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Combined Therapeutic Plasma Exchange and Continuous Renal Replacement Therapy in Children With Dengue-Associated Acute Liver Failure and Shock Syndrome: Single-Center Cohort From Vietnam*

Luan Thanh Vo, MD[1]
Viet Chau Do, MD[1]
Tung Huu Trinh, MD[1]
Thien Vu, PhD[2,3]
Thanh Tat Nguyen, MD[1,4]

OBJECTIVES: Pediatric acute liver failure (PALF) is a fatal complication in patients with severe dengue. To date, clinical data on the combination of therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT) for managing dengue-associated PALF concomitant with shock syndrome are limited.

DESIGN: Retrospective cohort study (January 2013 to June 2022).

PATIENTS: Thirty-four children.

SETTING: PICU of tertiary Children's Hospital No. 2 in Vietnam.

INTERVENTIONS: We assessed a before-versus-after practice change at our center of using combined TPE and CRRT (2018 to 2022) versus CRRT alone (2013 to 2017) in managing children with dengue-associated acute liver failure and shock syndrome. Clinical and laboratory data were reviewed from PICU admission, before and 24 h after CRRT and TPE treatments. The main study outcomes were 28-day in-hospital mortality, hemodynamics, clinical hepatoencephalopathy, and liver function normalization.

MEASUREMENTS AND MAIN RESULTS: A total of 34 children with a median age of 10 years (interquartile range: 7–11 yr) underwent standard-volume TPE and/or CRRT treatments. Combined TPE and CRRT ($n = 19$), versus CRRT alone ($n = 15$), was associated with lower proportion of mortality 7 of 19 (37%) versus 13 of 15 (87%), difference 50% (95% CI, 22–78; $p < 0.01$). Use of combined TPE and CRRT was associated with substantial advancements in clinical hepatoencephalopathy, liver transaminases, coagulation profiles, and blood lactate and ammonia levels (all p values < 0.001).

CONCLUSIONS: In our experience of children with dengue-associated PALF and shock syndrome, combined use of TPE and CRRT, versus CRRT alone, is associated with better outcomes. Such combination intervention was associated with normalization of liver function, neurological status, and biochemistry. In our center we continue to use combined TPE and CRRT rather than CRRT alone.

KEY WORDS: continuous renal replacement treatment; dengue; hepatic encephalopathy; pediatric acute liver failure; therapeutic plasma exchange

Dengue-associated pediatric acute liver failure (PALF) is rarely seen and is characterized by extensive liver necrosis and rapid deterioration in hepatic function, resulting in hepatoencephalopathy and death (1). The incidence of dengue-associated PALF was reported to range from 0.31% to 0.77% from Thai and Vietnamese adult cohorts (2, 3). Despite its rarity,

***See also p. 874.**

DOI: 10.1097/PCC.0000000000003304

RESEARCH IN CONTEXT

- Pediatric dengue-associated acute liver failure (PALF) is a rare but fatal complication.
- Dengue shock syndrome is a significant predictor of mortality of PICU-admitted children.
- Clinical descriptions of therapeutic plasma exchange (TPE) and/or continuous renal replacement therapy (CRRT) for managing children experiencing dengue-associated PALF accompanied with shock syndrome are limited.

dengue-associated PALF has a high fatality rate, requiring a multidisciplinary approach for timely diagnosis and intensive management (2–5). Therapeutic plasma exchange (TPE) is shown to have survival benefit for patients with acute liver failure, based on eliminating liver-associated toxins, harmful cytokines, and supplementing coagulation factors (6, 7). Importantly, TPE substantially improves multiple organ dysfunction, hepatic encephalopathy and increases liver transplant-free survival (6–8). Acute renal failure, high increases in serum lactate and ammonia levels are commonly observed in PALF-experienced patients (8). In this regard, continuous renal replacement therapy (CRRT) plays a vital role in improving kidney functions, eliminating metabolic substances and downregulate excessive cytokines (9, 10). Therefore, combined TPE and CRRT treatments have been shown an effective intervention in patients with non-dengue acute liver failure (6–9).

To date, clinical descriptions of using TPE and/or CRRT as treatment for children with dengue-associated PALF and shock syndrome are limited (11, 12). Therefore, we aimed to review our single-center experience of using TPE and CRRT in children admitted to the PICU with dengue-associated acute liver failure and shock syndrome. We compared clinical characteristics in those who had undergone TPE and CRRT versus CRRT alone, and the retrospective-associated outcomes.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Children's Hospital No. 2, Vietnam (approval number 391/QĐ-BVND92, March 22, 2022). The study was conducted in compliance with the principles of good clinical practice and the Declaration of Helsinki.

Study Design and Participants

This retrospective, single-center cohort study reviewed experience at the Children Hospital No. 2, Ho Chi Minh City, Vietnam. Our center is one of the three largest tertiary referral pediatric hospitals in southern Vietnam, with a capacity of approximately 1,400 in-hospital beds. We screened all critically ill children with dengue shock syndrome and PALF who were admitted to the PICU between January 2013 and June 2022 and managed with CRRT and/or TPE. Notably, CRRT had been performed for dengue-associated PALF in our PICU before 2018; then, the combination intervention of CRRT and TPE was commenced from 2018 onward. The eligibility criteria included aged less than 18 years, laboratory-confirmed dengue infection, dengue shock syndrome, and dengue-associated acute liver failure, regardless of other causes of liver injury in patients with dengue infection (1, 13).

Study Definitions

Dengue infection was defined according to the World Health Organization (2009) criteria, with laboratory confirmation by the Dengue-IgM antibody test or nonstructural 1 (NS1) antigen test (13).

PALF was defined as an acute episode of severe hepatic dysfunction with biochemical evidence of liver injury in children without pre-existing chronic liver diseases, liver-induced coagulopathy not corrected by vitamin K supplementation, an international normalized ratio (INR) greater than 1.5, if the patient has encephalopathy, or INR greater than 2.0, with or without encephalopathy (1).

Continuous Renal Replacement Therapy

CRRT was carried out, using the Gambro Prismaflex hemofiltration system (Baxter; Gambro Industries, Meyzieu, France) and a polymembrane AN69 filters. Different subtypes of AN69 filters were used, depending on patient's weight. More specifically, HF20 filter was used for children weighing less than 10 kg, M60 filter for children from 10 to 15 kg, and M100 filter for

patients greater than 15 kg (14, 15). A dialysis catheter (Balton Sp.z o.o, Warsaw, Poland) was inserted into the internal jugular or femoral vein. The size of the catheter was determined by child weight. The filtration mode of continuous venovenous hemodiafiltration combined with convection and dialysis was applied. The CRRT dose was adjusted from 60 to 90 mL/kg/h based on ammonia level. Prismasol B0 (Gambro Dasco S.p.A., Sondalo, Italy) was used for dialysis. If the extracorporeal circulatory volume was greater than 15% of the blood volume, the priming procedure was performed by mixing red blood cells with normal saline 0.9% to obtain a hematocrit of 45% (14, 15).

Therapeutic Plasma Exchange

A Gambro Prismaflex system (Baxter) was used for plasma exchange. The TPE-1000 filter membrane was applied to small children weighing 9–20 kg, whereas the TPE-2000 device was used for children weighing greater than 20 kg (16, 17). Patients were given IV unfractionated heparin at doses ranging from 10 to 20 IU/kg/h. Blood was extracted at a rate of 4.0–6.0 mL/kg/min. The estimated amount of plasma was calculated using the formula, weight (kg) × (1-hematocrit) × coefficients (from 0.07 to 0.09, adjusted by children's age). The TPE solution was fresh frozen plasma, and the standard-volume TPE was set at 1.5 times the patient's total plasma volume. We did extracorporeal priming with red blood cells mixed with normal saline 0.9% to achieve a hematocrit of 45% (equivalent to 90 mL) in children weighing less than 9 kg (16, 17). Patient vital signs were closely monitored during TPE. All received IV 10% calcium chloride to prevent hypocalcemia. Additionally, diphenhydramine and methylprednisolone were used prophylactically to prevent anaphylaxis.

Criteria for Combining TPE and CRRT in Patients With Dengue-Associated PALF

We performed the combination intervention of CRRT and TPE in dengue patients meeting the definition of PALF (1), plus either one of the following criteria: 1) hepatoencephalopathy grades I and II, poor response within 12–24 hours of intensive treatments, or 2) hepatoencephalopathy grades III and IV at any time during hospitalization, 3) serum ammonia level greater than or equal to 150 μmol/L, poor therapeutic response within 6–8 hours of treatments or ammonia concentration greater than or equal to 200 μmol/L at any time during hospitalisation, or 4) a significant increase in serum lactate with poor treatment response (12).

The rationale that CRRT should be combined with TPE was based on high prevalence of acute renal failure, highly elevated serum lactate acidosis and ammonia levels reported in patients with acute liver failure (8). In term of intervention sequence, the CRRT procedure was first started and continued until there was no indication for CRRT. Then TPE was performed after the CRRT, on average of three cycles (a maximum of five cycles) per each patient (12).

Data Extraction and Review

The primary outcomes of our retrospective before versus after study were 28-day in-hospital mortality, hemodynamics, clinical hepatoencephalopathy, and liver function. These data were extracted by chart review from PICU admission (baseline), before the first use of CRRT and 24 hours after the last use of TPE and/or CRRT.

Data Measurements

Multiple organ failures were assessed, based on the criteria from the international pediatric sepsis consensus conference in 2005 (18). Vasoactive-inotropic score (VIS) was used to study degrees of hemodynamic support in PALF-experiencing patients before and after CRRT and TPE performances (19).

Statistical Analysis

Patient treatment characteristics were described using summary statistics, with continuous variables presented as medians and interquartile ranges (IQRs). Categorical variables are presented as numbers (n) and percentages (%). Univariable and multivariable logistic regression analyses, adjusted for severe bleeding and positive hemoculture were performed to study the effect of treatments (combined TPE and CRRT vs CRRT alone) on patient's survival outcome. Survival analyses for the whole cohort and subgroup comparisons were performed using the Kaplan-Meier method and log-rank test. Significance level was set at p less than 0.05 for all statistical comparisons. The R statistical software (version 4.1.3; RStudio, Boston, MA) was used for all analyses.

RESULTS

Patient Characteristics

We identified 34 patients with dengue infection who had been treated in our PICU with CRRT and/or TPE between January 2013 and June 2022, including 19 patients with combined support and 15 patients treated with CRRT alone. The median age of all patients was 10 (IQR, 7–11) years, and 19 of 34 (56%) were male. The median body mass index was 21 (IQR, 18–24) kg/m^2. The clinical and laboratory characteristics of the cohort are shown in **Table 1**.

Six participants had comorbidities, including asthma, stable maintenance therapy of COVID-19-associated multisystem inflammatory syndrome in children with low-dose oral steroids, and thalassemia. Five patients in the CRRT group experienced severe bleeding. Most patients had grades III and IV clinical hepatoencephalopathies. Patients in CRRT group presented with slightly lower mean arterial pressure and higher shock index comparable to TPE and CRRT group. High intra-abdomimal cavity pressure was observed in both groups, with a median of 28 cmH_2O (IQR, 26–30). Full blood counts were quite similar in both groups. All patients experienced critical liver failure, manifesting with substantial increases in transaminases, heavy coagulation disorders, and disturbances of metabolic parameters (serum bicarbonate, lactate, and ammonia). Noticeably, all patients in CRRT group were not performed serum ammonia testing on PICU admission, due to limited testing availability during the study period. Most patients presented with mild lung injury with a median oxygenation index of 6.1 (IQR, 2.7–14.8). Multiple organ failure was commonly observed in patients with dengue shock accompanied by PALF. In particular, the pediatric risk of mortality score was quite homogenous in both comparison groups, reflecting the similar disease severity of participants on PICU admission.

Lengths of Hospital Stay, Mechanical Ventilation, and Vassopressor Support

Overall, the median length of hospital stay was 13 (IQR, 5–23) days (Table 1). The average duration of providing mechanical ventilatory and vassopressor support was roughly 1 week. Notably, use of combined TPE and CRRT was associated with longer in-hospital stay, mechanical ventilation, and vassopressor use, but this may be a reflection of greater survival, that is, early mortality in the CRRT alone group **(see Fig. 1**).

Association Between Treatments (Combined TPE and CRRT vs CRRT Alone) and Mortality Rate of Dengue-Associated PALF

Seven of 19 (37%) patients in the combined TPE and CRRT group died within 28-days of hospitalization, in comparison with 13 of 15 (87%) patients in the CRRT alone group. The log-rank test revealed a difference in the 28-day in-hospital survival outcomes ($p < 0.001$), with the combined interventions being associated with greater survival (Fig. 1). Combined TPE and CRRT ($n = 19$), versus CRRT alone ($n = 15$), was associated with lower proportion of mortality 7 of 19 (37%) versus 13 of 15 (87%); difference 50% (95% CI, 22%–78%, $p < 0.01$). Both univariable and adjusted multivariable analyses showed associations between the treatment effect of combined TPE and CRRT and improved survival of patients with dengue-associated PALF (**Table 2**). TPE and CRRT intervention was significantly associated with 86% decrease in the odds of death, compared with CRRT alone (adjusted odds ratio = 0.14; 95% CI, 0.02–0.86). The causes of death among patients in the CRRT alone group were prolonged shock and abdominal compartment syndrome, due to severe plasma leakage and nonreversible multiple organ failures. In contrast, patients managed with the combined TPE and CRRT died of PICU-associated complications, including ventilator-associated pneumonia, hospital-acquired sepsis, and intracranial hemorrhage.

Hemodynamics, Mechanical Ventilatory Support and Inflammatory and Biochemical Parameters

Table 3 summarizes changes in hemodynamics and oxygenation index before and after combined TPE and CRRT. Significant associated improvements occurred in the biochemical parameters. Of note, there was a decrease in serum ferritin level. In addition, there was improvement in clinical hepatoencephalopathy ($p = 0.001$), hepatic transaminases ($p < 0.001$), INR, serum albumin and metabolic biomarkers, including blood lactate, ammonia, and bicarbonate (all $p < 0.001$; Table 3 and **Fig. 2**).

TABLE 1.
Baseline Clinical and Laboratory Characteristics of Study Participants on PICU Admission

Characteristics	All Patients (*n* = 34)	TPE + CRRT (*n* =19)	CRRT (*n* =15)
Age (yr)	10 (7–11)	10 (7–11)	10 (6–12)
Male, *n* (%)	19 (56)	13 (68)	6 (40)
Body mass index (kg/m^2)	21 (17.9–24)	21.8 (19–24.5)	19.3 (16.1–24)
Obesity adjusted by age	13/31 (41.9)	10/19 (52.6)	3/12 (25)
Comorbidity, *n* (%)	6 (18)	4 (21)	2 (13)
Severe bleeding, *n* (%)[a]	5 (15)	0 (0)	5 (33)
Hepatoencephalopathy, *n* (%)[b]			
Grade I	0	0	0
Grade II	1	0	1
Grade III	18	9	9
Grade IV	15	10	5
Mean arterial pressure (mm Hg)	80 (68–87)	80 (77–90)	68 (62–86)
Systolic shock index (bpm/mm Hg)	1.25 (0.97–1.62)	1.06 (0.92–1.61)	1.45 (1.21–1.62)
Intra-abdominal pressure (cm H_2O)	28 (26–30)	27 (23–30)	28 (27–36)
WBC count (× 10^9/L)	16.8 (10.7–21)	18.5 (12.4–21)	14.9 (9.6–18.7)
Hemoglobin (g/dL)	11.4 (9.1–13.4)	11.2 (8.4–13)	12.3 (10.6–13.8)
Hematocrit (%)	35 (32–41)	35 (30–40)	39 (33–41)
Platelet cell count (× 10^9/L)	46 (20–78)	34 (15–76)	49 (39–79)
Aspartate aminotransferase (IU/L)	6,552 (4,091–11,619)	7,036 (5,128–12,628)	3,990 (3,100–10,900)
Alanine aminotransferase (IU/L)	1,588 (1,209–2,401)	1,598 (1,246–2,350)	1,570 (1,171–2,740)
International normalized ratio	2.96 (2.16–4.57)	2.95 (1.91–8.64)	3.36 (2.39–3.55)
Prothrombin time (s)	37 (27–48)	40 (30–103)	34 (25–43)
Activated partial thromboplastin time (s)	78 (57–120)	67 (56–126)	91 (72–120)
Serum creatinin (µmol/L)	102 (71–136)	108 (75–133)	82 (43–150)
Serum ammonia (µmol/L) [c]	–	127 (83–170)	–
Serum lactate (mmol/L)	10.8 (6.3–13.3)	10.8 (6.9–13)	11.5 (5.0–15.3)
Serum bicarbonate (mmol/L)	12.6 (10.1–15.5)	14.3 (9.8–15.5)	11.5 (10.7–16.1)
Troponin I (ng/mL)	0.67 (0.18–1.24)	0.47 (0.25–1.08)	1.28 (0.14–3.31)
Oxygenation index	6.1 (2.7–14.8)	8.2 (3.9–17.3)	3.3 (2.3–9.3)
Number of organ failures	5 (3–6)	4 (3–6)	5 (5–6)
Organ failures, *n* (%)			
Neurological failure	26 (76)	14 (74)	12 (80)
Respiratory failure	34 (100)	19 (100)	15 (100)
Circulatory failure	18 (53)	7 (37)	11 (73)
Liver failure	34 (100)	19 (100)	15 (100)
Kidney failure	17 (50)	10 (53)	7 (47)
Hematological failure	22 (65)	9 (47)	13 (87)
Days of mechanical ventilation	7 (5–15)	8 (7–16)	4 (2–11)
Days of vasopressor support	5 (2–7)	6 (3–8)	4 (2–7)

(*Continued*)

TABLE 1. (*Continued*)

Baseline Clinical and Laboratory Characteristics of Study Participants on PICU Admission

Characteristics	All Patients (*n* = 34)	TPE + CRRT (*n* =19)	CRRT (*n* =15)
Length of hospital stay (d)	13 (5–23)	19 (11–38)	7 (3–15)
Pediatric Risk of Mortality Score III	19 (18–22)	21 (19–24)	19 (18–19)

CRRT = continuous renal replacement therapy, TPE = therapeutic plasma exchange.

[a]Severe bleeding is defined as the World Health Organization (2009) Dengue guidelines.

[b]West Haven score was used to assess patient's hepatic encephalopathy.

[c]Patients in CRRT alone group were not performed serum ammonia on PICU admission.

Data are presented as median and interquartile range for continuous variables, and frequency (%) for categorical variables.

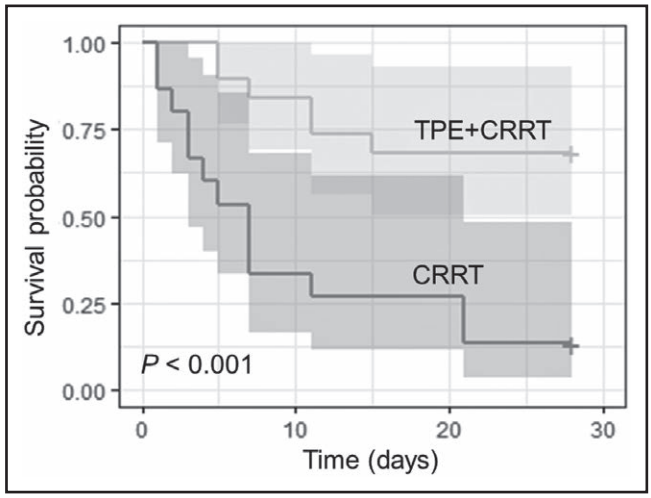

Figure 1. Kaplan-Meier curves and *p* value from log-rank test. There was a substantial improvement in 28-day in-hospital mortality of patients in the combined therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT) group compared with the single-intervention CRRT group.

AT THE BEDSIDE

- In our center's experience, change to combined use of TPE and CRRT, from CRRT alone in children with dengue-associated PALF and shock syndrome was associated with improved survival.
- In association with the combined intervention there was improvement in clinical hepatoencephalopathy, liver transaminases, coagulation profiles, and metabolic biomarkers.
- In our center, we continue to use combined TPE and CRRT for dengue-associated PALF.

DISCUSSION

This retrospective reviews our institutional change in practice for the management of children with dengue-associated PALF concomitant with shock syndrome, that is, from using CRRT alone (2013–2017) to using TPE and CRRT (2018–2022). Of note, we found that the change was associated with better survival and improvements in clinical and biochemical features.

Dengue-associated PALF is associated with a high mortality rate (2–5). Multiple organ failure, including altered sensorium, respiratory failure, acute kidney failure, and shock, are independent factors associated with death in patients with dengue-associated ALF (5, 20). In addition, multiple vasopressor requirements and high blood lactate are associated with increased risk of death among such dengue-infected patients (21). By all these criteria, as well as encephalopathy our patients were at high risk of death (22). Markedly, the CRRT was shown to significantly improve the survival rates and reduce deterioration in critically ill children with PALF (10). Importantly, TPE has increased survival benefit for patients with acute liver failure with strong effects on liver by eliminating liver-associated toxins, detrimental cytokines, and supplementing coagulation factors (6–8). Based on the pathogenesis, we believe that combination of TPE and CRRT will render more advanced treatment effects on PALF than any single interventions with either CRRT or TPE. However, there is to date lacking comparison between CRRT alone and TPE, and/or TPE combined with CRRT for managing acute liver failure, particularly dengue-associated PALF. Our study clearly showed that combined use of TPE and CRRT, versus CRRT alone was associated with 86% reduction in risk of 28-day in-hospital death from logistic regression

TABLE 2.
Associations Between Treatments and Mortality Rate in Children With Dengue-Associated Acute Liver Failure

Interventions	Fatal	Alive	Crude OR[a] (95% CI)	p^a	Adjusted OR (95% CI)	p^b
Combined therapeutic plasma exchange and CRRT, ($n = 19$)	7 (37)	12 (63)	0.07 (0.01–0.42)	< 0.001	0.14 (0.02–0.86)	0.03
CRRT alone, ($n = 15$)	13 (87)	2 (13)				

CRRT = continuous renal replacement therapy, OR = odds ratio.

[a]Crude OR and *p* values from univariate model.

[b]The OR and *p* values from multivariable logistic analysis adjusted for severe bleeding and hemoculture.

Severe bleeding was defined according to the World Health Organization (2009) Dengue guidelines.

analyses after adjusted with severe bleeding and positive hemoculture, as main causes of fatality in dengue-associated PALF (12). Such combination intervention was associated with normalization of liver function, neurologic status, and biochemistry. In our center, we ongoingly use combined TPE and CRRT rather than CRRT alone.

Liver is the most common organ targeted by dengue viruses, with various levels of damage from mild to severe injury to hepatocytes, particularly dengue-associated PALF (20). Remarkably, dengue-associated PALF may progress rapidly to multiple organ failure and death. Our study data revealed that transaminases, coagulation profiles, and deranged biochemical parameters peaked at the time of starting the combined TPE and CRRT interventions, and these parameters rapidly normalized after patients had undergone, on average, three TPE and CRRT sessions. This combined approach was also associated with improved serum albumin concentration. This change is particularly helpful for patients with dengue-associated PALF because it improves the blood colloid pressure, increases the intravascular volume, and reduces the rate of plasma leakage.

Hepatic encephalopathy is a commonly observed complication of ALF and associated with an increased fatality (23, 24). Similarly, patients with PALF commonly experience high serum lactate acidosis, ammonia, and acute kidney injury (8, 25). Accordingly, CRRT plays a critical role in improving kidney function, eliminating toxic substances, and modulating the levels of acid–bases, electrolytes, and fluid balance. Thus, CRRT may boost the therapeutic effect of TPE in PALF treatment (10, 26), and it can improve hepatic encephalopathy caused by PALF (27). Most importantly, patient's survival rate is said to increase by 50%, corresponding to every 10% reduction in serum ammonia concentration by CRRT from baseline within 48 hours (10). On this basis, at our institution we elected to combine CRRT with TPE in 2018, so as to optimize the potential therapeutic benefits.

In our experience, dengue-associated PALF is aggravated by prolonged dengue hemorrhagic shock and abdominal compartment syndrome due to severe plasma leakage (28). Hemodynamically, PALF causes peripheral vasodilation, microcirculatory vasoconstriction, and decreased visceral perfusion, resulting in damage to multiple organs (28). In addition to extracorporeal support for multiple organ failures, sustaining blood perfusion to vital body organs, particularly hepatic perfusion, is the cornerstone for treating PALF patients accompanied by dengue shock syndrome (13). During the combined CRRT and TPE interventions, patients were continuously administered intensive fluid resuscitation under the guidance of bedside point-of-care ultrasonography. Norepinephrine is our first-line vasoconstrictor for the treatment of vasodilation caused by PALF, and epinephrine may be co-administered in the presence of a reduced ejection fraction (1). Moreover, norepinephrine enhances venous return to the heart and cardiac contractility, resulting in increased cardiac output, particularly in the presence of systemic vasodilation (29–31). Concurrently, appropriate decompression of the peritoneal cavity to maintain visceral perfusion pressure reduces the mortality rate (32). In our review, survival was associated with improved VIS, indicating that combined CRRT and TPE was associated with amelioration of hemodynamics. There are four possible mechanisms for our findings. First, combined

TABLE 3.
Clinical and Laboratory Data Before and After Combined Therapeutic Plasma Exchange and Continuous Renal Replacement Therapy in 18 Patients

Variables	Before	After	*p*
Clinical presentations			
HE, *n* (%)			
Normal neurological status	0	2 (11)	0.001[a]
HE grades I and II	0	9 (47)	
HE grade III	9 (47)	3 (16)	
HE grade IV	10 (53)	5 (26)	
Hemodynamic parameters			
Mean arterial pressure (mm Hg)	80 (74–90)	81 (74–97)	0.07
Systolic shock index (bpm/mm Hg)	1.1 (0.9–1.3)	1 (0.7–1.2)	0.01
Diastolic shock index (bpm/mm Hg)	2.2 (1.9–2.5)	1.9 (1.4–2.5)	0.02
Vasoactive-inotropic score			
All participants ($n = 18$)	30 (30–80)	0 (0–5)	0.37
In alive patients ($n = 12$)	30 (10–53)	0 (0–0)	< 0.001
Laboratory values			
WBC counts (× 10^9/L)	17.2 (12.4–21)	18.9 (11.2–24.9)	0.23
Platelet cell count (× 10^9/L)	34 (15–76)	46 (26–96)	0.26
Aspartate aminotransferase (IU/L)	6,605 (4,777–12,628)	772 (419–1,221)	< 0.001
Alanine aminotransferase (IU/L)	1,598 (1,082–2,350)	339 (190–469)	< 0.001
International normalized ratio	3.2 (2.7–8.7)	1.4 (1.2–1.7)	< 0.001
Serum albumin (g/L)	19 (15–26)	29 (26–31)	< 0.001
Total bilirubin (µmol/L)	76 (46–133)	76 (49–149)	0.70[b]
Serum lactate (mmol/L)	10.8 (8.5–13)	2.6 (2.0–7.3)	< 0.001
Serum bicarbonate (mmol/L)	14.5 (9.8–16.7)	21.4 (19.6–24.5)	< 0.001
Serum ammonia (µmol/L)	182 (142–257)	80 (64–99)	< 0.001
Serum creatinine (µmol/L)	108 (75–133)	79 (55–140)	0.71
Troponin I (ng/mL)	0.46 (0.19–1.15)	0.12 (0.05–0.35)	0.01[b]
Oxygenation index	8 (6–12)	6 (4–9)	0.42[b]
C-reactive protein (mg/dL)	19.5 (10.7–39)	16 (8.9–31)	0.52[b]
Ferritin (× 10^3 ng/mL)	40 (33.5–40)	22.8 (10–33.5)	0.001[b]

HE = hepatic encephalopathy.
[a]*p* value from Fisher exact test.
[b]*p* values from Mann-Whitney *U* tests for non-normally distributed variables.
Data are presented as median (interquartile range) for continuous variables and frequency (%) for categorical variables. Data are available for 18 of 19 patients managed with therapeutic plasma exchange (TPE) + continuous renal replacement therapy (CRRT), since one patient died soon after the first TPE + CRRT; thus, clinical and laboratory data could not be collected for comparisons. *p* Values were withdrawn from paired *t* tests, significance level < 0.05.

CRRT and TPE treatment shortens the duration of vasopressor use in patients with PALF (6, 25, 33). Second, TPE can minimize the adverse effects of cytokine storm (34). Remarkably, excessive proinflammatory cytokines are associated with mortality in PALF patients (9). In this regard, combined CRRT and TPE could aid in the rapid modulation of cytokine levels in dengue patients with PALF. Additionally, recent

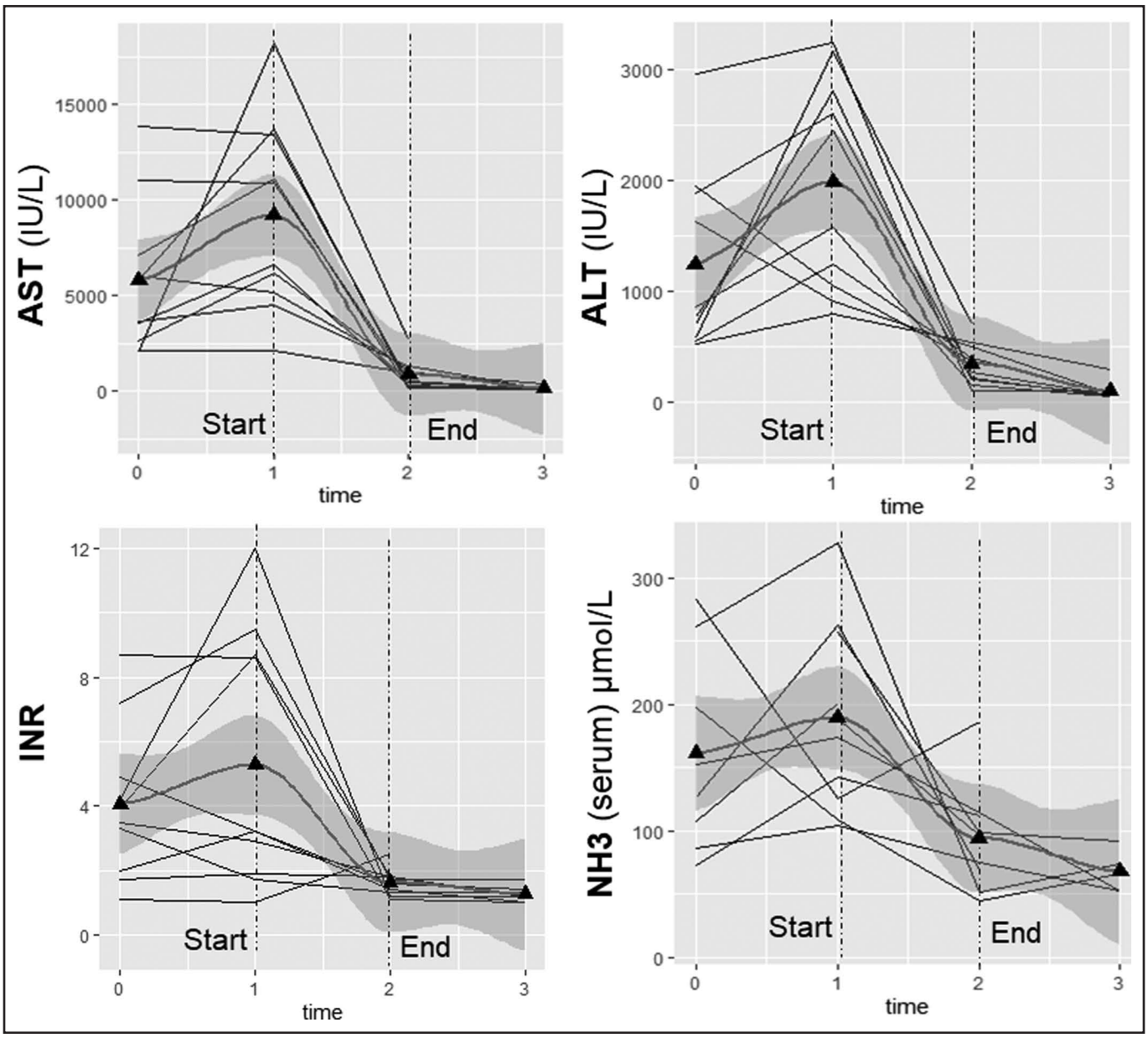

Figure 2. Substantial improvement in liver function tests, including liver transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), coagulation (international normalized ratio [INR]) and metabolic chemical (serum ammonia [NH3]) in patients ($n = 18$) treated with combined therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT) at various time points, indicated by *triangle symbols*: T0, on PICU admission; T1, starting TPE + CRRT procedures (indicated by *left-sided dashed line*); T2, completing TPE + CRRT treatments (*right-sided dashed line*); T3, at PICU discharge. The *bold smooth curves* indicate mean values with 95% CI of parameters.

studies show associations between ferritin level and poor outcome in dengue (35, 36). We identified a fall in ferritin in our patients. Third, each TPE cycle was associated with improved coagulation, which was also associated with control of intractable bleeding. Hence, there was less massive bleeding in our contemporary patients. Finally, high-volume CRRT was associated with rapid amelioration of acidosis, reducing both vascular dilatation and IV fluid demands.

To date, there is still limited understanding about mechanisms of hepatocellular injury in dengue-associated PALF. Current evidence advocates the roles of immune and inflammatory responses, including T-CD8+ cells, natural killer (NK) cells, Th1 cells, and excessive cytokine response in PALF (37). Tumor necrosis factor alpha is elevated when dengue-virus (DENV) endothelial cells are triggered by antibody-enhanced DENV-infected monocytes. Consequently,

this leads to the severe inflammatory response and apoptosis with excessive releases of multiple cytokines known as cytokine storm (37). On this basis, high-volume plasma exchange can regulate the detrimental immunodulatory responses by reducing monocyte activation, damage-associated molecular patterns (or DAMPS) circulation, T-CD4+ and NK cells, and cytokine production (6). Maiwall et al (38) conducted a standard-volume plasma exchange for patients with nonparacetamol acute liver failure and showed the similar efficacy data. Plasma exchange significantly decreases proinflammatory cytokines, DAMPs and endotoxin levels. These results will pave promising avenues for immunodulatory therapies in the future.

Our review has several limitations inherent to the nature of a single-center, retrospective before-versus-after cohort study of small sample size. Other limitations included unstandardized collections of clinical and laboratory data during the TPE and CRRT sessions.

CONCLUSIONS

In our single-center experience of children with dengue-associated PALF and shock syndrome, a change in practice in 2018 to the combined use of TPE and CRRT was associated with improved survival, as well as normalization of clinical and biochemical parameters. Hence, in our practice we continue to use combined TPE and CRRT rather than CRRT alone.

ACKNOWLEDGMENTS

We thank the administration and study staffs (N.T.D., N.T.M.P., T.N.T., M.T.H.T., N.T.B., N.S.H., and T.T.A.) for their assistance in medical data retrieval.

1 *Infectious Disease Department, Children Hospital 2, Ho Chi Minh City, Vietnam.*

2 *NCD Epidemiology Research Center, Shiga University of Medical Science, Otsu, Shiga, Japan.*

3 *AI Nutrition Project, National Institutes of Biomedical Innovation, Health and Nutrition, (NIBIOHN), Ibaraki, Osaka, Japan.*

4 *Woolcock Institute of Medical Research, Ho Chi Minh City, Vietnam.*

Drs. Luan, Thanh, Thien, Viet, and Tung conceptualized and designed the study. Drs. Luan and Thanh were involved in clinical data collection. Dr. Thanh was involved in formal data analysis. Drs. Luan and Thanh contributed to the writing the original article. Drs. Luan, Thanh, Thien, Viet, and Tung critically reviewed article. All authors read and approved the final article.

The authors have disclosed that they do not have any potential conflicts of interest.

New affiliation for Dr. Nguyen: Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

For information regarding this article, please e-mail co-corresponding authors: Dr. Thanh Tat Nguyen (thanhhonor@gmail.com) and Dr. Thien Vu (thienvuyd01@gmail.com)

The study data are available, and can be obtained from the corresponding authors upon request.

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