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# Polymyxin B Hemoperfusion in Pediatric Septic Shock: Single-Center Observational Case Series

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**OBJECTIVES:** To evaluate the use of direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) as adjunctive therapy during pediatric patients with septic shock.

**DESIGN:** Prospective observational study.

**SETTING:** Nine-bed PICUs at university referral hospital.

**PATIENTS:** Children (30 d to 15 yr) with septic shock and Pediatric Logistic Organ Dysfunction (PELOD)-2 score greater than or equal to 10 or Pediatric Risk of Mortality (PRISM) 3 score greater than or equal to 15, who were also receiving at least one inotrope.

**INTERVENTION:** Patients received 2–4 hour treatment with PMX-DHP 20R column on 2 consecutive days.

**MEASUREMENTS AND MAIN RESULTS:** We enrolled six children aged 21–167 months old (median, 99-mo old), with a body weight of 10–50 kg (median, 28 kg). All six patients had both PELOD-2 greater than or equal to 10 and PRISM-3 greater than or equal to 15, required invasive mechanical ventilation, and received standard treatment for septic shock before enrollment. We observed significant improvement in PELOD-2 score from baseline to 72 hours after the start of PMX-DHP (mean [95% CI] from 14.3 [12.2–16.5] to 6.0 [0.3–11.7]; $p = 0.006$). The vasoactive inotropic score (VIS) and lactate concentration also significantly decreased from baseline to 72 hours (VIS, 60 mmol/L [25–95 mmol/L] to 4.0 mmol/L [44.1–12 mmol/L]; $p = 0.003$; lactate, 2.4 mmol/L [1.0–3.8 mmol/L] to 1.0 mmol/L [0.5–1.5 mmol/L]; $p = 0.01$). Five of six patients survived. There was no device-related adverse event in these patients.

**CONCLUSIONS:** In this case series of treatment with PMX-DHP as adjunctive therapy in children with refractory septic shock and high baseline severity, we have shown that patient recruitment is feasible. We have also found that clinical hemodynamic and severity of illness scores at 72 hours may be potential end points for testing in future randomized controlled trials.

**KEY WORDS:** blood purification; children; pediatric intensive care; Pediatric Logistic Organ Dysfunction 2 score; polymyxin B hemoperfusion; septic shock

Sepsis is a complex disease caused by the body's dysregulated response to infection, which may result in a cytokine storm and, potentially, fatal multiple organ failure (1). This powerful reaction to sepsis can be triggered by endotoxin released by Gram-negative bacteria. In addition, since high levels of endotoxin and proinflammatory cytokines are associated with a high mortality rate (2), blood-purification techniques that remove both endotoxin and proinflammatory cytokines from the blood of septic patients have been developed (3–5).

Direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) is a blood purification technique designed to reduce blood endotoxin levels (6) and proinflammatory cytokines such as interleukin-6 in sepsis (7, 8). Results of randomized controlled trials and observational studies have shown rapid



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stabilization of patient hemodynamics and improvement of organ dysfunction and outcomes (9–11). However, to date, most studies have involved adults, rather than pediatric patients. In this pilot study, we aimed to determine the feasibility of using direct hemoperfusion with PMX-DHP as adjunctive therapy in children with high severity of illness scores and refractory septic shock.

## MATERIALS AND METHODS

### Study Design

We conducted this prospective observational study at a nine-bed PICU at a university referral hospital. The patients were enrolled between July 2017 and May 2018. The protocol was approved by the institutional review board (IRB) of King Chulalongkorn Memorial Hospital (IRB no 687/59). This study was registered at Thai Clinical Trials Registry (TCTR20180418002), and we obtained informed consent from the families of all patients.

### Patients

We enrolled children with sepsis, as defined by the Surviving Sepsis Campaign guideline 2012 (12), who were admitted to our PICU during the study period. All children initially received standard treatment for septic shock, including IV fluid resuscitation, antibiotics, removal of source of infection, and inotropic drugs within 6 hours after the diagnosis of sepsis. Patients were enrolled if they: 1) were 30 days to 15 years old, 2) required any dose of at least one vasopressor, and 3) had a Pediatric Logistic Organ Dysfunction (PELOD)-2 score greater than or equal to 10 or Pediatric Risk of Mortality (PRISM)-3 score greater than or equal to 15. Patients were excluded from recruitment if they were receiving end-of-life care or were allergic to polymyxin B, or if they had uncontrolled bleeding.

### PMX-DHP Treatment

In general, the volume required in the extracorporeal circuit during PMX-DHP treatment should be less than 10% of circulatory volume (13). Even though there are small PMX cartridge sizes available in Japan, only the largest cartridge size (PMX-20R) is available in Thailand. Therefore, in order to reduce the volume requirement in the extracorporeal circuit, we used a modification with small blood tubing. However, in cases 2, 3, and 6, the volume of the extracorporeal circuit was over 10% of the patient's circulatory volume. Therefore, we primed the blood circuit and the cartridge with 5% albumin or packed red cells (PRCs) to avoid hemodynamic instability. We then gradually increased the blood flow in the continuous renal replacement therapy (CRRT) machine with real-time hemodynamic monitoring of blood pressure and vital signs. There was no device-related adverse event observed during the treatment.

Therefore, we used a PMX column (PMX-20R; Toray Industries, Tokyo, Japan), whose blood volume is 135 mL, with a CRRT machine (Aquarius, Nikkiso America, San Diego, CA; or Infomed, Meinier, Switzerland). We selected a blood circuit for each machine according to the patient's body weight. For the Aquarius machine, Aqualine size S (64-mL blood volume) was used for body weight less than 30 kg, and Aqualine (105-mL blood volume) was used for weight greater than or equal to 30 kg. Three types of blood circuit were used with the Infomed machine, including Infomed baby set (25 mL) for weight less than 15 kg, Infomed child set (50 mL) for weight 15–30 kg, and Infomed adult set (100 mL) for weight greater than or equal to 30 kg. After rinsing with normal saline solution with heparin, we primed the blood circuit and the cartridge with normal saline solution; we used 5% albumin or PRC when the volume of the extracorporeal circuit was more than 10% of the circulatory volume of the patient. If the albumin level was below 3.5 g/dL and hematocrit was above 30%, 5% albumin was used for priming. If the hematocrit was below 30%, packed RBCs were used. Vascular access was established with ultrasound-guided insertion of a double-lumen venous catheter into the right internal jugular or femoral vein. The size of the double-lumen catheter was 8F for patients weighing 6–15 kg, 9–10F for those weighing 15–30 kg, and 11.5F for those weighing greater than 30 kg.

In general, PMX-DHP was started within 24 hours when a patient fulfilled the inclusion criteria for study. PMX-DHP was performed for a maximum of 4 hours, and the second session was started approximately 24 hours after the end of the first session. Unfractionated heparin was used in patients with normal coagulation to maintain activated clotting time within 150–180 seconds. The blood flow rate was started low and gradually increased while monitoring real-time blood pressure and

vital signs with an arterial-line monitor. After the end of the PMX-DHP session, CRRT was continued if required.

### Data Collection and Study End Points

Demographic data, underlying disease, source of infection, and type of respiratory support were extracted from patients' hospital charts. Blood gas data, dose of vasopressors, and laboratory data were recorded at baseline, 24 hours, 48 hours, and 72 hours after the beginning of PMX-DHP. The baseline was defined as the time before PMX-DHP treatment was started. The severity of organ dysfunction or failure was expressed with the PELOD-2 score (14) and PRISM-3 score (15). Both scores were recorded at base line, and PELOD-2 score was also recorded at the three additional time points noted above. The total dose of vasoactive/vasopressor agents was summarized using the vasoactive inotropic score (VIS) validated for pediatric sepsis (16) and calculated as: dopamine dose + dobutamine dose + (epinephrine dose × 100) + (norepinephrine dose × 100) + (milrinone dose × 10) + (vasopressin dose × 10,000), with doses expressed as μg/kg/min for most drugs and as U/kg/min for vasopressin. We analyzed the reduction in PELOD-2 score, VIS, oxygenation index, serum creatinine, base excess, and lactate from baseline through to the 72-hour time point. We also observed length of PICU stay, hospital stay and mechanical ventilation, and 28-day mortality.

### Statistical Analysis

This case series has been reported in accordance with the Preferred Reporting Of CasE Series in Surgery Guideline. Data are presented as mean and 95% CI. Continuous variables were analyzed with the Friedman test. Categorical variables are presented as proportions. The statistical analyses were carried out using SPSS (version 23; IBM Corp., Armonk, NY), with $p < 0.05$ considered statistically significant.

## RESULTS

Between June 2017 and May 2018, we had six patients who went on to receive PMX-DHP during treatment for refractory septic shock. **Supplemental Table 1** (http://links.lww.com/PCC/C58) shows patient background characteristics and details on the individual diagnosis, and source of infection. Patients were (median [range]) 99 months (21–167 mo) old and weighed 28 kg (10–50 kg). Two patients had gastrointestinal infection, and another had pulmonary infection. No source of infection was identified in the other two patients. All patients had both severity of illness scoring criteria for inclusion, that is, PELOD-2 greater than or equal to 10 and PRISM-3 greater than or equal to 15. All six patients required invasive mechanical ventilation, and three patients received CRRT.

The average PELOD-2 score decreased significantly from 14.3 (95% CI, 12.2–16.5) at baseline to 6.0 (95% CI, 0.3–11.7) at 72 hours ($p = 0.006$) (**Fig. 1** and **Table 1**). The mean VIS significantly decreased from baseline to 72 hours (60 [95% CI, 25–95] vs 4.0 [95% CI, 4.1–12], respectively; $p = 0.003$). The base excess and lactate levels decreased significantly from baseline to 72 hours, $p = 0.05$ and 0.01, respectively (Table 1). Two patients (cases 3 and 4) finished CRRT at 48 hours (data not shown). We failed to find a significant change in oxygenation index and creatinine level from baseline

## TABLE 1.
### Hemodynamic and Metabolic Observations From Baseline to 72 hr

| Parameters | Baseline ($n = 6$) | 24 hr ($n = 5$) | 48 hr ($n = 5$) | 72 hr ($n = 5$) | $p$[a] |
|---|---|---|---|---|---|
| Pediatric Logistic Organ Dysfunction-2 | 14.3 (12.2–16.5) | 11.2 (8.1–14.3) | 9.0 (5.6–12.4) | 6.0 (0.3–11.7) | 0.006 |
| Oxygenation index | 10.5 (–2.9 to 25) | 5.7 (0.3–11) | 3.4 (0.9–6.0) | 3.9 (0.2–7.5) | 0.32 |
| Vascular inotropic score | 60 (25–95) | 25 (–3.6 to 54) | 14 (–6.3 to 34) | 4.0 (–4.1 to 12) | 0.003 |
| Creatinine, mg/dL | 1.5 (0.03–3.0) | 1.2 (–0.7 to 3.1) | 1.3 (–1 to 3.5) | 1.1 (–1.0 to 3.3) | 0.85 |
| Base excess, mEq/L | -8.9 (–12 to –5.7) | –1.8 (–10 to 6.5) | 0.6 (–7.0 to 8.2) | 0.46 (–7.7 to 8.6) | 0.05 |
| Lactate, mmol/L | 2.4 (1.0–3.8) | 1.2 (0.3–2.2) | 1.2 (0.6–1.8) | 1.0 (0.5–1.5) | 0.01 |

[a]Friedman test.

All data are reported as average (95% CI). Two-sided 95% CI was calculated using *t* distribution. Therefore, the lower limit may be negative.

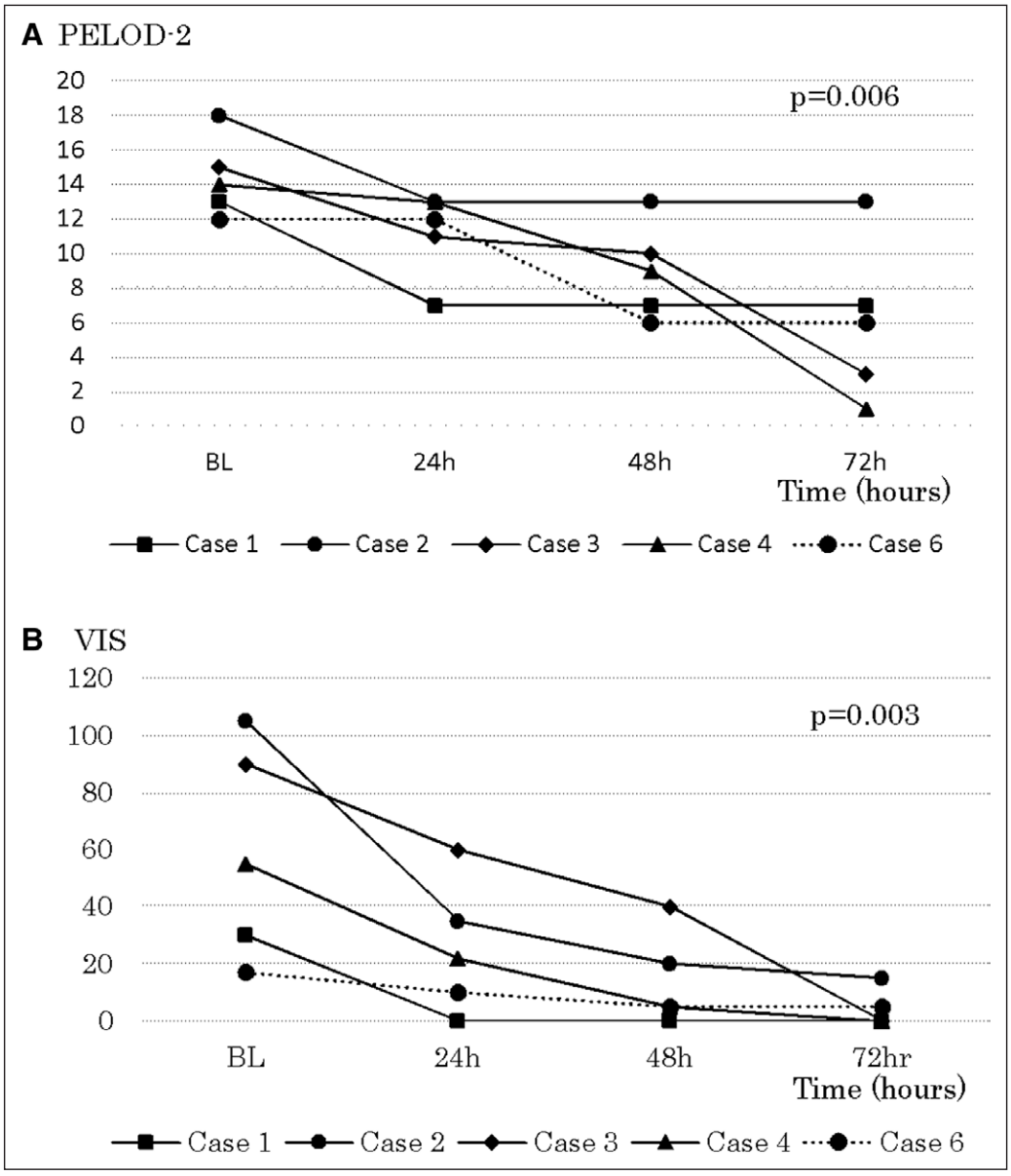


**Figure 1.** Changes in Pediatric Logistic Organ Dysfunction (PELOD)-2 scores (**A**) and vascular inotropic score (VIS) (**B**) from baseline (BL) until 72 hr. Case 5 is not shown in this figure because of death. Friedman test was used to compare the values.

to 72 hours. One out of the six patients died. That patient was diagnosed with submersion injury that required cardiac resuscitation and was referred from the primary care hospital to our hospital 5 days after the event. Because he developed severe acute respiratory distress syndrome, venovenous extracorporeal membrane oxygenation (ECMO) with CRRT was started on the second day after admission. The patient developed intracranial bleeding from severe coagulopathy resulting from his clinical condition and ECMO, which led to death. There were no device-related adverse events in these six patients.

## DISCUSSION

In this study, we prospectively enrolled six children with refractory septic shock and high baseline clinical severity scores to receive adjunctive treatment with PMX-DHP in addition to their standard therapy for sepsis. PELOD-2, VIS, and lactate values decreased over the first 72 hours after using PMX-DHP. This new information adds to our knowledge about direct hemoperfusion with PMX-THP as adjunctive therapy in children with high severity of illness scores and refractory septic shock.

PMX-DHP has been widely demonstrated to improve hemodynamics in adult patients with septic shock (9, 10). However, there are a few reports describing clinical experience with PMX-DHP in pediatric patients. Saito et al (17) used PMX-DHP to treat a 2-year-old boy who developed septic shock during chemotherapy for stage IV neuroblastoma. The patient successfully discontinued vasopressors 48 hours after the start of PMX-DHP, with a decrease in PELOD score from 42 to 11. A similar finding was reported in a neonate with septic shock who received ECMO (18). Similar experiences with smaller sized PMX columns have been shared in other reports. For example, in Japan, there are three sizes of PMX column: PMX-20R, PMX-05R, and PMX-01R, with blood volumes 135, 40, and 8 mL, respectively. The PMX-05R was used to treat sepsis in 10 children 9–48 months old (19),

and PMX-01R was used in preterm infants (20, 21). There were no reports of treatment complications. Taking all of these studies together, the reports all describe rapid improvement in hemodynamics when PMX-DHP is used in patients of various ages with septic shock. In addition, in our study, we also observed changes in VIS and lactate concentration.

There are also reports of use of PMX-DHP being associated with improvement in pulmonary function, such as the $Po_2$-to-$Fio_2$ ratio in adults (9) and the arterial-to-alveolar $Po_2$ ratio in neonates (21). In this regard, use of PMX-DHP is associated with improvement in oxygenation in patients with sepsis and various lung diseases (22–25). In our study, we failed to see any improvement in oxygenation through the first 72 hours, but this is most likely due to sample size, and we do not have a control group for our case series.

We observed that the PELOD-2 score at 72 hours was significantly decreased in our case series. This result may be related to the rapid improvement in hemodynamics with PMX-DHP, as also demonstrated by the improvement in VIS and lactate concentration. The average PELOD-2 score in our PMX-DHP group was 14.3, which is of high severity and risk of mortality (26). Based on our current experience, we believe that it would certainly be worthwhile evaluating whether PMX-DHP improves PELOD-2 score and hemodynamics in children with refractory septic shock and baseline severity in a large study with a control group. According to the results of the current study, we tried to calculate a sample size for our future randomized controlled trial using PELOD-2 score as a primary end point and a historical control with the same criteria as the PMX group. The control group was selected from May 2016 to May 2017 in our hospital. Absolute reductions of PELOD-2 score from BL to 72 hours were 4.8 (SD, 3.8) in the PMX group and 1.0 (SD, 5.2) in the non-PMX group, respectively. The sample size was estimated to 15 patients per group to provide 90% power at a significance level of 0.05 (two-sided) with 6.0 as conservative, common SD, although there may be a limitation because of a historical control. The same number was obtained when we estimated the samples size for the end point of VIS at 72 hours.

This study had some limitations. First, it is a purely descriptive case series lacking a control group. Second, the number of patients was small, which limits generalization of the results and any assessment of safety outside of our setting. Third, the multiple interventions (i.e., PMX-DHP, CRRT, antibiotics, and vasopressors) used to treat the complex conditions in these patients make it difficult to draw any conclusions about efficacy.

## CONCLUSIONS

In this pilot study of using PMX-DHP as adjunctive therapy in pediatric refractory septic shock, we have shown that recruiting critically ill patients in a timely manner in our setting is feasible. We have also shown that PELOD-2 score and VIS at 72 hours may be potential end points for testing in future randomized controlled trials.

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