



Original Research

Therapeutic Plasma Exchange in Pediatric Intensive Care and Brief Overview of the Literature

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Abstract

Objectives: This study aimed to evaluate the therapeutic plasma exchange (TPE) procedures performed in our pediatric intensive care unit (PICU) and to review the relevant literature.

Methods: This retrospective study was conducted between 2020 and 2024. Forty-nine patients who received TPE at any point during their PICU stay were included. The groups were categorized as survivors and non-survivors.

Results: Of the 49 cases, 71.4% were male, with a median age of 54 months (range 20–135 months). A total of 274 TPE sessions were performed. The three most common indications for TPE were sepsis, trauma induced multiple organ dysfunction syndrome/disseminated intravascular coagulation, and neurological diseases. The non-survivor group had higher rates of chronic illness ($p<0.001$), pediatric risk of mortality score III, and pre- and post-procedure vasoactive inotropic scores ($p=0.005$, $p<0.001$, and $p<0.001$, respectively). The use of invasive mechanical ventilation and continuous renal replacement therapy ($p=0.005$, $p<0.001$, respectively), as well as TPE in cases with sepsis ($p<0.001$), were more frequent in non-survivors. The most common complication during the procedures was hypotension (9.9%).

Conclusion: Sepsis remains the most frequent indication for TPE in PICUs. Although the most common complication of TPE in our study was hypotension, there were no life-threatening complications, suggesting it is a safe treatment modality.

Keywords: Critical care, encephalitis, multiple organ failure, multiple trauma, sepsis

Please cite this article as "Ozel A, Kocoglu Barlas U, Yuce S, Boyraz M, Erol M. Therapeutic Plasma Exchange in Pediatric Intensive Care and Brief Overview of the Literature. Med Bull Sisli Etfal Hosp 2025;59(3):366-372".

Therapeutic plasma exchange (TPE) is an extracorporeal treatment modality used in critically ill adult and pediatric patients requiring intensive care management.^[1] In pediatric patients, challenges such as difficulty in establishing a well-functioning vascular access, the risk of circuit clotting due to slow blood flow, fluid overload or anemia

resulting from issues in returning circulated blood, and hypothermia pose significant barriers to its feasibility.^[2] The use of TPE in critically ill patients in pediatric intensive care units (PICUs) is further limited by existing hemodynamic instability.^[2, 3] Nevertheless, there are reports in the literature of TPE procedures being performed even in neonates.^[4]

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Submitted Date: February 24, 2025 **Revised Date:** April 30, 2025 **Accepted Date:** May 15, 2025 **Available Online Date:** October 13, 2025

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TPE exerts its therapeutic effects by removing pathogenic autoantibodies, immune complexes, cytokines, and toxins or by replacing deficient A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13 (ADAMTS-13) in various neurological, inflammatory, renal, and hematological conditions.^[5] The American Society for Apheresis (ASFA) provides guidelines with recommendations for numerous indications at varying levels of evidence; however, most of the supporting evidence is derived from adult studies.^[6] Consequently, the role of apheresis in critically ill pediatric patients remains uncertain and is categorized under category III, where clinical decision-making relies on the clinician's expertise and experience. This also highlights the limited number of publications on TPE in critically ill pediatric populations, most of which are confined to case reports and retrospective studies.^[7]

In this study, we aimed to evaluate the application methods, indications, complications, and effects on prognosis of TPE procedures performed in our PICU, while reviewing the current literature and comparing our findings with contemporary PICU studies.

Methods

Study Design

This single-center retrospective cohort study was conducted between January 2020 and August 2024 in our eight-bed tertiary-level PICU. Ethical approval was obtained from the University of Health Sciences Turkey, Bagcilar Training and Research Hospital's Clinical Research Ethics Committee prior to the study (date: September 19, 2024; approval number: 2024/09/07/073). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from the parents of the patients before hospitalization in the pediatric intensive care unit and all interventional procedures.

Inclusion criteria were defined as: 1) being between 1 month and 18 years of age, 2) admission to the PICU, and 3) undergoing TPE at any point during their PICU stay.

Therapeutic Plasma Exchange (TPE)

Although no written protocol exists in our unit, TPE is generally performed using the following approach: Double-lumen dialysis catheters appropriate for the patient's age and weight are used for vascular access. Catheter placement is prioritized based on the patient's age and weight in the following order: internal jugular vein, subclavian vein, and femoral vein. In our unit, the Prismaflex® (Baxter, USA) TPE 1000 and TPE 2000 sets are utilized, and the procedure is performed using the centrifugal filtration method.

The plasma volume to be exchanged (in liters) is calculated using the formula:

$\text{Plasma volume} = 0.070 \times \text{body weight (kg)} \times (1 - \text{hematocrit}).$

The first session typically involves exchanging 1.5 times the calculated plasma volume, while subsequent sessions use the calculated plasma volume, adjusted based on the patient's clinical condition. Fresh frozen plasma (FFP) serves as the replacement fluid.

Prior to each procedure, the circuit is primed with blood or 0.9% NaCl, depending on the patient's age, weight, and hemodynamic status. Anticoagulation is achieved with an initial bolus of heparin (10–30 IU/kg), followed by a continuous infusion at a rate of 10 IU/kg/h, tailored to the patient's bleeding risk. Blood flow rates are adjusted according to the patient's age, weight, and hemodynamic status, ranging between 2–6 mL/kg/min.

Each procedure is completed within approximately 3–4 hours, during which heart rate, respiratory rate, peripheral oxygen saturation, and systolic/diastolic blood pressure are closely monitored. Sedation infusions are administered as needed for patients who do not tolerate the procedure well. Pre- and post-procedure blood samples, including serum electrolytes and coagulation tests, are obtained, and any necessary corrections are made accordingly.

Data Collection

Medical records of the patients were retrospectively reviewed, and the following demographic and clinical data were collected: age, sex, presence of chronic illness, PICU length of stay, Pediatric Risk of Mortality Score III (PRISM III), pre- and post-procedure Vasoactive Inotropic Score (VIS), need for invasive mechanical ventilation (IMV) and duration of IMV, central venous catheter placement site, need for continuous renal replacement therapy (CRRT), number of failing organs, indications for TPE and their categorization based on ASFA recommendations, number of TPE sessions, complications directly related to TPE, and mortality/morbidity status.

New-onset mental or motor retardation, epilepsy, tracheostomy requirement, and limb loss at the time of PICU discharge were defined as morbidity. Patients were categorized into two groups: survivors and non-survivors, and comparisons were made between these two groups.

Data analysis and Brief Literature Overview

A brief literature review was conducted to provide context and compare our findings with existing studies. PubMed and Google Scholar databases were searched for studies on TPE procedures performed in PICUs between 2020 and 2024. The search terms included 'apheresis, children, intensive care, pediatric, plasmapheresis, therapeutic plasma exchange,' and only studies published in English were included.

Statistical Analysis

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used to compare non-normally distributed continuous variables between the two groups, while the Pearson chi-square test was applied to assess the relationships between categorical variables. Results were evaluated at a 95% confidence interval, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 274 TPE sessions were performed on 49 patients included in the study. Of the patients, 71.4% were male, and the median age of all patients was 54 months (range: 20 – 135 months). The general characteristics and PICU follow-up data of all patients are shown in Table 1.

The most common indication for TPE was sepsis with multi-organ dysfunction syndrome (MODS) (53%), followed by trauma induced MODS/disseminated intravascular coagulation (DIC) at 20.4%. The most frequently observed complication during TPE procedures was hypotension (9.9%) (Table 2).

Table 1. Demographic and clinical characteristics of pediatric patients in intensive care

Characteristics	Values
Age (month), median (IQR)	54 (20 – 135)
Gender, % (n)	
Female	28.6% (14/49)
Male	71.4% (35/49)
Chronic illness, % (n)	49% (24/49)
PICU stay (day), median (IQR)	18 (9 – 27)
PRISM III, median (IQR)	13 (9 – 22)
VIS, pre-procedure, median (IQR)	10 (0 – 35)
VIS, post-procedure, median (IQR)	0 (0 – 35)
Respiratory support	
IMV, % (n)	65.3 (32/49)
IMV stay (day), median (IQR)	5 (0 – 18)
Central venous catheter location, % (n)	
Internal jugular vein	51 (25/49)
Subclavian vein	42.9 (21/49)
Femoral vein	8.1 (4/49)
CRRT, % (n)	49 (24/49)
Number of organ dysfunction, median (IQR)	2 (1 – 3)
0-1 organ, n (%)	34.7 (17/49)
Multiple organs (≥ 2), n (%)	65.3 (32/49)
Mortality, % (n)	38.8 (19/49)
Morbidity, % (n)	34 (16/49)

CRRT: Continuous renal replacement treatment; IMV: Invasive mechanical ventilation; PICU: Pediatric intensive care unit; PRISM: Pediatric risk of mortality score; VIS: Vasoactive inotropic score.

Patients were divided into two groups: survivors and non-survivors, and comparisons were made between these groups (Table 3). The prevalence of chronic illness was significantly higher in the non-survivor group ($p < 0.001$). There were significant differences between the survivors and non-survivors in terms of PRISM-III scores and pre- and post-procedure VIS values ($p = 0.005$, $p < 0.001$, $p < 0.001$, respectively). The non-survivor group had higher rates of IMV and CRRT use ($p = 0.005$, $p < 0.001$, respectively). In the survivor group, the total number of procedures and the number of sessions per patient were significantly higher ($p = 0.032$, $p = 0.032$, respectively). The non-survivor group also showed a higher rate of TPE use in cases of sepsis with MODS ($p < 0.001$).

Table 4 summarizes the literature on the use of TPE in critically ill pediatric patients.^[3, 8-22]

Discussion

The ASFA recently published a systematic review of apheresis indications, introducing new recommendations and updates. In the 2022 ASFA Ninth Guidelines, 27 category I, 44 category II, 91 category III, and 4 category IV indications were identified following the updated recommendations.^[6] In our study, 2% of patients fell under category II, 69.4% under category III, and 28.6% were non-categorized (NC). Consistent with previous reports, category III indications were the most common among critically ill pediatric patients undergoing TPE, with sepsis with MODS being the leading indication (Table 4).

TPE remains a category III treatment for sepsis with MODS. Previous studies report TPE use in 24–44.4% of pediatric sepsis with MODS cases (Table 4). Although a systematic review found no mortality benefit of TPE in severe pediatric sepsis overall, benefits were observed in cases associated with TAMOF.^[23] A large retrospective study also linked TPE to reduced mortality in pediatric sepsis, though the proportion involving thrombocytopenia-associated multiple organ failure (TAMOF) was unclear.^[24] Similarly, a 2014 study showed higher survival in TAMOF patients treated with TPE.^[25] In our cohort, sepsis with MODS was the most common TPE indication (53%), all involving TAMOF. The mortality rate in this subgroup was 61.5% (16/26). TPE may contribute to survival by clearing endotoxins and inflammatory cytokines and restoring hemostatic balance via FFP replacement.^[5, 23, 24] Although we did not specifically assess the impact of TPE on mortality, non-survivors had higher chronic disease rates, PRISM III scores, and VIS values, as well as more frequent IMV and CRRT use. Survivors underwent more TPE sessions, possibly reflecting longer treatment courses. Thus our findings should be interpreted cautiously.

Table 2. Therapeutic plasma exchange indications, asfa categories, and procedural complications in pediatric patients

Indications and Complications	% (n/49)	Number of sessions	ASFA category
TPE Indications, % (n)			
Sepsis with MODS	53 (26/49)	114	III
Trauma induced MODS/DIC	20.4 (10/49)	47	NC
Neurologic diseases			
Encephalitis of unknown origin	4.1 (2/49)	12	NC
Transverse myelitis	4.1 (2/49)	22	NC
ADEM	2 (1/49)	31	II
Acute hepatic failure	6.1 (3/49)	15	III
Drug poisoning	4.1 (2/49)	8	III
Toxic epidermal necrolysis	4.1 (2/49)	15	III
Idiopathic dilated cardiomyopathy	2 (1/49)	10	III
Total procedures of TPE, n	274		
TPE procedure number per patient, mean	5.6±4.5		
TPE procedural complications (per procedure), % (n)			
Hypotension	9.9 (27/274)		
Hypocalcemia	9.5 (26/274)		
Catheter occlusion	5.1 (14/274)		
Bleeding	4 (11/274)		
Occlusion of filter	3.3 (9/274)		
Vomiting and nausea	2.6 (7/274)		
Signs of infection at catheter site	1.8 (5/274)		
Anaphylaxis	0.4 (1/274)		
Total	36.5 (100/274)		

ADEM: Acute disseminated encephalomyelitis; ASFA: American Society for Apheresis; DIC: Disseminated intravascular coagulation; MODS: Multiple organ dysfunction syndrome; TPE: Therapeutic plasma exchange.

Table 3. Comparison between survivors and non-survivors

Parameter	Survivors (n=30)	Non-Survivors (n=19)	p
Age (month), median (IQR)	113 (21-154)	38 (17-93)	0.142
Gender, % (n)			0.277
Female	36.7 (11/30)	15.8 (3/19)	
Male	63.3 (19/30)	84.2 (16/19)	
Chronic illness, % (n)	26.7 (8/30)	84.2 (16/19)	<0.001**
PICU stay (day), median (IQR)	20 (11-31)	16 (5-22)	0.103
PRISM III, median (IQR)	12 (6-18)	22 (12-35)	0.005*
VIS, pre-procedure, median (IQR)	0 (0-20)	35 (20-50)	<0.001*
VIS, post-procedure, median (IQR)	0 (0-0)	40 (10-50)	<0.001*
IMV, % (n)	50 (15/30)	89.5 (17/19)	0.005**
CRRT, % (n)	30 (9/30)	78.9 (15/19)	<0.001**
Total procedures of TPE	201	73	0.032†
TPE procedure number per patient, mean	6.7±5.2	3.9±2.2	0.032†
Indications for TPE, % (n)			
Sepsis with MODS	10 (33.3)	16 (84.2)	<0.001**
Trauma induced MODS/DIC	7 (23.3)	3 (15.8)	0.523

*Mann-Whitney U test; **Pearson chi-square test; †Independent-samples t-test. CRRT: Continuous renal replacement treatment; DIC: Disseminated intravascular coagulation; IMV: Invasive mechanical ventilation; MODS: Multiple organ dysfunction syndrome; NC: Non-categorized; PICU: Pediatric intensive care unit; PRISM III: Pediatric risk of mortality score III; VIS: Vasoactive inotropic score.

Our center's location likely explains the relatively high rate (20.4%) of TPE for trauma-induced MODS/DIC compared to other studies (Table 4). Among 10 patients treated for this indication, three died. TPE was typically administered for at least three days, guided by thrombocytopenia resolution and MODS improvement. Disseminated intravascular coagulation (DIC) represents a severe hemostatic challenge, particularly in critically ill pediatric patients with trauma or sepsis. It is characterized by the activation of the coagulation cascade, leading to the excessive consumption of coagulation factors and platelets. In trauma-induced DIC, suppression of the anticoagulant pathway, impaired fibrinolysis, and excessive clotting activity result in microvascular thromboses, contributing to MODS.^[26] Furthermore, a sustained systemic inflammatory response, driven by neutrophil activation and endothelial damage, plays a significant role in the progression to MODS in trauma-induced DIC patients.^[27] Recent studies have demonstrated that, similar to sepsis, severe trauma can lead to endothelial injury and ADAMTS13-von Willebrand factor imbalance. TPE has been shown to restore ADAMTS13 activity, improve platelet levels, and enhance renal function, among other parameters, in these patients.^[28]

Neurological diseases are the most common pediatric TPE indications. While Bustos et al.^[9] reported autoimmune encephalitis as the leading cause, Fateen et al.^[14] found Guillain-Barré syndrome most frequent. In our cohort, TPE was performed for five cases of neurological diseases: two cases of transverse myelitis, two cases of encephalitis of unknown etiology, and one case of acute disseminated encephalomyelitis (ADEM), which is classified as an ASFA category II indication. The encephalitis cases were refractory to intravenous immunoglobulin (IVIG) and steroid treatment, presenting with progressive neurological deficits before TPE initiation. Following TPE, both patients were discharged with only mild neurological deficits.

We also encountered two rare cases of toxic epidermal necrolysis (TEN), both resistant to IVIG and steroids. One recovered fully, while the other required amniotic membrane transplantation.

There remains limited evidence supporting TPE in many critical illnesses, and many indications are off-label. Durak et al.^[11] reported 27.4% of TPE cases as MIS-C, but its role remains inconclusive due to the retrospective study design. MIS-C was reclassified under vasculitis in the 2022 ASFA guidelines.^[6] Other off-label uses included Henoch-Schönlein purpura nephritis^[30] and Crimean-Congo hemorrhagic fever.^[17] Randomized controlled trials are needed to clarify TPE's role in such contexts.

TPE complications are relatively rare. In adults, allergic reactions to FFP, bleeding, and hypocalcemia are most com-

mon.^[31] In Türkiye, FFP is often used due to albumin's cost. In our study, the only major complication was FFP-related anaphylaxis. Hypotension remains the most common complication in the literature (Table 4).^[9, 11, 13, 14, 16, 19, 22]

This study's limitations include its retrospective, single-center design, lack of standardized TPE timing and session numbers, small sample size, and absence of dedicated subspecialists, possibly underrepresenting some TPE indications.

Conclusion

Our findings align with the literature, showing that sepsis is the most common indication for TPE in the PICU. The presence of rare indications, such as trauma-induced MODS/DIC and TEN, in our study supports the idea that patients with these conditions may also benefit from TPE. Given the lack of life-threatening complications observed, we believe that our study demonstrates TPE to be an effective and safe extracorporeal treatment modality in critically ill pediatric patients when managed by experienced personnel.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Bagcilar Training and Research Hospital's Clinical Research Ethics Committee in September 19, 2024 (approval number: 2024/09/07/073).

Author Contributions: Conception – A.O., U.K.B.; Design – A.O., U.K.B., M.E.; Supervision – A.O. M.B.; Materials – A.O., U.K.B., S.Y., M.E.; Data Collection and/or Processing – A.O. U.K.B. S.Y., M.B.; Analysis and/or Interpretation – A.O. S.Y., M.B.; Literature Review – A.Ö.; Writing – A.Ö., U.K.B. S.Y.; Critical Review – A.O., U.K.B., S.Y., M.E.

Financial Disclosure: The authors declared no financial support.

Conflict of interest: The authors declared no conflict of interest.

Use of AI for Writing Assistance: The authors declared that Artificial intelligence-supported technologies were not used at any stage of the study.

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