkusumo Hospital, Jakarta. Data obtained from medical records were, age, sex, immunology status, port d'entrée of sepsis, inotropic and vasopressor usage, mechanical ventilation, corticosteroid type, hospital length of stay (LoS), and mortality outcome.

Results Of 217 children with septic shock, 12 patients (5.5%) received corticosteroid therapy. The most common corticosteroid given was hydrocortisone (80%), with a 2 mg/kg BW loading dose, followed by a continuous infusion dose of 2-50 mg/kg BW/day. Almost all patients (11/12) received corticosteroid therapy until they died. Median duration of corticosteroid use was 2 (range 1-7) days, median number of inotropes and vasopressors used was 3 (range 2-4) agents, median LoS was 3 (range 1-9) days, and mortality rate was 100%.

Conclusion A small proportion of pediatric septic shock patients received corticosteroid therapy. Their mortality rate was 100%. Further clinical study is needed to evaluate the benefit of corticosteroid therapy in pediatric septic shock patients. [Paediatr Indones. 2019;59:67-71; doi: <http://dx.doi.org/10.14238/pi59.2.2019.67-71>].

Keywords: corticosteroid; mortality; pediatric septic shock; septic shock

Sepsis is defined as a life-threatening condition of organ dysfunction caused by a dysregulated host response to infection.¹ Sepsis is still one of the major causes of morbidity, and the leading cause of pediatric intensive care unit (PICU) admissions.² The World Health Organization (WHO) reported 80% mortality of children below 4 years of age with sepsis.³ Based on medical record data in Cipto Mangunkusumo Hospital in 2009, the incidence of sepsis in children admitted to the PICU was 19.3% and the mortality rate was 10%. Also, 5-30% of pediatric sepsis cases can progress to septic shock.⁴ Rusmawatiningtyas *et al.*⁵ reported an 88.2% mortality rate in children with septic shock admitted to the PICU.

The American College of Critical Care Medicine (ACCM) developed an algorithm to target an initial resuscitation fluid of 20 mL/kg BW of crystalloid or colloid which can be repeated to 60 mL/kg BW, until perfusion improves or unless rales or hepatomegaly develop. For fluid refractory shock, vasopressors and inotropes must be given. If the shock does not resolve, it may progress to catecholamine-resistant shock.

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This condition is related to adrenal insufficiency, which requires corticosteroid administration such as hydrocortisone.

Several studies on intravenous hydrocortisone administration for catecholamine-resistant shock yielded varying results. Wong *et al.*⁸ suggested that corticosteroid administration for catecholamine-resistant shock be reconsidered, due to side effects including gastrointestinal bleeding, delayed wound healing, hyperglycemia, and immunosuppression. In addition, Atkinson *et al.*⁹ reported that corticosteroid administration in children with refractory septic shock had no benefits.

In Cipto Mangunkusumo Hospital, corticosteroid administration for pediatric septic shock has not been well studied. As such, we aimed to assess corticosteroid therapy for pediatric septic shock to see the prognosis or outcomes as a treatment consideration for future pediatric shock patients.

Methods

This cross-sectional study was done with patients' medical records in Cipto Mangunkusumo Hospital. Subjects were children aged 1 month to 18 years diagnosed with septic shock in the emergency room/PICU from January 2014 to July 2018. Patients with incomplete medical records were excluded from the study. Data obtained from medical records were, age, sex, immunology status, *port d'entrée* of sepsis, inotropic and vasopressor usage, and mechanical ventilation. The type, dose, and duration of corticosteroid therapy were collected for all subjects. Outcomes data were hospital LoS and mortality.

Results

From January 2014 to July 2018, 217 children were diagnosed with septic shock at Cipto Mangunkusumo Hospital, of whom 132 (60.8%) were male. Twelve patients received corticosteroid therapy for septic shock, 8 (67%) of whom were male. Subjects' median age was 165 (range 11-553) months. Six patients were immunocompromised, of whom 2 patients had systemic lupus erythematosus (SLE), 2 patients had poor nutritional status, 1 patient had lymphoma

and poor nutritional status, and 1 patient received post-liver transplantation immunosuppressant drugs. The sources of sepsis were respiratory tract (6/12), abdominal organs (5/12), and urogenital tract (1/12). Patients' characteristics are described in **Table 1**.

Table 1. Characteristics of pediatric septic shock patients receiving corticosteroid therapy

Variables	(N=12)
Median age (range), months	165 (11-533)
Sex, n	
Male	8
Female	4
Immunity status, n	
Immunocompromised	6
Not immunocompromised	6
<i>Port d'entrée</i> sepsis, n	
Respiratory tract	6
Abdominal organ	5
Urogenital tract	1

The most common type of corticosteroid given was hydrocortisone (83%). One patient received dexamethasone as a hydrocortisone replacement. One remaining patient received hydrocortisone, followed by methylprednisolone as a hydrocortisone replacement. The hydrocortisone loading dose was 2 mg/kg (equal to 50 mg/m²), followed by a continuous infusion dose of 2-50 mg/kg/day (equal to 50-1,250 mg/m²/day). In our study, the maximum hydrocortisone dose recorded was 48 mg/kg/day (equal to 1,125 mg/m²/day). The dexamethasone dose used was 1.8 mg/m²/24 hours. One patient received hydrocortisone at a dose of 2 mg/kg/day (equal to 50 mg/m²/day) that was increased gradually to 4 mg/kg/day (100 mg/m²/day) in one day, before getting methylprednisolone at a dose of 0.4 mg/kg/day (equal to 10 mg/m²/24 hours) that was increased gradually to 0.8 mg/kg/day (equal to 20 mg/m²/day).

Corticosteroid doses were adjusted during administration. Most patients (58.3%) experienced that the corticosteroid dose was gradually increased until they died. However, one patient (8.3%) experienced tapering down to cessation of hydrocortisone during 7 days of administration. Almost all patients (92%) were still receiving corticosteroid therapy when they died. **Table 2** shows that the median duration of corticosteroid use was 2 (1-7) days. The median number of inotropes and vasopressors used was 3 (2-4). The

median LoS of patients with septic shock receiving corticosteroid therapy was 3 (1-9) days and the mortality rate was 100%.

Table 2. Outcomes of pediatric septic shock patients receiving corticosteroid therapy

Outcomes	(N=12)
Median duration of corticosteroid use (range), days	2 (1-7)
Median number of inotropic and vasopressor agents used (range)	3 (2-4)
Median LoS (range), days	3 (1-9)
Mechanical ventilation, n	12
Mortality, n	12

Discussion

The proportion of pediatric septic shock patients given corticosteroids was only 12 of 217 patients (5.5%) in the 4-year period at Cipto Mangunkusumo Hospital. Corticosteroid therapy was given when shock had not resolved after administering a minimum two types of vasopressors and inotropes. In contrast, Chrysostomos *et al.*¹⁰ noted a larger proportion of septic shock patients receiving corticosteroids because the corticosteroid administration did not depend on the number, but on the duration, of inotropes and vasopressors used. They found that early initiation of corticosteroid administration, after 9 hours vasopressor and inotrope administration, resulted in better prognoses compared to late initiation of corticosteroid administration in patients with catecholamine-resistant septic shock.¹⁰

We found high usage of inotropic and vasopressor agents prior to corticosteroid therapy in our subjects, with median of 3 (range 2-4) drugs. Although corticosteroid therapy was usually given to patients after a combination of a minimum of two inotropic and vasopressor agents with maximum dose did not overcome shock, there was no standard protocol among physicians for starting corticosteroid therapy in such cases. In comparison, Menon *et al.*¹¹ reported that corticosteroid therapy was given to patients who had a minimum of two vasoactive infusions and had received 50 mL/kg of resuscitation fluids. Nichols *et al.*¹² reported lower numbers of vasopressor and inotropes used, [median 2 (range 1-2)]. In their study, corticosteroids were given to patients with continuous

need for catecholamine infusion for 6 or more hours following initial fluid resuscitation of ≥ 60 mL/kg of crystalloid and/or colloid solutions. The cut-off for starting the corticosteroid therapy was not the amount of catecholamine used, but the duration of catecholamine infusion. Nichols *et al.*¹² also showed the catecholamine included dopamine $> 5 \mu\text{g/kg/min}$, vasopressin, and any dose of dobutamine, epinephrine, norepinephrine, phenylephrine, or milrinone.

We noted that corticosteroid therapy was given without cortisol level examinations, in accordance with the Surviving Sepsis Campaign guidelines which state that in catecholamine-resistant shock, hydrocortisone administration should be given immediately without cortisol level examination. Nichols *et al.*¹² also showed the same statement and in contrast, Casartelli *et al.*¹⁴ concluded that the cortisol assay should be used in deciding whether or not to give corticosteroids in septic shock.

The most commonly used corticosteroid in our study was hydrocortisone (10/12). Similarly, a previous study reported that 78% of subjects were prescribed hydrocortisone, 16% methylprednisolone, and 6% dexamethasone.⁹ However, another previous study reported that 53% of subjects were prescribed hydrocortisone, 29% dexamethasone, 14% methylprednisolone, and 4% prednisolone.¹⁵

Gibbison *et al.*¹⁶ also mostly used hydrocortisone as corticosteroid of choice to treat catecholamine-resistant septic shock, since the advantages of hydrocortisone are increased capillary permeability and cardiovascular activity. Furthermore, hydrocortisone has the lowest risk of side effects such as hyperglycemia, severe infection, and gastrointestinal bleeding compared to other corticosteroids. Hydrocortisone administration may affect cortisol assay results in catecholamine-resistant septic shock, while dexamethasone administration does not.¹³

We noted hydrocortisone loading doses of 2mg/kg, followed by 2-50 mg/kg/d infusion dose. The initial loading dose was similar to that reported by Menon *et al.*,¹¹ who used a hydrocortisone dose of 2 mg/kg. Their hydrocortisone infusion dose of 1 mg/kg was given every 6 hours and weaned to every 8 hours until all vasoactive infusions had been discontinued for 12 hours. Nichols *et al.*¹² reported an initial hydrocortisone dose of ≥ 50 mg/m² (or ≥ 1 mg/kg) followed by a dose ≥ 50 mg/m²/d (or ≥ 1 mg/kg/d).

The median duration of corticosteroid usage in our subjects was 2 (range 1-7) days, with 11/12 patients still receiving corticosteroids when they died. The maximum duration was similar to the Menon *et al.* study,¹¹ in which corticosteroids were given for a maximum of 7 days to prevent adrenal suppression. However, Nichols *et al.*¹² reported a median of 4 (range 2-4) days corticosteroid therapy in the group with random cortisol level (rSTC) < 18 µg/dL and 4 (range 2-5) days in the group with rSTC ≥ 18 µg/dL. Atkinson *et al.*⁹ also showed a higher median duration of corticosteroid use of 5 (range 3-7) days.

In our study, the mortality rate was high (100%), with a median LOS of 3 (range 1-9) days. The high mortality rate may have been caused by the extreme severity of illness among subjects, as indicated by the high use of vasopressor and inotropic agents [median 3 (range 2-4) types] and the high use of mechanical ventilation in 100% of subjects. Menon *et al.*¹¹ noted a 2% mortality in patients receiving corticosteroid therapy, with PICU median LoS of 8.3 (range 3.7-15.0) days. The median PELOD score of their corticosteroid group was 6 (range 4-9), with 65.2% mechanical ventilation use. According to Dewi Metta *et al.*²⁰, PELOD scores at 20 increasing mortality to 50%. Nichols *et al.*¹² showed a 24% mortality rate among septic shock patients in the stress dose hydrocortisone therapy group, with median LoS of 10 (range 5-20) days. The median *Pediatric Risk of Mortality* (PRISM) III score at 12 hours was 16 (range 10-12) and 88% of subjects were mechanically ventilated. Vineet Popli *et al.*²¹ showed *Pediatric Risk of Mortality* (PRISM) III had a biphasic effect on the length of stay (LOS). Their study showed length of stay increased with increasing PRISM III score up to the score of 14; while score of 19, length of stay decreased gradually because an increasing severity of illness as the mortality reaches almost 100%.

Some guidelines recommend the use of corticosteroids in catecholamine-resistant shock, however, we noted no benefit to such therapy, as 100% of the patients who received corticosteroids died. Menon *et al.*¹¹ stated that there were no statistically significant differences in outcomes or adverse events between the hydrocortisone and placebo groups. Furthermore, Nichols *et al.*¹² stated that stress dose hydrocortisone therapy in children with catecholamine-dependent septic shock was associated with worst outcomes. In

addition, 2 previous studies reported that adjunctive corticosteroid therapy in severe pediatric sepsis showed no definitive improvement.^{9,15} Also, a pediatric meta-analysis by Menon *et al.*¹⁷ showed no benefit of corticosteroids for treating shock.

Despite the lack of convincing evidence, a Canadian survey revealed that almost all pediatric intensivists (91.4%) would administer corticosteroids to patients in persistent shock who had received 60 mL/kg of fluid and were on two or more vasoactive medications.¹⁸ Possible rationales for the use of corticosteroids in sepsis are beneficial pharmacologic effect on the cardiovascular system and anti-inflammatory properties. Nonetheless, high dose corticosteroid administration in septic shock has been associated with higher infection rates, such as disseminated candidiasis and hospital-acquired pneumonia.¹⁹ Other potential side effects include hyperglycemia, bleeding, critical illness associated neuropathy/myopathy, and hypernatremia.^{15,19} Corticosteroid use was also associated with suppression of genes corresponding to adaptive immunity.⁸

In conclusion, we find that a small proportion of pediatric septic shock patients received corticosteroid therapy, mostly hydrocortisone. The mortality rate of patients who received corticosteroids is 100% and their LoS is short. Corticosteroids do not seem to have beneficial results in our sepsis patient population.

Conflict of Interest

None declared .

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