Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.21209

Use of Therapeutic Plasma Exchange in the Pediatric Intensive Care Unit

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What is already known on this topic?

- *Therapeutic plasma exchange (TPE) has, in recent years, been used as a primary or supportive treatment for several diseases and has achieved satisfactory results for most of these diseases. TPE is used in many clinical conditions, including was thrombocytopenia-associated multi-organ failure with sepsis (TAMOF), liver failure, neurological conditions, poisoning, autoimmune diseases, nephrological diseases, and post-solid organ rejection in pediatric intensive care units.*

What this study adds on this topic?

- *There is a great need for further studies on sepsis, thrombocytopenia-associated multi-organ failure with sepsis (TAMOF), and neurologic disorders, particularly in the pediatric age group. We believe that the mechanisms TPE provides for recovery should be demonstrated, and there should be American Society for Apheresis categories specific to the pediatric age groups because the disease progress of many ailments and response to therapies differ between pediatric patients and adult patients.*

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Received: August 18, 2021
Accepted: October 8, 2021

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ABSTRACT

Objective: Therapeutic plasma exchange has been used as a primary or supportive treatment in many diseases in recent years and has achieved satisfactory results in lots of diseases in children. Therapeutic plasma exchange procedure is changing plasma component of a patient's blood with the new plasma as a replacement solution. The aim of this study is to share our experience of therapeutic plasma exchange on varying indications in critically ill children who were accepted to our pediatric intensive care unit.

Materials and Methods: We conducted this study between December 2010 and February 2020, retrospectively. Patients' data such as age, sex, indication, number of sessions, vascular access route, and type of replacement fluid used were obtained from medical records. Indications for therapeutic plasma exchange were classified according to the 2019 American Society for Apheresis categorization. The patient's follow-up, clinical courses, therapeutic plasma exchange season count, complications, and outcome were evaluated according to each indications and their overall condition.

Results: This study included a total of the 84 patients who underwent therapeutic plasma exchange, and their median (minimum-maximum) ages were 7.07 years (0.2-18), 57.1% were male (n = 48) and 42.9% were female (n = 36). A total of 463 sessions of therapeutic plasma exchange were performed in 84 patients. The most common indication was thrombocytopenia-associated multi-organ failure with sepsis (40.4%, n = 34) followed by liver failure/hepatic encephalopathy (28.5%, n = 24) and autoimmune encephalitis (9.5%, n = 8), and according to The American Society for Apheresis 2019 category, patients distributions were as follows: 15.4% of the patients were placed in category 1 (n = 13), 5.9% in category 2 (n = 5), 77.3% in category 3 (n = 65), and 1.1% in category 4 (n = 1). Therapeutic plasma exchange was combined to extracorporeal membrane oxygenation in 10 patients (11.9%) and continuous renal replacement therapies in 39 (46.4%) patients. Finally, the survival rate was 50% in all patients, and the lowest survival rate was 41.5% (n = 27) in category 3 group.

Conclusion: Therapeutic plasma exchange is enlarging to varying indications and showing to be more effective on a lot of disorders in children. Also, it is available in pediatric age groups and in different states like combined with other extracorporeal therapies.

Keywords: Acute liver failure, children, pediatric intensive care, plasmapheresis, sepsis, therapeutic plasma exchange

INTRODUCTION

Therapeutic plasma exchange (TPE) has, in recent years, been used as a primary or supportive treatment for several diseases and has achieved satisfactory results for most of these diseases. The TPE procedure involves replacing plasma and other components of the patient's blood with a replacement solution—typically fresh-frozen plasma and albumin.[1] Therapeutic

Cite this article as: Gökcan Öztürk A, Erva Küçük Z, Özcan S, et al. Use of therapeutic plasma exchange in the pediatric intensive care unit. *Turk Arch Pediatr.* 2022;57(2):186-192.

plasma exchange is performed using 1 of 2 methods: centrifugal separation or membrane-based (filtration) separation and neither method is superior to the other.[1-3] Specific target molecule properties increase the efficiency of TPE, chief of which is the target molecule having a large molecular weight. This characteristic makes TPE superior to other extracorporeal therapeutic methods. Properties such as a slow formation rate, low turnover, low dispersion volume, and a defined etiologic agent may also constitute favorable target molecule properties for TPE.[2]

The American Society for Apheresis (ASFA) criteria are used for TPE. The American Society for Apheresis updated and published the indications of TPE in 2019. However, these criteria were developed for adult patients. Because there are no specific standards for pediatric patients, TPE is performed based on adult guidelines, case reports, and clinical experiences. Therapeutic plasma exchange is used in many clinical conditions, including thrombocytopenia-associated multi-organ failure with sepsis (TAMOF), liver failure, neurological conditions such as Guillain–Barré syndrome and myasthenia gravis, poisoning and intoxications, immunologic and rheumatologic diseases, nephrological diseases such as Hemolytic Uremic Syndrome (HUS), and post solid organ rejection in pediatric intensive care units (PICUs). However, the indications of all these diseases are categorized based on adult guidelines.[1,4,5] Our aim in this study is to present our TPE experience in our PICU and to examine the indications, complications, and prognosis of patients who underwent TPE.

MATERIALS AND METHODS

Study Design

This study was conducted retrospectively between December 2010 and February 2020. Patients' data, such as age, sex, indications, number of TPE sessions, vascular access route, and replacement fluid type used, were obtained from medical records. Patients' follow-up, clinical courses, TPE session count, and outcomes were evaluated according to each indication and their overall condition. This study was carried out at a tertiary academic center in concordance with international ethical standards and the World Health Organization Helsinki Declaration. Written approval was obtained from our University Faculty of Medicine Clinical Research Ethical Committee for this study (Decision No: 2021/269).

ASFA Categorization

Indications for TPE were classified according to the 2019 ASFA categorization. Category 1: disorders of which apharesis is accepted as first-line therapy; category 2: disorders of which apharesis is accepted as second-line therapy; category 3: optimum role of apheresis therapy is not established; category 4: disorders in which published evidence demonstrates or suggests apharesis to be ineffective or harmful.[1]

TPE Sessions

Therapeutic plasma exchange sessions were performed by experienced staff using the centrifugation method with a Fresenius COM.TEC® device and appropriate anticoagulation and total blood volume were calculated. The required plasma volume was calculated using the following formula: (patient weight × 70) × (1 − hematocrit). The volume of replacement fluid and the replacement plasma volume were the same for all patients. The femoral and jugular veins were chosen as the vascular access routes, and fresh-frozen plasma (FFP) was used as the replacement solution. During the TPE procedure, the patients were followed-up by an experienced team to monitor vital signs while they were in the PICU.

Data Collection and Analysis

Age, gender, vital signs, mechanical ventilation, ASFA categorization, vascular access, whole blood count, biochemical laboratory values, and adverse events (e.g., hypotension, allergic reactions, hypocalcemia, and vascular complications) were extracted from patient charts and electronic hospital records. Hematocrit values in the whole blood count were used to calculate the plasma volume that would change. Thrombocytopenia was defined as platelet count below 150 000/mm^3. Hypotension was defined based on normograms adjusted for patients' age. A serum calcium level of <8.5 mg/dL was evaluated as hypocalcemia. For some patients, TPE was used in combination with extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) (Figure 1A and 1B). We investigated the relation between the indications, clinical course, other extracorporeal treatments, and outcomes.

Statistical Analysis

The data obtained were analyzed using The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA). Number (n) and percentage (%) are used to denote categorical variables. Median and interquartile ranges were used for non-normally distributed data. Chi-square and Fisher's exact tests were used to examine the relationship between 2 qualitative variables. Fisher–Freeman–Halton test was used to compare mortality rates according to categories. Bonferroni correction was applied in post hoc analysis. $P < .05$ was considered statistically significant.

RESULTS

Study Population

In total, 84 patients underwent the TPE procedure for a total of 463 sessions, 57% (n = 48) of the patients were male, and the median (minimum-maximum) age of all patients was 7.07 (0.2-18) years.

Characteristics of Therapeutic Plasma Exchange

The indications for the TPE performed on patients are presented in Table 1 and are based on the 2019 ASFA categorization. The distribution of the patients was as follows: 15.4% of the patients were placed in category 1 (n = 13), 5.9% in category 2 (n = 5), 77.3% in category 3 (n = 65), and 1.1% in category 4 (n = 1). For 79 patients (94.1%), TPE was performed via a jugular catheter and via a femoral catheter for 5 (5.9%) patients. Fresh-frozen plasma was used as the replacement fluid for all patients. Therapeutic plasma exchange was performed on 15 patients using the ECMO set. While the mean change in total plasma volume was 1613 mL, the replacement amount was calculated as 2116 mL.

Indications of Therapeutic Plasma Exchange

Patients were evaluated in groups, and the distribution according to disease subgroups was as follows: TPE was performed on 40.4% (n = 34) of the patients as part of treatment for sepsis or TAMOF; 28.5% (n = 24) for liver failure; 9.5% (n = 8) for

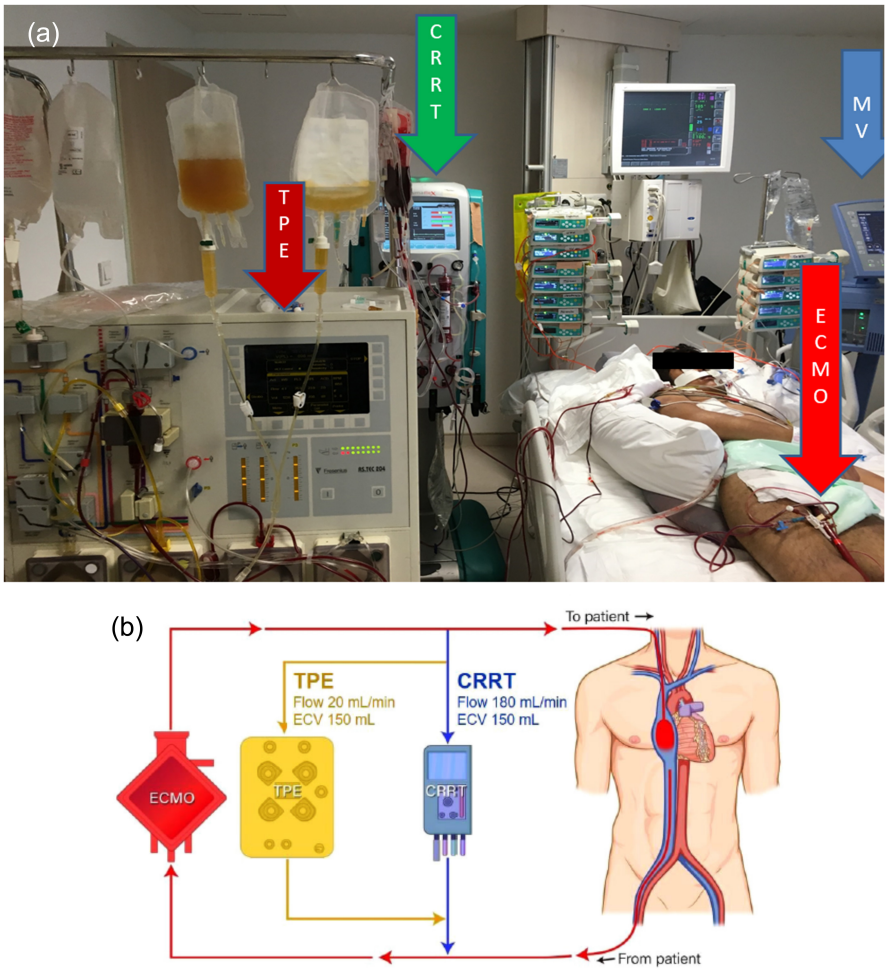

Figure 1. (A) A patient undergoing a combination of therapeutic plasma exchange (TPE), continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) at our unit. (This image is from the archives of our University Children Hospital Pediatric Intensive Care Unit.) (B) Triple-modality of ECMO, TPE, and CRRT.[24]

autoimmune encephalitis or Hashimoto encephalitis (1 of 4), refractory epilepsy, and superrefractory status epilepticus; 3.6% (n = 3) for mushroom intoxication; 1.2% (n = 1) for poisoning; 3.6% (n = 3) for atypical HUS; 1.2% (n = 1) for hemophagocytic lymphohistiocytosis; 2.4% (n = 2) for Guillain–Barré syndrome; 1.2% (n = 1) for macrophage activation syndrome; 1.2% for antiphospholipid syndrome due to systemic lupus erythematosus (SLE); 3.6% (n = 3) for heart transplant rejection; 1.2% (n = 1) for autoimmune hemolytic anemia; and 2.4% (n = 2) for acute rejection after liver transplant.

Survival of Therapeutic Plasma Exchange

The distribution of non-surviving patients (n = 42), according to the ASFA categorization, is as follows: 7.1% (n = 3) were classified as category 1, 2.4% (n = 1) as category 2, and 90.5% (n = 38) as category 3. All patients classified as category 4 survived. Among the survived patients (n = 42), 23.8% (n = 10) were classified as category 1, 9.5% (n = 4) as category 2, 64.2% as category 3 (n = 27), and 2.3% (n = 1) as category 4. A significant difference was found between mortality rates according to the ASFA category ($P = .020$). Although the mortality of the patients in the ASFA category 3 was higher than the other categories, no significant difference was observed between the categories in the pairwise comparisons made in the post hoc analysis. A significant difference was found between intubation and mortality. The mortality rate of intubated patients was found to be significantly higher ($P < .05$). The patients' indications for TPE and survival rates are summarized in Table 2.

Combination Therapies with Therapeutic Plasma Exchange

Continuous renal replacement therapy was performed on 39 (46.4%) patients, and 10 (11.9%) patients were on ECMO in combination with TPE. The indications for ECMO were pulmonary hemorrhage in 1 patient, dilated cardiomyopathy in 7 patients, fulminant myocarditis in 1 patient, and refractory septic shock in 1 patient. There were 9 (90%) non-surviving patients on whom a combination of TPE and ECMO combined therapy was performed. The mortality rate was found to be significantly higher in patients who used ECMO and TPE together. There was statistically significant difference in mortality between ECMO combined with TPE and TPE alone ($P = .007$). There were 26 (72%) non-surviving patients among those who underwent both TPE and CRRT. The mortality rate was found to be significantly higher in patients who used CRRT and TPE together. There were statistically significant differences for TPE with and without CRRT ($P = 0.004$). There were 5 patients (for dilated cardiomyopathy in 4 patients, and for fulminant myocarditis in 1 patient) who underwent TPE, ECMO, and CRRT therapies, and all of them died.

Table 1. Patients' Demographics and Clinical Features

Parameters		Value	
Male, n (%)/female (%)		48 (57)/36 (43)	
Age (years) median (minimum-maximum)		7.07 (0.2-18)	
Total sessions (n)		463	
Vascular access			
Jugular/femoral catheter (n)		79/5	
CRRT+TPE		39	
ECMO+TPE		10	
ECMO+CRRT+TPE		5	
Invasive mechanic ventilation n (%)		58 (69)	
Length of stay at PICU (days) median (minimum-maximum)		27.4 (1-262)	
Combined therapies and invasive mechanic ventilation with TPE			
Combined Therapies	Survivors	Non-survivors	*P*
CRRT+TPE (n = 39)	13	26	.004[a]
TPE	29	16	
ECMO+TPE (n = 10)	1	9	.007[a]
TPE	41	33	
Invasive MV	16	42	,000[a]
Non-invasive MV	26	0	

TPE, therapeutic plasma exchange; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MV, mechanic ventilation.
[a]Chi-square test.

Complications

No complications related to TPE were observed in any of the patients who underwent TPE, with 50% of the patients discharged from the PICU (n = 42) and the other 50% of them are non-surviving. All non-surviving patients were intubated. During follow-up, 58 (69%) of the patients were intubated, and 16 of these intubated patients survived.

DISCUSSION

In recent years, the TPE procedure has been performed increasingly, with promising results for various pediatric patients. In our study, ASFA category 3 diseases constituted 76.2% (n = 64) of the TPE indications. The majority of the patients in this category also had cases of TAMOF. This is a group of diseases for which the optimum role of TPE cannot be determined.[1]

It is established that TPE procedures are performed more frequently on patients with sepsis and TAMOF diagnoses.[3,6-8] Sepsis and its related complications are important causes of mortality, despite antibiotic therapy and supportive treatments. Another major and common cause of mortality is the condition described as TAMOF, which is characterized by an early onset of thrombocytopenia, multiple (three or more) organ failure, and lactate dehydrogenase (LDH) elevation. Routine treatments for sepsis and TAMOF do not include plasmapheresis, but the results of plasmapheresis in these cases have been quite satisfactory in recent times. A study conducted by Fortenberry et al[9] reported

Table 2. Indications for Therapeutic Plasma Exchange and Its Related Outcomes

ASFA Categorization	Number of Patients	Survivors, n (%)	Diagnosis	Number of Patients, n (%)	Survival Rate, n (%)	*P*
I	13	10 (76)	Autoimmune encephalitis, other encephalitis (Hashimoto), refractory epilepsy	8 (9.5)	5 (62.5)	.020[b]
			HUS	3 (3.6)	3 (100)	
			GBS	2 (2.4)	2 (100)	
II	5	4 (80)	Mushroom poisoning	3 (3.6)	3 (100)	
			AIHA	1 (1.2)	1 (100)	
			SLE	1 (1.2)	0 (0)	
III	65	27 (41.4)	MOF+TAMOF (including sepsis or sepsis+MOF)	34 (40.4)	12 (35.2)	
			Liver Failure+hepatic encephalopathy	24 (28.5)	13 (54.1)	
			HLH-MAS	2 (2.4)	0 (0)	
			Liver transplant rejection	2 (2.4)	0 (0)	
			Heart transplant rejection	3 (3.6)	2 (66.6)	
IV	1	1 (100)	Poisoning	1 (1.2)	1 (100)	

MOF, multi-organ failure; TAMOF, thrombocytopenia-associated multi-organ failure with sepsis; HUS, hemolytic uremic syndrome; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; GBS, Guillain-Barré syndrome; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus.
[b]Fisher-Freeman-Halton test.

that the mortality rate was lower in the TPE group than in the standard treatment group, and organ dysfunction regressed more quickly in the TPE group than in the standard treatment group. However, these positive results were not statistically significant.[9] In septic cases, the effect of TPE is evidenced by the regulation of hemostasis, reduction of dead leukocyte concentration in circulation, and in the tissues, replacement of immunoglobulins and anticoagulant-profibrinolytic mediators, and removal of endotoxins, proinflammatory cytokines, and thrombogenic-antifibrinolytic mediators from circulation. The ASFA criteria classify sepsis-related cases of multiorgan failure (MOF) under category 3 (diseases for which the optimum role could not be determined precisely). In our study, TPE was performed on 36.9% (n = 31) of the patients for TAMOF cases. Mortality occurred in 22 of 34 (64.7%) patients during follow-up. In a single-center study by Güntülü et al.[10] 25% mortality was recorded among patients who underwent TPE for sepsis.[10] A single-center study by Emeksiz et al reported a mortality rate of 17.4% (3). We hypothesize that the high mortality rates in our center are attributable to most of the patients who underwent TPE for sepsis or TAMOF having primary immunodeficiencies and hematological malignancies, with some being dilated cardiomyopathy patients on a heart transplant program and simultaneous CRRT and/or ECMO support patients.

Liver failure is a rare but fatal clinical condition seen in the pediatric age group. In particular, it presents with clinical and laboratory findings, such as hepatic encephalopathy, hepatic cardiopathy, hepatorenal syndrome, and coagulopathy caused by substances such as toxins, aromatic amino acids, ammonia, endotoxins, and indoles. Therapeutic plasma exchange for liver failure is performed as a *bridge* treatment to buy time for liver transplantation or for therapeutic purposes that facilitate full recovery. Therapeutic plasma exchange should be considered among the first-line treatments for fulminant hepatic failure, especially in life-threatening coagulopathy and bleeding conditions.[12] In our study, liver failure was the second most common indication for TPE. There was full recovery in 13 (54.1%) patients, 15 patients were bridged to liver transplantation, 11 of 24 patients did not survive, and 54.1% survived. Nine of the patients were lost due to MOF. Bridge treatment was administered to 15 patients before preparation for liver transplantation. While complete recovery was achieved in 13 patients, and during follow-up, 1 of these patients had a diagnosis of spinocerebellar ataxia, liver enzyme elevation, and INR elevation, and the patient was removed from follow-up because of patients' family. In a systematic review of adult patients published by Tan et al[12] in 2020, it was reported that TPE reduced mortality at the 30th and 90th days in acute liver failure patients. In a study published by Chien et al[13] in 2020 including 23 patients with a diagnosis of pediatric acute liver failure, the mortality rate was reported as 39%, and there was a higher survival rate among patients with liver transplantation indication who underwent TPE.

Another important indication of TPE in the pediatric age group is neurological diseases. It is recommended to perform TPE, especially in neurological conditions due to autoantibody formation, with a defined etiologic agent. It was recommended that TPE should be the first-step treatment method for category 1 cases such as Guillain–Barré syndrome and myasthenia gravis and that clinical conditions should be monitored after 5-7 sessions. Therapeutic plasma exchange is the second-line therapy for patients who do not respond to intravenous immunoglobulin (IVIG) and steroid treatment within 48-72 hours, indicated by conditions such as acute transverse myelitis, limbic encephalitis, and neuromyelitis optica.[14] In our study, there were TPE cases in which autoantibodies such as autoimmune encephalitis were detected and cases of resistant epilepsy unresponsive to antiepileptic drugs. The most remarkable case is Hashimoto encephalopathy presenting with status epilepticus unresponsive to antiepileptic drugs and positive thyroid autoantibodies.[15] In a case report presented by Gedik et al.[16] TPE was applied to a 5-year-old patient with super refractory status epilepticus who did not respond to any treatments due to meningoencephalitis, and seizures were controlled. In our study, TPE was performed on 10 patients due to neurologic disorders. Eight of these patients had autoimmune encephalitis and treatment-resistant status epilepticus, 3 of whom died during follow-up. Therapeutic plasma exchange was performed on 2 patients due to Guillain–Barré syndrome, and significant improvement in symptoms was observed in both patients.

Poisoning due to various substances comprises another indication group for TPE, which should be among the considered treatment modalities, especially for patients with severe intoxication, high mortality, and clinical worsening despite the application of known treatment modalities. In a study, TPE was reported to be particularly useful for fungal intoxications related to the Amanita species. The addition of TPE to standard treatment was found to be beneficial in poisoning related to the Amanita species within 24-48 hours. Therapeutic plasma exchange should be considered the standard treatment for poisoning due to snake bites in patients with an allergy to antivenom or if the antivenom is not accessible.[17] In our study, successful results were obtained in 3 fungal intoxication cases, and another success was with tricyclic antidepressant intoxication in 1 case. None of the patients in the intoxication cases were lost during follow-up.

The use of TPE in combination with immunosuppressive therapy is also common in cases of rejection after solid organ transplantation. Therapeutic plasma exchange is one of the most effective therapies for clearing the blood of donor-specific antibodies that cause antibody-related rejection.[1] In our study, TPE was used together with other immunosuppressive drugs in 3 patients for cardiac transplant rejection and in 2 patients for liver transplant rejection. All patients who developed rejection after liver transplantation died. One of the 3 patients who developed rejection after heart transplantation died.

In our study, atypical HUS was the most common indication for TPE among patients with nephrological diseases. Hemolytic uremic syndrome is classified into 2 groups (typical HUS and atypical HUS) based on the clinical course of the disease, whether diarrhea is seen or not. Typical HUS covers the vast majority of patients, and the most common cause is the Shiga toxin of *Escherichia coli*. Atypical HUS, on the other hand, is associated with various genetic mutations, with new mutations being identified each year. Hemolytic uremic syndrome patients fall under different ASFA categories based on their HUS subtypes. Typical HUS cases fall under category 4, while atypical HUS cases are category 1 if associated with the factor H antibody,

and category 2, if factor H mutation is detected. Although new treatment options such as eculizumab have been discussed in recent years, TPE is still recommended in the first 24 hours in cases of atypical HUS and for rapidly worsening cases with no underlying cause. In HUS patients, TPE is performed until hemolysis improves, clinical indications regress, and positive results are obtained.[18,19] In our study, plasmapheresis was performed in 3 atypical HUS patients due to the progression of neurological symptoms and intubation for eculizumab treatment. All 3 patients were discharged after being extubated during follow-up following regression in neurological symptoms.

All patients who underwent ECMO and CRRT in combination with TPE died during follow-up due to MOF. We can attribute the high mortality rate, especially in CRRT+TPE and ECMO+CRRT+TPE applications, to the high severity of the patients' primary diseases and the development of MOF during follow-up. In addition, the mortality rate of patients who were intubated during TPE was found to be significantly higher than that of those who did not undergo intubation. The cases where TPE and ECMO are used together are as follows: antibody-mediated heart rejections, sepsis/TAMOF, and acute lung injury. In the pediatric age group, TPE can be performed using the ECMO setup due to vascular pathway difficulties.[20] In our study, TPE was administered to patients who received TPE and ECMO together due to sepsis or TAMOF, acute heart rejection, and liver failure. Acute kidney injury is one of the major complications of ECMO, increasing mortality and morbidity. Therefore, CRRT therapy should be administered to patients with fluid overload, electrode abnormality, and uremia.[21] In our study, CRRT and TPE were administered together for sepsis or TAMOF and atypical HUS cases. The cases where CRRT, TPE, and ECMO are used together are as follows: development of heart failure due to dilated cardiomyopathy and development of sepsis or TAMOF.

In our study, TPE was performed in 1 patient for SLE and in 2 patients for hemophagocytic lymphohistiocytosis (HLH) and macropage activation syndrome(MAS). However, all patients were lost during follow-up. Severe autoimmune hemolytic anemia developed in 1 patient who underwent hematopoietic stem cell transplantation due to interleukin-2 receptor deficiency and the patient was transferred to the service when the patient's whole blood and biochemistry parameters improved after intravenous immunoglobulin, steroid, and TPE treatment. All patients were classified as ASFA category 3. In a multicenter study by Demirkol et al.[22] it was shown that the use of TPE together with medical treatment in the treatment of HLH and MAS positively affects the prognosis.

Complications such as fever, urticaria, hypocalcemia, pruritus, and hypotension may arise due to TPE. Most of the complications are catheter or procedural-related.[23] In our study, no complications or deaths due to TPE were observed in any patient. This may be related to the retrospective nature of this study and nonserious adverse complications not being recorded at the time of treatment.

The limitations of our study include the retrospective nature of the study and the deficiencies in some patients' records and files due to change in the patient registration system.

CONCLUSION

In conclusion, as shown in this study, TPE is performed for a variety of indications and is associated with the patient survival rate. TPE supports healing in many diseases and provides multiple benefits, including buying time for transplantation and preventing rejection after transplantation. It can be performed at the PICU bedside without the need for patient mobilization. There is a great need for further studies on sepsis, TAMOF, and neurologic disorders, particularly in the pediatric age group. We believe that the mechanisms TPE provides for recovery should be demonstrated, and there should be ASFA categories specific to the pediatric age groups because the disease progress of many ailments and response to therapies differ between pediatric patients and adult patients.

Availability of Data and Materials we obtained data from patients' medical records, which can be shared on request. Data were extracted from the hospital database of Ankara University Hospitals and a specified children's hospital research database.

Ethics Committee Approval: Written approval was obtained from Ankara University Faculty of Medicine Clinical Research Ethical Committee for this study (Decision No: 2021/269).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G.O, Z.E.K., M.H., S.O, E.G., E.B.; Design – A.G.O., Z.E.K., T.K .; Supervision – T.K.; Resources – A.G.O, Z.E.K., M.H., S.O, E.G., E.B, T.K.; Materials – A.G.O, Z.E.K., M.H., S.O, E.G., E.B, T.K.; Data Collection and/or Processing – A.G.O, Z.E.K., M.H., S.O, E.G., E.B, T.K.; Analysis and/or Interpretation A.G.O., Z.E.K., T.K.; Literature Search – A.G.O., Z.E.K.,.; Writing Manuscript – A.G.O., Z.E.K.; Critical Review – T.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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