

Personalized Adjunctive Hemoperfusion Therapy for Refractory Septic Shock Caused by *Vibrio Cholerae* in Thalassemia Patient

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Abstract:

This case report describes a patient with Beta-thalassemia/hemoglobin E that developed *Vibrio cholerae* septicemia, leading to refractory septic shock with a maximum norepinephrine equivalent dose of 1.84 µg/kg/min and multi-organ failure. As the patient remained in refractory shock despite receiving proper antibiotics and organ support for 48 hours, adjunctive therapy including, HA330 hemoperfusion, was initiated. Shock reversal and significant reduction of inflammatory cytokines were achieved after two intervention sessions. The patient was discharged home, despite an initial predicted mortality rate of 85% based on Acute Physiology and Chronic Health Evaluation II (APACHE II).

Keywords: adjunctive therapy, blood purification, β-thalassemia

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Introduction

Septic shock has a high mortality rate due to profound hemodynamic, metabolic, and immune derangements. The intricate interaction between pathogens and host immune responses leads to extensive organ failure. Management of sepsis targets rapid control of infection with antimicrobials and organ support until the immunological response subsides. Presently, there are no established guidelines for adjunctive treatments that adequately address the dysregulated immune response in sepsis. Strategies for treatment beyond standard therapy necessitate a personalized approach that takes into account the patient's progression and the virulence factors of the pathogen.

Case report

A 17-year-old man having Beta-thalassemia/hemoglobin E (β E-thalassemia) and dependent on transfusions presented to Songklanagarind Hospital in Thailand, with fever and voluminous diarrhea lasting 10 hours (hrs). He reported consuming rice noodle soup with seafood and shaved ice 2 hrs before symptom onset. On arrival, his vital signs included: a high-grade fever of 38.6 °C, blood pressure of 102/46 mmHg, pulse rate of 143 beats/min and a respiratory rate of 28/min. Initial arterial lactate was 5.8 mmol/L, leading to a diagnosis of septic shock. Treatment commenced promptly with ceftriaxone being administered within 1 hour (hr) for empirical therapy, along with simultaneous resuscitation using 3 L of balanced crystalloid solution within 3 hrs. Replacement fluid was continued due to persistent diarrhea. The patient received initial respiratory support via a high-flow nasal cannula. Laboratory investigations revealed leukocytosis (white blood cell $14.8 \times 10^3/\mu\text{L}$ with left shift), a hemoglobin level of 6.9 g/dL, hematocrit of 22.6%, serum creatinine level of 1.55 mg/dL, and a total bilirubin level of 9.12 mg/L;

with indirect hyperbilirubinemia resulting from hemolysis. Despite ongoing resuscitation efforts, the patient's clinical condition rapidly deteriorated, leading to respiratory failure, oliguric renal failure, hypoglycemia, and refractory shock. He was intubated in the emergency department and required norepinephrine (NE) at 0.6 $\mu\text{g}/\text{kg}/\text{min}$ to stabilize his blood pressure as well as hydrocortisone being administered before transfer to the intensive care unit (ICU).

Hemodynamic monitoring, using Flotrac/EV1000 (Edwards Lifesciences), revealed an initial cardiac output (CO) of 23 L/min and a systemic vascular resistance (SVR) of 182 dynes-sec/cm⁵: indicative of vasoplegia. Peak arterial lactate levels reached 6.5 mmol/L. During the first 24 hrs in the ICU, 10 L of fluid was administered, with a maximum dose of NE at 1.6 $\mu\text{g}/\text{kg}/\text{min}$ combined with epinephrine at 0.24 $\mu\text{g}/\text{kg}/\text{min}$. This was a 1.84 $\mu\text{g}/\text{kg}/\text{min}$ of NE equivalent dose, which was needed to maintain a mean arterial pressure of 65 mmHg. Ciprofloxacin was administered to ceftriaxone to broaden its spectrum of coverage for presumed severe gram-negative septicemia. Following adequate fluid resuscitation, a furosemide stress test was performed: urine production was 1–1.5 mL/kg/hr. However, a session of venovenous hemodiafiltration was necessary to address the refractory metabolic acidosis despite treatment with intravenous sodium bicarbonate. The initial Sequential Organ Failure Assessment (SOFA) was 14, and the Acute Physiology and Chronic Health Evaluation (APACHE) II was 36; predicting an 85% mortality rate.

Blood cultures revealed a gram-negative organism within 24 hrs, and *Vibrio cholerae* via biochemistry within 50 hrs. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometer identification revealed *Vibrio albensis*, which is a non-O1, non-O139 serogroup of *Vibrio cholerae*. We confirmed its sensitivity to both empirical antibiotics. Despite this, the patient continued to require high-dose NE at 1.4 $\mu\text{g}/\text{kg}/\text{min}$ and epinephrine at 0.16

µg/kg/min. Ongoing multi-organ involvement was observed, with a decline in PaO₂/FiO₂ ratio, thrombocytopenia, hemolysis, and liver dysfunction that caused an increase in the SOFA score to 17. Bedside ultrasonography and intra-abdominal pressure assessment indicated the absence of intra-abdominal hypertension, with a recorded pressure of 7 mmHg having neither collection nor ascites. Inflammatory panels showed interleukin-6 (IL-6) and C-reactive protein of >30,000 pg/mL and 305 mg/L, respectively. Therefore, considering the toxin-mediated effects of gram-negative septicemia, hemoperfusion using the HA330 adsorbent was initiated at a blood flow rate of 150 mL/min for 4 hrs.

A notable improvement in the patient’s hemodynamic parameters, as well as a reduction in IL-6, were observed after initiation of the hemoperfusion therapy (Figure 1). IL-6 was measured before the initiation of hemoperfusion at 6 a.m. for the next two consecutive days. At 16 hrs from the initiation, IL-6 decreased to 12,257 pg/mL, and the level declined to 2,231 pg/mL at 40 hrs. The patient was free from vasopressor within the second day of the intervention. His lactate level decreased to 1.5 mmol/L,

with steady urine output. Hemoperfusion was performed 4 hrs daily for three consecutive days. The decision to discontinue hemoperfusion was based on a marked improvement in hemodynamic parameters, which no longer required vasopressors. The combination of ceftriaxone and ciprofloxacin for synergistic effect was continued for 10 days. His SOFA score was improved on day 7 and day 14, with a SOFA of 12 following the initiation of hemoperfusion. There was no intervention-related adverse events in this study.

The patient subsequently developed mesenteric ischemia on day 10 and required exploratory laparotomy with ileostomy. Before hospital discharge, he tolerated an oral diet, regained his ability to walk with assistance after intensive rehabilitation, and did not require oxygen supplementation. His total ICU and hospital length of stay were 50 and 63 days, respectively. Moreover, the hospital’s infectious control unit reported this index case to the Ministry of Public Health for investigation, and an active case finding was performed in the affected areas to prevent *Vibrio cholerae* outbreaks.

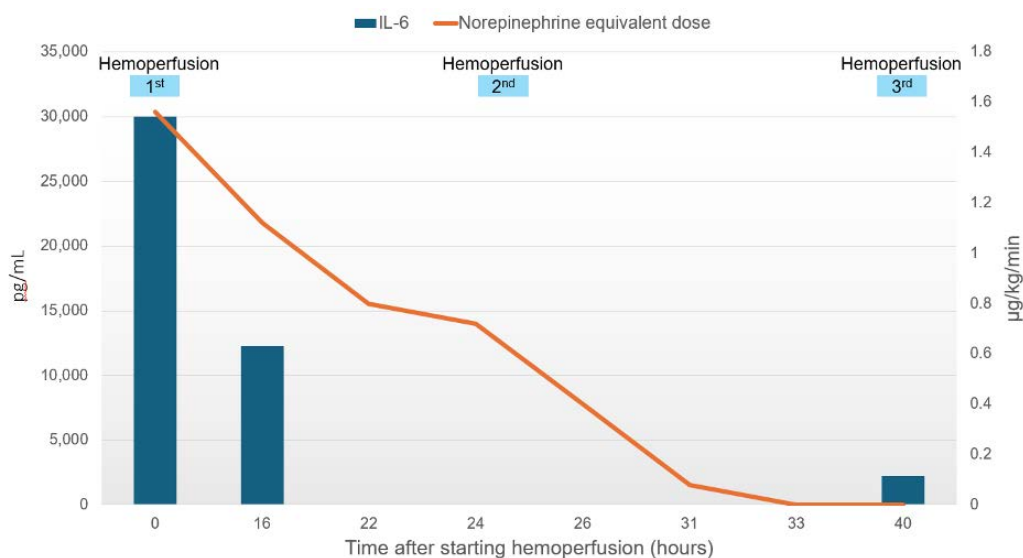


Figure 1 Norepinephrine equivalent dose and inflammatory markers from initiation of HA330 hemoperfusion

Discussion

Vibrio cholerae is a gram-negative bacterium having rod-shaped morphology, found in marine environments. Cholera infection may be asymptomatic, mild, moderate, or severe, potentially life-threatening and cause of hypovolemic and/or septic shock¹. Toxins are the primary components of bacterial pathogenicity. The outer membrane of gram-negative bacteria contains endotoxin, also known as lipopolysaccharide (LPS), which accounts for approximately 75% of the outer membrane and can cause fatal shock². Several pro-inflammatory cytokines, such as IL-8, IL-6, IL-1 β , IL-1, IL-12, and IFN γ , are expressed by inflammatory cells when exposed to LPS². Aside from stimulating cytokines, TNF α also triggers the activation of cyclooxygenase-2 and nitric oxide synthase that facilitate the production of prostaglandin E2 (PGE2) and nitric oxide (NO)³. Both NO and PGE2 are vasodilators that may reduce the migration of neutrophils to the site of infection by inhibiting the endothelium-leukocyte binding⁴. In cases of cholera infection, replenishing fluids is fundamental, whereas antibiotic treatment helps accelerate recovery and alleviates the need for rehydration. The World Health Organization (WHO) advises the use of antibiotics for patients with severe cholera, regardless of age, and for those requiring hospitalization⁵. Cholera can be effectively treated with several antibiotics, including tetracycline, co-trimoxazole, doxycycline, ciprofloxacin, erythromycin and azithromycin. The selection of antibiotics is influenced by local antibiotic susceptibility patterns⁶.

In patients with refractory septic shock, the outcome and response to treatment are significantly influenced by host factors. These factors encompass various patient-specific characteristics, including underlying comorbidities, immune status, genetic predispositions and physiological reserves. Thalassemia is an autosomal recessive disease that arises from a mutation in the β -globulin gene,

resulting in decreased levels or the absence of synthesis of the β -globulin chain. Considering that immunodeficiency coexists with thalassemia, patients with thalassemia are usually vulnerable to infections. Reduced complement levels, decreased absorption and phagocytic capabilities of polymorphonuclear neutrophils, in addition to altered intracellular metabolic processes, are among the defects of the innate immune system associated with β -thalassemia^{7,8}. In β -thalassemia, infectious complications represent the second most prevalent cause of death, and a significant factor contributing to morbidity⁸. Understanding the mechanism responsible for processes of immunological insufficiency in people with β -thalassemia could facilitate the development of optimizing personalized treatments and ultimately enhance outcomes.

Extracorporeal blood purification techniques have been reported as an effective treatment approach in managing patients with sepsis and septic shock by eliminating inflammatory mediators⁹. Hemoadsorption (HA) is an extracorporeal method in which solutes are extracted by direct binding to the sorbent substance. Blood or plasma is passed through a cartridge, which is divided into selective, such as polymyxin B (PMX) and non-selective types such as CYTOSORB[®]. Because the cut-off point of non-selective cartridges (~60 kilodalton; kDa) is lower than the molecular weight of endotoxin (~100 kDa), they are unable to adsorb endotoxin¹⁰. HA330 is a Jafron HA resin hemoperfusion cartridge belonging to the non-selective group¹¹. The pore size of the resin is 500 daltons (Da) to 60 kDa in HA330, which, when molecular weighted, removes 10–60 kDa that can remove cytokines¹¹. Additionally, there have not been any safety issues associated with its use¹¹.

The Surviving Sepsis Campaign 2021, recommends against the use of polymyxin B hemoperfusion in adults with septic shock, with no evidence to support the recommendation of other blood purification methods¹².

However, a recent review of the literature in 2024¹³ suggested using blood purification for personalized medicine in patients whose perfusion has not improved and who require a dose of NE greater than 0.5 µg/kg/min or need two vasopressors. Consideration types of blood purification therapies are demonstrated and compared in Table 1.

There have been some studies on the impact of HA330 hemoperfusion adsorbent adjunct to standard treatment. In 2010, Huang et al.¹⁴ conducted a study involving 44 patients with sepsis/septic shock. The patients were divided into two groups: standard treatment alone (n=20) and standard treatment plus HA330 hemoperfusion (n=24). The results indicated that the latter group had significantly lower levels of IL-6 and IL-8 at day 3 and a significant reduction in vasopressor dose compared to the control group. No significant difference in 28-day mortality and SOFA scores was noted between the groups from the initiation of therapy until the seventh day; however, by the 14th day, the SOFA scores substantially improved in the group receiving standard treatment plus HA330 hemoperfusion. The notable decline in vasopressor dose and IL-6 level was in line with the disease course of our patient. Furthermore, our patient demonstrates an improvement in SOFA scores on both the 7th and 14th days following the initiation of hemoperfusion. Erkurt et al.¹⁵ studied the cases of 150 patients with sepsis or septic shock in Turkey, reported from 2019 to 2021. In the study population, 68% were diagnosed with septic shock, and the mean APACHE II score of the study sample was 15.3±4.8. All patients underwent a median of three hemoperfusion sessions, each lasting 2.5–3 hrs. The study reported a 69.3% mortality rate, with no significant impact on inflammatory markers and end-organ damage. Notably, patients who underwent HA330 hemoperfusion in the previous study had a mortality rate of approximately 90%. In contrast, our patient had an 85% mortality rate, as

predicted by the APACHE II score; however, hemoperfusion provided an advantage in reducing inflammatory cytokines, ultimately leading to the patient's survival.

In this case, despite the early initiation of appropriate antimicrobial therapy and ensuring adequate fluid replacement and hemodynamic management with organ support, refractory shock persisted even after 48 hrs. Hemodynamic parameters continued to indicate extreme vasoplegia, necessitating a sustained high dose of vasopressors. Furthermore, the level of inflammatory markers was high, indicating ongoing systemic inflammation or cytokine storm. Hence, additional therapy, such as hemoperfusion, was considered and may have been utilized because of the coexisting immunodeficiency and bacterial virulence factor of *Vibrio cholerae*, such as secreted endotoxins. HA330 hemoperfusion methods are designed to remove cytokines from the bloodstream and these techniques aim to attenuate the harmful effects of systemic inflammation and improve hemodynamic stability. Continuous assessment of hemodynamic parameters, inflammatory markers, and organ function enables clinicians to adjust the duration and intensity of hemoperfusion therapy.

Table 1 Comparison types of blood purification therapies¹³

Time from refractory septic shock (NE equivalent dose 0.5 µg/kg/min of the need for two vasopressors)	Membrane	Adsorption capacity
8 hours	PMX	Endotoxin
24 hours	OXIRIS	Endotoxin and Cytokine
24–48 hours	CYTOSORB®, HA330/JAFRON	Cytokine

PMX=polymyxin B

Because this is a single case report, it examines one individual and its retrospective design lacks the ability to generalize. Nonetheless, this comprehensive clinical data that provided step-by-step approaches, from fundamental to advanced treatment, in this case has educational value. This example highlights the value of a multidisciplinary adjunctive therapeutic strategy customized for each patient's unique clinical course, and pathophysiology in the management of refractory septic shock. The survival outcome depends on multi-modalities of treatment interventions during the ICU stay, hemoperfusion is one component that influences favorable outcomes. Hence, further case selection to design a prospective study to control confounding factors is required for the outcome of hemoperfusion-based therapies in the management of refractory septic shock.

Conclusion

Standard treatment remains the cornerstone for the management of septic shock, and personalized adjunctive therapies should be based on pathophysiology when patients are refractory to standard approaches. Hemoperfusion has been proposed as a potential strategy, particularly in cases in which endotoxins play a significant role. However, the current evidence does not support its use in all cases. Further studies are required to design patient selection and treatment protocols to achieve the desired outcomes.

Ethical approval

Human Research Ethics Committee of Faculty of Medicine, Prince of Songkla University approved this research (REC. 67-162-14-1).

Author contribution

Conceptualization: NS. Data curation: NS. Writing-original draft: NS. Writing-review & editing: BK, NA, SK.

Conflict of interest

There are no conflicts of interest to declare.

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