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Research Article,

Therapeutic Plasma Exchange in Critically ill Pediatric Patients

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Abstract:

Background: Therapeutic plasma exchange (TPE) represents a highly effective extracorporeal procedure for selected indications. It is rarely used in children due to safety concerns such as difficult vascular access, low plasma volume and lack of experienced personnel. In this study, we reviewed the TPE indications, the complications we encountered, and the treatment results in critically ill children.
Methods: In this study, 46 pediatric patients who underwent TPE in the pediatric intensive care were evaluated retrospectively.
Results: Total of 2142 patients were hospitalized over a 3-year period, and TPE was applied to 46 (2.1%) patients. TPE was performed most frequently in hematological diseases (26 patients, 56%), and neurological diseases (9 patients, 20%). While 15 patients were classified as ASFA category I, one patient as category II, 25 patients as category III, and 5 patients could not be classified. TPE was also applied to FIRES and transverse myelitis patients who were not included in the ASFA category. The best response was obtained in hematological diseases. Minor complications were observed in 19 (7%) procedures. There were no serious side effects or deaths associated with TPE in any of the patients.
Conclusion: TPE appears to be safe in this study, which detected no significant adverse events or deaths, linked to it. TPE was also applied to patients not included in the ASFA category, such as FIRES and TM. ASFA criteria may need to be revised as the number of centers performing TPE and the number of experiences increases.

Key words: American Apheresis Association guideline; Children; Pediatric Intensive Care; Therapeutic Plasma Exchange, Thrombotic Microangiopathy

Introduction:

In therapeutic plasma exchange (TPE), the patient`s plasma removed using centrifugation or filtration separation method. And it is replaced using replacement fluid, which can be fresh frozen plasma or 5% human albumin. The target of TPE is to remove pathological substances (autoantibodies, alloantibodies, monoclonal proteins, immune complexes, coagulation factors, cytokines, toxins, etc.) from the plasma and to replace a defective molecule as in atypical hemolytic uremic syndrome (aHUS) [(1)]. The American Apheresis Association (ASFA) guideline, which is the reference source for TPE and the current version was published in 2019, includes a list of evidence-based indications from which four categories were created [(1)]. However, ASFA data are based on adult patient data. Although apheresis is performed using the same principles as in adults, there are technical differences specific to children such as appropriate vascular access and volume distribution [(2)]. Despite the fact that TPE is a life-saving extracorporeal treatment modality, it cannot be used in patients due to some limitations. These limitations are: the indications are not clear, the blood product is not wanted to be used, the budget cannot be created to procure TPE devices and sets, and the lack of experienced personnel. Since this procedure is technically challenging in children, in our country it is performed only in centers where pediatric intensive care specialists are present. TPE studies in pediatric patients have been investigated in certain diseases, usually with a

small number of patients [3-5]. In order to improve the management of critical diseases, we planned to contribute to the literature by reviewing the indications, complications and treatment results of pediatric patients who was applied TPE according to the ASFA guideline.

Materials and Methods:

In this study, pediatric patients who underwent TPE in the pediatric intensive care unit between January 2018 and January 2021 were evaluated retrospectively. Our seventeen-bed pediatric intensive care unit (PICU) is a tertiary referral unit, where interventional procedures, such as TPE and CRRT can be performed safely. A total of 2142 patients were hospitalized over a 3-year period, and TPE was applied to 46 (2.1%) patients. Forty-six patients older than 28 days and younger than 18 years who had at least one TPE session were included in this study. *The study protocol was approved by the Institutional Ethics Committee with the decision number 2011-KAEK-25 2019/07-20.* Age and gender of patients, hospitalization diagnosis, admission location, pediatric risk of mortality (PRISM) score, TPE indication, number of TPE sessions, treatment complications, the need for mechanical ventilation, the need for vasoactive drug, number of organ failure, replacement fluid used, length of PICU and total hospital stay and outcomes were recorded. PRISM score was calculated at 24 h of admission. Patients who underwent TPE alone and along with continuous renal replacement therapy (CRRT) were recorded (Table 1). All patients were classified according to ASFA 2019 Guidelines[(1)]. Category I includes diseases in which TPE is accepted as first-line treatment, Category II in which TPE is second-line (alone or along with other agents), Category III diseases in which the optimum role of cannot be exactly determined and category IV in which no beneficial effect was shown or defined as harmful in existing studies [(1)].

TPE indications were divided into four groups as hematological disorders, neurological disorder, Sepsis with multiorgan dysfunction syndrome and others (renal, hepatic, rheumatological). The number of patients according to the groups, the ASFA category and the number of TPE sessions are indicated in Table 2. The International Pediatric Sepsis Consensus Conference guidelines were used to diagnose organ failure based on sepsis and organ dysfunction criteria for pediatric age groups [(6)]. To diagnose hemophagocytic lymphohistiocytosis (HLH), the HLH 2004 diagnostic criteria were used [(7)].

A temporary double-lumen central venous catheter suitable for the age of the patient was placed into the internal jugular vein or femoral vein. The inserted catheter was used only for extracorporeal procedures. It was closed with heparinized 0.9 percent saline after every use. TPE procedure was applied at the bedside by an experienced apheresis technician. The procedures were performed using Plasmart Versatile (Medica, Medolla, Italy) in 31 (67%) patients, and Plasma filters plasma Flux® Series P1dry/P2dry (Fresenius, Bad Homburg, Germany) in 15 (33%) patients using the filtration technique. Any device available in the hospital was used when needed. Acid-Citrate-Dextrose Formula A (ACD-A) was used as an anticoagulant. Routinely, 1 ml/kg calcium gluconate was supplied intravenously, and the ionized calcium level in blood gas was kept between 1 and 1.25 mmol/L. Fresh frozen plasma and 5% human albumin were used as replacement fluid.

All statistical analysis was performed using SPSS, ver. 22 (SPSS, Chicago, IL) and are displayed as median (range) and frequency (percentages) as appropriate. Comparative analysis between survivors and non-survivors was performed using the Mann–Whitney rank sum test and Pearson chi-square test. The distribution of variables was performed using the Shapiro-Wilk normality test and the Kruskal-Wallis test for the comparison of non-normally distributed variables between groups. Differences were considered statistically significant at p values less than 0.05.

Results:

In this study, total of 2142 patients were hospitalized over a 3-year period, and TPE was applied to 46 (2.1%) patients. Fourty six patients and 254 (1 – 14) sessions of TPE were retrospectively evaluated. Thirteen (28%) patients were younger than two years old. Thirteen (28%) patients needed invasive mechanical ventilation with a median duration of 15 (6–25) days. Ten (22%) patients needed inotropes and the PRISM score was 16.5 (10–24.5). While TPE was performed as sole procedure in 23 (50%) patients, the remaining 23 (50%) patients additionally received CRRT. As replacement fluid, fresh frozen plasma (FFP) was used in 35 (76%) patients, FFP and 5% human albumin in 7 (15%)

patients, and only 5% human albumin in 4 (8%) patients. Patient characteristics and technical details are shown in Table 1.

Table 1: patient characteristics and technical aspects of therapeutic plasma exchange

Patient characteristics	Median (IQR), n (%)
Age (months)	39 (19.5-112.7)
Gender (male/female)	20/26 (44/56)
Total number of procedures	254
Ventilated (yes/no)	13/33 (28/72)
Mechanical ventilation duration (days)	15 (6-25)
Need for inotropes (yes/no)	10/36 (21.7/78.3)
Number of organ failure	2 (2-3.25)
PRISM score	16.5 (10-24.5)
PICU LOS (day)	10 (6-18.25)
Hospital LOS (day)	24 (14-32.2)
Temporary catheter location **Internal jugular vein** **Femoral vein**	 41 (89) 5 (11)
Only TPE **TPE+ CRRT**	23 (50) 23 (50)
Replacement fluid **FFP** **FFP+ %5 Albumin** **%5 Albumin**	 35(76) 7(15) 4(9)

Abbreviation: CRRT, continuous renal replacement therapy; FFP, fresh frozen plasma; LOS, length of stay; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; TPE, Therapeutic Plasma Exchange

The most common indication for TPE was hematological diseases (26 patients, 56%). This was followed by neurological diseases (9 patients, 20%) and sepsis/multiple organ dysfunction syndrome (MODS) (5 patients, 11%). The remaining patients were classified as other. Fifteen (33%) patients were ASFA category I, 1 (2%) patient was category II, 25 (54%) patients were category III, and 5 (11%) patients could not be classified. TPE indications and ASFA category are shown in Table 2. While no life-threatening complications were observed in any of the 254 TPE sessions, minor complications were observed in 19 (7.4%) sessions. During the TPE procedure, the most common complication was set occlusion (n = 8; 3.1%), while hypotension (n = 4), allergic rash (n = 3), nausea-vomiting (n = 2) and hypocalcemia (n = 2) were other ones. Hypocalcemia and hypotension were noted only if it was symptomatic. The length of stay in PICU was 10 (6–18.2) days, and the total length of stay in the hospital was 24 (14–32.2) days.

Table 2: Diagnosis/Indication for Therapeutic Plasma Exchange and disease category

Diagnosis/ Indication for Therapeutic Plasma Exchange	n (%)	Number of TPE session	ASFA	Response to treatment
Hematologic disorder	26 (56)	169		22/26 (85%)
Hemolytic uremic syndrome				3 full response+ 2 no response
Atypical (complement mutations)	5 (11)	40	I	13 full response+ 4 partial response
Classical (STEC-HUS)	17(37)	111	III	full response+ no response
Thrombotic thrombocytopenic purpura	2(4)	10	I	full response+ no response
HLH	2(4)	8	III	
Neurologic disorder	9 (20)	43		7/9 (78%)
Guillain-Barre syndrome	4 (9)	20	I	4 full response
Autoimmune encephalitis	3 (7)	12	n.c.	2 full response+ no response
FIRES	1 (2)	6	n.c.	full response
Transverse myelitis	1 (2)	5	n.c.	no response
Sepsis with multiorgan dysfunction syndrome	5(11)	19	III	no response
Others	6(13)	23		3/6 (50%)
Steroid resistant glomerulosclerosis (FSGS)	2(4)	8	III	No response

Renal transplantation (antibody-mediated rejection)	1(2)	1	II	Partial response
Acute liver failure	2(4)	6	I	Full response
Wegener´s granulomatosis	1(2)	8	I	No response

Abbreviations: ASFA, American Society for Apheresis; FIRES, febrile infection-related epilepsy syndrome; HUS, hemolytic uremic syndrome STEC, shiga toxin- producing escherichia coli

The relationship between disease groups and age, organ failure count, PRISM score, replacement fluid used, need for invasive mechanical ventilation (MV), CRRT, inotrope requirement and mortality rate were evaluated. The age of the patients with hematological disease was significantly lower than the other groups (p: 0.027). Sepsis-MODS group had the highest PRISM score, organ failure, mechanical ventilation need, inotrope need and mortality rate (p<0.001). Table 3 gives results according to the diseases.

Table 3: Disease-specific outcomes

Variables	Hematologic Diseases median(IQR), n(%)	Neurological Diseases median(IQR), n(%)	Sepsis with MODS median(IQR), n(%)	Others Median(IQR), n(%)	P
Number of patients (n)	26	9	5	6	
Number of sessions	169	43	19	23	0.028
Age (mo)	27.5(17.7-50.2)	74(36-117.5)	64(5.5-162)	119(87.7-133)	0.027
Gender (male/female)	12/14(46/54)	4/5(44/56)	5/0(100/0)	2/4(33/67)	0.95
PRİSM score	15(9.5-23.2)	16(9-20)	31(27-36.5)	12(5.5-18.5)	0.005
Number of organ failure	2(2-3.2)	1(1-2)	4(4-4.5)	1(1-1.2)	<0.001
Need for MV n (%)	5(20)	3(33)	5(100)	-	0.001
Need for inotropes n (%)	4(15)	1(11)	5(100)	-	<0.001
Temporary catheter location n(%) **Internal juguler vein** **Femoral vein**	 22(85) 4(15)	 9(100)-	 4(80) 1(20)	 6(100) -	 0.43
Replacement fluid n(%) **FFP** **%5 Albumin** **FFP+ %5 albumin**	 26(100) - -	 0(0) 3(33) 6(67)	 5(100)- -	 4(68) 1(16) 1(16)	 <0.001
Only TPE n(%) **TPE+ CRRT n(%)**	8(31) 18(69)	9(100) -	1(20) 4(80)	5(84) 1(16)	 0.001
Number of complications n(%)	12(7.1)	2(22)	5(26)	2(32)	0.47
PICU stay (d)	14.5(8-16.5)	9(5-26.5)	11(5.5-24)	4(1.7-11.5)	0.13
Total hospital stay n (%)	25(22.5-31)	21(14.5-49.5)	29(15-42.5)	11(6.7-21)	0.13
Mortality, n (%)	3(11)	-	5(100)	-	<0.001

Others: Liver diseases, renal diseases, Rheumatologic disorder
Kruskal-Wallis Test

Eight (17%) patients died due to their existing illnesses. When comparing survivors and non-survivors, the non-survivors had significantly higher PRISM score, higher organ failure, more ventilation, inotrope and more CRRT need at admission to intensive care (respectively, p:<0.001, <0.001, <0.001, <0.001, 0.023). It was remarkable that TPE complications were more in those who did not survive (p:0.002). It was found that the number of TPE sessions, the duration of intensive care and hospital stay did not have a significant effect on mortality (p>0.05) (Table 4).

Table 4: Comparison of survivors and nonsurvivors

Variables	Survivors (n=38) Median (IQR), n (%)	Nonsurvivors(n=8) Median (IQR), n (%)	p
Age (mo)	39(21.5-100.5)	45(9.2-153.5)	0.7[a]
PRISM	14.5(8-20)	29.5(26.5-34.2)	<0.001[a]
Number of organ failure	2(1-1)	4(4-4.7)	<0.001[a]
Need for MV	5(13)	8(100)	<0.001[b]

MV time (d)	0(0-0)	15.5(5-24)	<0.001[a]
Need for inotropes (d)	2(5.2)	8(100)	<0.001[b]
Need for CRRT (d)	16(42)	7(87)	0.023[b]
Number of sessions	5(4-6.2)	4(1.5-9.2)	0.46[a]
PICU stay (d)	9(6-16.5)	13(5.2-25.5)	0.6[a]
Total hospital stay (d)	23.5(14-31)	28(9-40)	0.57[a]
TPE indication			
Hematological	23	3	
Neurological	9	-	<0.001[b]
Sepsis-MODS	-	5	
Others	6	-	
Complication			
No	25	2	
A blockage in the catheter	7	1	
Hypotension	-	4	
Allergic rash	2	1	0.002 [b]
Nausea and vomiting	2	-	
Hypocalcemia	2	-	

[a]Mann-Whitneu U test
[b]Ki-Kare test

Discussion:

The usage of TPE has been increasing over the past decades in patients who do not respond to conventional treatment. TPE data in pediatric patients are limited and most of them are based on adult studies [2, 8, 9]. Due to a lack of suitable equipment and experienced personnel in each hospital, its usage in children was limited. TPE indications in different pediatric centers vary depending on the specific areas of expertise of these centers. In centers with nephrology, hematology, neurology, and transplant facilities, there was a significant change in TPE indication rates [3, 5, 10, 11]. Our hospital is a tertiary referral institution where extracorporeal therapies such as TPE and CCRT are performed safely and where all pediatric services are available. This study contributed to the scarce literature in terms of diversity in the patient population with TPE applications in critically ill pediatric patients. TPE was applied to 2.1% (46 patients, 254 sessions) of patients over a three-year period.

Thrombotic microangiopathy (TMA) is defined with microangiopathic hemolytic anemia, thrombocytopenia and microvascular thrombosis causing end organ damage. Another point that should be considered is that some centers list TMA in the category of nephrological and some in the category of hematological diseases. The difference between TPE indications can only be understood by reviewing the categories, which the centers classify the diseases. In the TPE study by Cortina et al. in which 18 pediatric patients were evaluated, although renal diseases constituted 61% of patients, patients undergoing TPE due to TMA constituted 33% of all patients [12]. 60% of these patients had a response to TPE treatment [12]. In another study conducted on critical pediatric patients, where TMA was classified among hematological diseases, the most common indication for TPE was hematological diseases with a frequency of 30%, followed by nephrological diseases with 20% [5]. In this study, TMA was classified among hematological diseases. The indication for TPE in approximately half of the patients (56%) was hematological diseases. 22 (85%) patients had response to treatment in hematological diseases.

Complement-related HUS (aHUS) and infection-related STEC-HUS are classified as category III in ASFA 2019 TPE indications [1]. Although TPE is not the first choice for treating HUS, HUS is among the most common TPE indications, especially in studies conducted on pediatric patients [5, 12, 13]. It is decided according to the clinical response of the patient [1]. In this study, 17 (37%) patients received TPE due to STEC HUS, and 3 patients had seizures and acute changes in consciousness (decrease compared to baseline) as a neurological involvement. Six (35%) patients were under two years old. Thirteen (62%) patients recovered completely, four (19%) patients continue to use antihypertensive despite recovery. Neurological sequelae remained in none of the patients, and the seizure did not recur during

follow-up. aHUS, which is called complement-mediated TMA, is caused by the uncontrolled activation of the alternative complement system. In a study in which 273 patients with aHUS were screened, end-stage renal failure or death was reported as 48% in pediatric patients and 67% in adult patients [14]. Eculizumab, a monoclonal anti-C5 antibody, is a high-cost drug with proven efficacy for treating aHUS[15]. If Eculizumab cannot be started within the first 48 h, then TPE should be started [12]. Although the efficiency of TPE treatment has not been proven, it is commonly used in our country and many other countries when eculizumab cannot be reached immediately [3, 16, 17]. In this study, there were five (11%) cases of aHUS. Two of the patients are in remission and continue to use eculizumab. One patient achieved complete remission with TPE before eculizumab was available. A 26-month-old female patient with aHUS and Glutaric aciduria type 2 died due to MODS.

Thrombotic thrombocytopenic purpura (TTP) refers to TMA caused by ADAMTS13 deficiency, which is congenitally acquired by autoantibodies against ADAMTS13 and less frequently due to gene mutation [17].TTP should be suspected when unexplained thrombocytopenia and microangiopathic hemolytic anemia are present, and treatment should be initiated within the first 48 h, since it is mortal when untreated urgently [1]. TTP is one of the rarest indications for the emergency onset of TPE in ASFA recommendations [1]. In this study, two patients were accepted as TTP. One patient responded well to six sessions of TPE and steroids. The patient with low ADAMTS13 activity was accepted as an acquired TTP. Another patient was accepted as intubated from the external center intensive care unit due to status epilepticus and MODS. TPE performed four sessions daily, the patient who underwent simultaneous CRRT died on the fourth day of hospitalization. In this study, TPE was applied to two (4%) HLH patients. Seven sessions of TPE were performed on a 16-year-old patient. MODS were lost due to sepsis. Genetic analysis sent before the loss revealed the PRF1 p.Trp374 (c.1122G> A) mutation. HLH are a life-threatening disease characterized by excessive cytokine release from activated monocytes, macrophages and cytotoxic T lymphocytes (CTLs) [18]. HLH are in category III in the current ASFA classification. In a multi-center study conducted on critical pediatric patients, it was shown that 23 secondary HLH patients were successfully treated with plasma exchange, IVIG and steroids instead of the HLH-94 protocol [19].

One of the common indications of TPE is neurological diseases. The most common diseases are Guillain-Barré syndrome (GBS), N-methyl D-aspartate (NMDA)encephalitis and acute demyelinating encephalomyelitis (ADEM) [20]. In the study where 864 TPE sessions were applied to 230 adult patients, 89.5% of the patients were neurological diseases and 70.4% of them were GBS [10]. TPE is included in Category I for treating GBS, and it is recommended to apply it immediately [1]. Treatment should be started quickly as soon as the diagnosis is made. Plasmapheresis treatment accelerates recovery in motor nerves and decreases the duration of respiratory device support [21]. Four (9%) patients were treated for GBS, two (4%) patients needed mechanical ventilation (MV), all of them were transferred to the service with a good neurological clinic after plasmapheresis treatment. While NMDA encephalitis, one of the causes of autoimmune encephalitis, is in Category I for TPE in the ASFA guidelines, other autoimmune encephalitis have not been classified [1]. When the diagnosis of autoimmune encephalitis is considered, it is recommended to start TPE as a first-line treatment without waiting for antibody tests [22, 23]. TPE was applied to three (7%) patients due to autoimmune encephalitis, and two patients had significant clinical improvement. However, no improvement was observed in one (2%) patient. febrile infection-related epilepsy syndrome (FIRES) is a disease that occurs with refractory status epilepticus and progresses with cognitive and behavioral disorders in children with normal neuromotor development, and TPE is used in addition to immunotherapy [24]. In this study, one (2%) patient was evaluated as FIRES. The seizures of the patient who did not respond to IVIG treatment could be controlled with TPE. The American Academy of Neurology published an evidence-based guideline on the effectiveness of plasma exchange for neurological disorders, including transverse myelitis (TM) [25]. TM is not included among the categorized diseases in ASFA (1). However, plasma exchange may be considered in TM patients who do not improve with corticosteroid therapy [25]. Five sessions of TPE were performed in one (2%) patient for transverse myelitis and no clinical improvement was observed.

Sepsis is a systemic inflammatory response to infection caused by toxic mediators with tissue damage, multi-organ dysfunction (MODS), diffuse intravascular coagulopathy (DIC), and immune dysregulation [1]. Studies have shown that patients with multiple organ failure associated with thrombocytopenia (TAMOF) develop TMA and TPE can reverse organ dysfunction in this subgroup [26]. A decrease in mortality has been reported in patients with MODS who underwent TPE compared to standard treatment [27]. Sepsis induced MODS is considered ASFA category III. In a study evaluating 40 pediatric patients who underwent TPE, 10 (25%) patients died due to MODS due to sepsis [28]. In this study, 19 sessions of TPE were applied to 5 patients due to septic shock due to sepsis and MODS. TPE had no effect on survival. TPE had no effect on survival. The CRRT need, organ failure rate and PRISM score of the patients in this group were significantly higher than our other patient groups. All patients needed mechanical ventilation and inotropic. The reason for the high mortality in this group was attributed to the fact that it was performed in selected MODS patients with poor clinical conditions.

Immunosuppression therapy is used for treating of focal segmental glomerulosclerosis (FSGS), which causes nephrotic syndrome. The use of TPE together with corticosteroids and cyclophosphamide in recurrence is accepted as the standard treatment [21, 29]. In a study conducted with 174 patients, 14.5% of the patients and 22% of the TPE sessions were performed due to recurrent FSGS [30]. Steroid resistance in the native kidney is in category III in ASFA [1]. In this study, 8 sessions of TPE were performed in 2 patients due to steroid-resistant FSGS.

Acute liver failure has been defined as a rapid decline in liver function, which is characterized by jaundice, coagulopathy and hepatic encephalopathy in patients without liver disease [31]. Recently, the frequency of plasma exchange for treating liver failure has increased. In a randomized controlled study in 2016, it was reported that survival increased with plasma exchange in patients with acute liver failure [32]. It is category I in ASFA. In this study, 2 patients with acute liver failure due to Hepatitis A virus underwent 6 sessions of TPE, and their clinics completely recovered.

In this study despite the diversity of hematological diseases, we found a response to treatment in 22 patients (85%). Even though STEC-HUS was classified as Category III according to ASFA, 13 (62%) of the patients treated with TPE had complete remission and the others had partial remission. The course of patients in hematological diseases was more successful than the literature[3, 12]. Response was obtained in 7 (78%) of the patients treated for neurological diseases, which was consistent with the literature[20, 33]. However, patients in the sepsis with MODS group did not respond, and TPE did not contribute to the treatment. We think that our application to patients with severe septic shock, whose clinical course is worse than the literature, and whose general condition is very poor, is the reason for this[3]. Considering the TPE option in the early stages may provide a better response. Although we observed a very good clinical course in two patients with acute liver failure, there was no response in the patient with FSGS and Wegener's granulomatosis. Eight (17%) patients died due to their existing illnesses. When comparing survivors and non-survivors, the non-survivors had significantly higher PRISM score, higher organ failure, more ventilation, inotrope at admission to intensive care. It was determined that they needed CRRT. It was remarkable that TPE complications were more in those who did not survive. It was found that the number of TPE sessions, intensive care and hospital stay did not have a significant effect on mortality.

The limitation of this study is its retrospective nature and being single-center analysis.

Conclusion:

In this study, a total of 254 sessions of TPE were applied to 2.1% of the patients over a three-year period. There were no serious side effects or deaths associated with TPE in any of the patients. In children, TPE appears to be safe. TPE was also applied to patients not included in the ASFA category, such as FIRES and TM. ASFA criteria may need to be revised as the number of centers performing TPE and the number of experiences increases. More academic studies are needed to standardize the indications and technical aspects of TPE in children.

References:

[1] Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. Journal of clinical apheresis. 2019;34(3):171-354.

[2] Goldstein SL, editor Therapeutic apheresis in children: special considerations. Seminars in dialysis; 2012: Wiley Online Library.

[3] Sık G, Demirbuga A, Annayev A, Akcay A, Çıtak A, Öztürk G. Therapeutic plasma exchange in pediatric intensive care: Indications, results and complications. Therapeutic Apheresis and Dialysis. 2020;24(2):221-9.

[4] Chegini A, Moghadami M, Maghary AH. Therapeutic plasma exchange in Tehran between 2011 and 2014. Therapeutic Apheresis and Dialysis. 2020;24(2):230-4.

[5] Cortina G, McRae R, Chiletti R, Butt W. Therapeutic plasma exchange in critically ill children requiring intensive care. Pediatric Critical Care Medicine. 2018;19(2):e97-e104.

[6] Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine. 2005;6(1):2-8.

[7] Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric blood & cancer. 2007;48(2):124-31.

[8] Kim HC. Therapeutic pediatric apheresis. Journal of Clinical Apheresis: The Official Journal of the American Society for Apheresis. 2000;15(1-2):129-57.

[9] Carter CE, Benador NM. Therapeutic plasma exchange for the treatment of pediatric renal diseases in 2013. Pediatric Nephrology. 2014;29(1):35-50.

[10] Palma-Garcia L, Velásquez-Rimachi V, Pezo-Pezo A, Roig J, Perez-Villegas J. Therapeutic plasma exchange: Experience in a third level hospital, 2013–2016, Lima (Peru). Journal of clinical apheresis. 2018;33(4):480-5.

[11] Paglialonga F, Schmitt CP, Shroff R, Vondrak K, Aufricht C, Watson AR, et al. Indications, technique, and outcome of therapeutic apheresis in European pediatric nephrology units. Pediatric Nephrology. 2015;30(1):103-11.

[12] Cortina G, Ojinaga V, Giner T, Riedl M, Waldegger S, Rosales A, et al. Therapeutic plasma exchange in children: one center's experience. Journal of Clinical Apheresis. 2017;32(6):494-500.

[13] Conkar S, Mir S, Berdeli A. Genetics and Consequences of Atypical Hemolytic-uremic Syndrome in Turkish Children. Iranian Journal of Kidney Diseases. 2019;13(5).

[14] Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clinical Journal of the American Society of Nephrology. 2010;5(10):1844-59.

[15] Raina R, Krishnappa V, Blaha T, Kann T, Hein W, Burke L, et al. Atypical hemolytic-uremic syndrome: an update on pathophysiology, diagnosis, and treatment. Therapeutic Apheresis and Dialysis. 2019;23(1):4-21.

[16] Kara MA, Kılıç BD. Çocukluk Çağında Atipik Hemolitik Üremik Sendrom. Dicle Medical Journal/Dicle Tip Dergisi. 2018;45(4).

[17] Fernández-Zarzoso M, Gómez-Seguí I, de la Rubia J. Therapeutic plasma exchange: Review of current indications. Transfusion and Apheresis Science. 2019;58(3):247-53.

[18] Janka GE, Lehmberg K. Hemophagocytic syndromes--an update. Blood reviews. 2014;28(4):135-42.

[19] Demirkol D, Yildizdas D, Bayrakci B, Karapinar B, Kendirli T, Koroglu TF, et al. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: what is the treatment? Critical care. 2012;16(2):R52.

[20] Tolunay İ, Yıldızdaş D, İncecik F, Horoz ÖÖ, Ekinci F, Petmezci E, et al. Çocuk Yoğun Bakım Ünitemizde Terapötik Plazmaferez Uygulanan Nörolojik Hastalarımızın Değerlendirilmesi: 10 Yıllık

Deneyim. Çocuk acil Yoğun Bakım Dergisi. 2015;2:111-14.

[21] Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Writing Committee of the American Society for Apheresis: the seventh special issue. Journal of clinical apheresis. 2016;31(3):149-338.

[22] Zuliani L, Graus F, Giometto B, Bien C, Vincent A. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. Journal of Neurology, Neurosurgery & Psychiatry. 2012;83(6):638-45.

[23] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. The Lancet Neurology. 2013;12(2):157-65.

[24] Howell KB, Katanyuwong K, Mackay MT, Bailey CA, Scheffer IE, Freeman JL, et al. Long-term follow-up of febrile infection–related epilepsy syndrome. Epilepsia. 2012;53(1):101-10.

[25] Scott T, Frohman E, De Seze J, Gronseth G, Weinshenker BG. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011;77(24):2128-34.

[26] Nguyen TC, Han YY, Kiss JE, Hall MW, Hassett AC, Jaffe R, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. Critical care medicine. 2008;36(10):2878-87.

[27] Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive care medicine. 2002;28(10):1434-9.

[28] Keskin H, Paksu MŞ, Yener N, Köksoy ÖT, Kartal İ, Albayrak C, et al. Plasma Exchange in Critically Ill Children: A Single-center Experience. Cocuk Acil ve Yogun Bakım. 2018;5(1):10.

[29] Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clinical Journal of the American Society of Nephrology. 2017;12(3):502-17.

[30] Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. Journal of Clinical Apheresis: The Official Journal of the American Society for Apheresis. 2007;22(5):270-6.

[31] Tan EX-X, Wang M-X, Pang J, Lee G-H. Plasma exchange in patients with acute and acute-on-chronic liver failure: A systematic review. World Journal of Gastroenterology. 2020;26(2):219.

[32] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. Journal of hepatology. 2016;64(1):69-78.

[33] Bustos R, Hickmann L, Cruces P, Díaz F. Therapeutic plasma exchange in critically ill children: experience of the pediatric intensive care unit of two centers in Chile. Transfusion and Apheresis Science. 2021;60(5):103181.