International Journal of Nephrology and Renovascular Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Safety and Efficacy of Therapeutic Plasma Exchange in Pediatric Non-Neurological Diseases

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Introduction: Therapeutic plasma exchange (TPE) is a recognized treatment in pediatric immune-mediated and toxicological disorders, though evidence remains limited. This study assesses the safety and efficacy of TPE in children with non-neurological diseases treated at a tertiary hospital over 27 years. We focused on non-neurological indications to avoid excessive data heterogeneity.

Methods: This retrospective analysis included 97 children (51 nephrological, 46 non-nephrological), who underwent 380 TPE procedures between 1997 and 2023. Indications were categorized according to ASFA 2023 guidelines. Effectiveness was evaluated semi-quantitatively based on clinical and laboratory parameters up to 3 months post-treatment. Safety was assessed by incidence of adverse events (AEs), allergic AEs, and mortality.

Results: The most common indication was thrombotic microangiopathy (TMA, 23.7%), followed by toxicological and hematological disorders. TPE was effective (complete or partial improvement) in 67% of patients; full recovery occurred in 25.8%. In the nephrology group, eGFR increased 3.8-fold by 3 months post-TPE. However, immunosuppressive therapy was used 7.7 times more often in this group. The non-nephrological group had a higher mortality (26.1% vs 9.8%), mostly due to multiple organ failure. Intensive Care Unit admission and ASFA III indications significantly decreased survival odds. Fresh-frozen plasma (FFP) - based TPE was associated with significantly more AEs and interventions compared to TPE without FFP. Over time, FFP use declined, with 100% of TPEs in 2023 performed without FFP.

Conclusion: TPE is a safe and effective therapy in selected pediatric non-neurological conditions when performed in specialized centers.

Keywords: clinical adverse effects, pediatrics, therapeutic plasma exchange

Introduction

Therapeutic plasma exchange (TPE) is a procedure that involves exchanging the patient's plasma with either fresh-frozen plasma (FFP) or albumin solution and represents a highly effective extracorporeal procedure for selected immune - mediated diseases.

The American Society for Apheresis (ASFA) since 1986 have been publishing and in 2023 lastly updated the indications for TPE.[1] However, these criteria were developed for adult patients, as there are no specific standards for children population. Therefore, the decision to implement TPE in pediatric patients is usually based on adult guidelines and clinical experience. Although principles of TPE are the same in adults and children, there are some essential technical and physiological differences, such as vascular access, volume distribution value, or patient's hemodynamic stability, hence the risk of this form of therapy in children may seem to be higher comparing to adults, making decision about this type of treatment more demanding for pediatric nephrologists.[2–6]

https://doi.org/10.2147/IJNRD.S572328
Received: 5 October 2025
Accepted: 22 January 2026
Published: 30 January 2026

Although this problem has already been widely studied, we are convinced that clinicians' knowledge and awareness about TPE effectiveness and complications in children are still inadequate. Owing to the technically challenging nature of this procedure in children, it is mainly performed in specialized pediatric facilities. Hence, drawing on our experience, we conducted a retrospective study aimed at reporting our 27-year experience with TPE in pediatric patients who underwent the procedure for indications other than neurological disorders, with particular emphasis on its safety and efficacy. With these results we would like to expand the limited data on pediatric TPE in terms of their effectiveness and safety.

It should also be considered that indications for TPE are changing as disease-specific therapies evolve. For example, complement inhibitors have become central in complement-mediated thrombotic microangiopathy and modern immunosuppression strategies in immune-mediated diseases may increasingly refine the role of TPE over time.

We focused on non-neurological indications because neurological diseases have distinct pathophysiology and a separate evidence base; therefore, neurological TPE cases were analyzed separately to avoid excessive heterogeneity.[7]

Methodology

This study is a retrospective chart review of patients who were selected for the TPE procedure with membrane technique due to non-neurological diseases at the Department of Paediatric Nephrology and Hypertension Cracow, Poland, a tertiary reference center, during the period from January 1997 to December 2023. Studied population included patients from intensive care unit (ICU), nephrological and hematological units.

The local ethics committee approved the study (consent reference number 118.6120.187.2023), and informed consent was waived due to its retrospective nature. The study conducted a detailed analysis of data from the medical histories, TPE charts, and the outpatient documentation of each patient included in the study.

A TPE session was defined as a series of TPE procedures performed on a patient with less than a 4-week interval between each procedure. If the interval between TPE procedures was more than 4 weeks, then the TPE sessions were considered separate. It is related to the maximum duration for maintaining a double-lumen central venous catheter (CVC).

For statistical calculations, anthropometric data (age, body mass, height) recorded at the beginning of the given TPE session were considered. A detailed description of the studied population is presented in Table 1. The degree of indication for performing TPE for each patient was determined according to the most recent ASFA guidelines.[1] The decision to qualify a patient for TPE treatment was made, depending on the disorder, by a nephrologist, intensivist, or hematologist,

Table 1 Clinical Characteristics of the Studied Population and TPE Procedures, Along with a Comparison of Subgroups

Characteristics of Studied Population	**Non-Neph (46)**	**Neph (51)**	**Non-Neph vs Neph p-value (pW)**	**Total (97)**
Age [months]	115.0 (99.0)	135.5 (112.5)	NS	120.0 (104.4)
Age [years]*	9.6 (8.3)	11.3 (9.4)	NS	10.0 (8.7)
Body mass [kg]*	28.8 (24.6)	41.5 (34.5)	0.041	32.0 (32.4)
Body mass [pc]*	31.0 (59.8)	51.5 (59.5)	0.043	50.0 (58.0)
Height [cm]*	132.0 (42.8)	145.3 (49.5)	NS	137.5 (45.5)
Height [pc]*	34.0 (57.5)	45.5 (63.5)	NS	40.0 (60.8)
Hospitalization [number of days]	23.0 (25.0)	45.0 (42.8)	0.002	29.0 (39.3)
Duration of hospitalization to the start of TPE [days]	2.0 (5.5)	6.0 (13.0)	0.035	3.5 (10.5)
No. of days in ICU**	8.0 (14.0)	14.5 (44.5)	NS	9.0 (17.0)
QB [mL/kg/min]	2.5 (1.4)	2.1 (1.5)	0.042	2.2 (1.5)

(*Continued*)

Table 1 (Continued).

Characteristics of Studied Population	Non-Neph (46)	Neph (51)	Non-Neph vs Neph p-value (pW)	Total (97)
Duration of TPE procedure [min]	155.0 (60.0)	150.0 (101.3)	NS	150.0 (80.0)
Supplement exchange flow [mL/kg/h]	29.8 (26.1)	27.5 (21.0)	<0.001	28.5 (20.7)
Serum sodium after TPE [mmol/l]	140.0 (4.8)	139.0 (5.0)	0.006	139.0 (4.4)
Serum ionized calcium after TPE [mmol/l]	1.2 (0.1)	1.2 (0.1)	0.007	1.2 (0.1)
SBP median	110.0 (21.5)	125.0 (22.8)	<0.001	120.0 (22.0)
DBP median	65.0 (10.0)	78.0 (17.0)	<0.001	72.0 (21.0)
MAP median	80.0 (13.9)	93.3 (19.0)	<0.001	88.3 (21.3)
Median pc SBP	2.0 (3.0)	4.0 (3.0)	<0.001	3.0 (2.0)
Median pc DBP	2.0 (2.0)	4.0 (3.0)	<0.001	3.0 (3.0)
			p-value (pF)	
No. of sessions in ICU (% vs No. of sessions in the group) **	38 (80.9%)	16 (26.7%)	<0.001	54 (50.4%)
No. of TPE in ICU (% vs No. of TPE) **	81 (73%)	63 (23.4%)	<0.001	144 (37.9%)
Mean % of days in ICU (vs No. of hospitalization days) **	55.6	37.1	NS	50.0
No. of patients hospitalized in ICU during TPE session	31 (67.4%)	16 (31.4%)	0.001	47 (48.5%)
No. of patients with MOF during qualification to TPE	13 (28.3%)	1 (2%)	0.001	14 (14.4%)
No. of TPE FFP1 (% vs total no. of TPE)	96 (86.5%)	239 (88.8%)	NS	335 (88.2%)
No. of TPE FFP0 (% vs total no. of TPE)	15 (13.5%)	30 (11.2%)	NS	45 (11.8%)
ASFA I	2 (4.3%)	13 (25.5%)	0.004	15 (15.5%)
ASFA II	17 (37%)	14 (27.5%)	NS	31 (31.9%)
ASFA III	27 (58.7%)	9 (17.6%)	<0.001	36 (37.1%)
ASFA IV	0	5 (9.8%)	0.037	5 (5.2%)
ASFA not classified	0	10 (19.6%)	0.001	10 (10.3%)

Notes: Data are presented as medians and IQR (interquartile range), p-value Wilcoxon (pW) and absolute values with appropriately defined percentages, p-value one-sided Fisher test (pF). *Refers to 1 TPE procedure in each session **only patients who stayed in the Intensive Care Unit (ICU).

Abbreviations: TPE, therapeutic plasma exchange; Neph, nephrological; non-Neph, non-nephrological; NS, nonsignificant; QB, blood flow; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; pc, percentile; MOF, multiorgan failure; TPE FFP1, TPE with fresh frozen plasma; TPE FFP0, TPE without fresh frozen plasma; ASFA, American Society for Apheresis.

while the decision regarding the placement of an acute CVC and its size was made by nephrologist and an experienced surgeon. Dual-lumen catheters ranging from 8F to 12.5F were individually adapted to the child's morphology and body weight according to literature recommendations.[8,9]

Blood pressure values were presented in percentiles, rules of encoding are shown in Supplementary Data, as well as detailed data regarding TPE parameters, machines, anticoagulation, fluid supplementation.

The population was divided into a non-nephrological group (including cases with toxicological, hematological causes and patients in the ICU requiring TPE for various reasons) and a nephrological group. The semi-quantitative assessment of the effectiveness of TPE treatment was based on clinical evaluation of the patient and selected key laboratory parameters specific to the diagnosis, within a period of up to 3 months following the completion of TPE therapy. The treatment effectiveness was categorized as follows: 1) improvement – defined as the return of all clinical and laboratory

parameters to normal values or to pre-illness levels; 2) partial improvement – defined as a partial return of key clinical and laboratory parameters, relevant to the specific disease entity, to normal values or to pre-illness levels; 3) no improvement – defined as survival without improvement in the key clinical and laboratory parameters characteristic of the specific disease entity; 4) death.

Regarding 51 children from the nephrological group, the assessment of treatment effectiveness additionally included criteria developed by Paglialonga et al,[4] and the estimated glomerular filtration rate (eGFR) was calculated using the single-marker formula according to Schwartz et al.[10]

In the case of 46 children from the non-nephrological group, the clinical assessment additionally included liver injury criteria - applied to all children from the ICU population, the toxicology group, and 3 children from the hematology group—criteria described by Paglialonga et al.[4] In children with autoimmune hemolytic anemia, lactate dehydrogenase (LDH) activity and free bilirubin concentration were also assessed.

This article purposely does not encompass complications related to catheterization or technical issues associated with filters and machinery, as they were described in a separate paper.

Statistical Analysis

Statistical analysis was performed utilizing MATLAB software (The MathWorks Inc., 2022b; MATLAB version 9.13.0 (R2022b), Natick, MA, USA). Data were articulated as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) as appropriate. Distribution normality was assessed using the Shapiro–Wilk test with 0.1 threshold. Dependent upon the distribution of the variables, the following tests were employed: Student's *t*-test, rank Wilcoxon test, Fisher's exact test, and Pearson's linear correlation. For multivariate analysis, a generalized linear model (GLM) with backward elimination was utilized. A p-value of less than 0.05 was predetermined as the threshold for statistical significance. In the supplementary materials medians and IQR were featured for subgroups that did not meet the criteria for Shapiro–Wilk test.

Results

A total of 97 patients were enrolled in the analysis: 51 nephrological and 46 non-nephrological patients, in whom a total of 380 TPE procedures were performed (4.6 TPE/patient).

The study population consisted of:

1) 13 children hospitalized in the ICU with multiple organ failure (MOF), categorized as ASFA III, resulting from diverse etiologies: 5 patients with Reye's syndrome, 2 with hepatorenal syndrome, 1 with severe Crohn's disease, 1 with extensive burns, and 4 with sepsis of varying origins;

2) 21 patients with toxicological indications: 16 children had Amanita mushroom poisoning (ASFA II), and 5 had drug intoxications (ASFA III);

3) 12 hematological patients: 8 with hemolytic crisis due to hemolytic anemia (ASFA III), 2 with hyperviscosity syndrome secondary to hyperimmunoglobulinemia (ASFA I), 1 child with graft-versus-host disease (GvHD, ASFA II), and 1 child with MOF in the course of Hodgkin's disease (ASFA III);

4) 11 children with rapid progressive glomerulonephritis (RPGN): 3 with RPGN caused by granulomatosis with polyangiitis (GPA, ASFA I), 2 with RPGN - microscopic polyangiitis (MPA, ASFA I), 2 with RPGN - Goodpasture Syndrome (GPS, ASFA III), 3 with RPGN of unknown etiology without renal-replacement therapy (RRT, ASFA III), and 1 with RPGN of unknown etiology requiring RRT (ASFA I);

5) 13 children with severe systemic lupus erythematosus (SLE) and lupus nephritis (LN, ASFA II);

6) 4 children with focal segmental glomerulosclerosis (FSGS) in native kidneys due to steroid-resistant nephrotic syndrome (SRNS, ASFA III);

7) 23 children with thrombotic microangiopathy (TMA): 4 with deficiency of complement factor H-related plasma proteins and autoantibody positive associated hemolytic uremic syndrome (DEAP-HUS, ASFA I), 1 with complement factor H (FH) mutation (ASFA II), 1 with CD46 mutation (ASFA IV), 4 with Shiga toxin–producing Escherichia coli-associated HUS (STEC-HUS, ASFA IV), 3 with thrombotic thrombocytopenic purpura (TTP, ASFA I), and 10 with undiagnosed atypical HUS (aHUS, ASFA unknown).

The total number of TPE procedures over the study years, along with the number of TPE without FFP (FFP0) procedures, is presented in Figure 1. Trend analysis indicates that the overall number of TPE procedures decreased by an average of 0.5 per year between 1997 and 2023.

The largest group of children undergoing TPE were patients diagnosed with TMA/HUS (23.7% of patients; 26.3% of TPE procedures). The second most numerous group consisted of toxicology patients (21.6% of patients; 10.2% of TPE procedures).

In the nephrology group (Neph), the proportion of patients with ASFA I indications for TPE was 5.9 times higher compared to the non-nephrology group (non-Neph). Moreover, TPE procedures with ASFA IV and ASFA not classified indications occurred only in the Neph group, whereas the non-Neph group had more procedures for ASFA III indications.

In the Neph group, higher systolic, diastolic, mean arterial pressures, and corresponding percentiles were observed. This may result from the underlying disease profile, as hypertension is a common symptom in nephrological conditions (Table 1).

In the non-Neph group, both the total hospitalization time and the time to initiation of TPE were shorter compared to the Neph group. A detailed characterization of the study population, including the size of the analyzed subgroups and the number of TPE procedures performed within each, is presented in Tables 1, 2 and Supplementary Data – Tables 1S and 2S. Supplement dosing, configurations, premedication, and ASFA category distribution across subgroups are detailed in Supplementary Data Tables 2S–4S. Safety of the procedure was assessed by comparing TPE with FFP (FFP1) versus

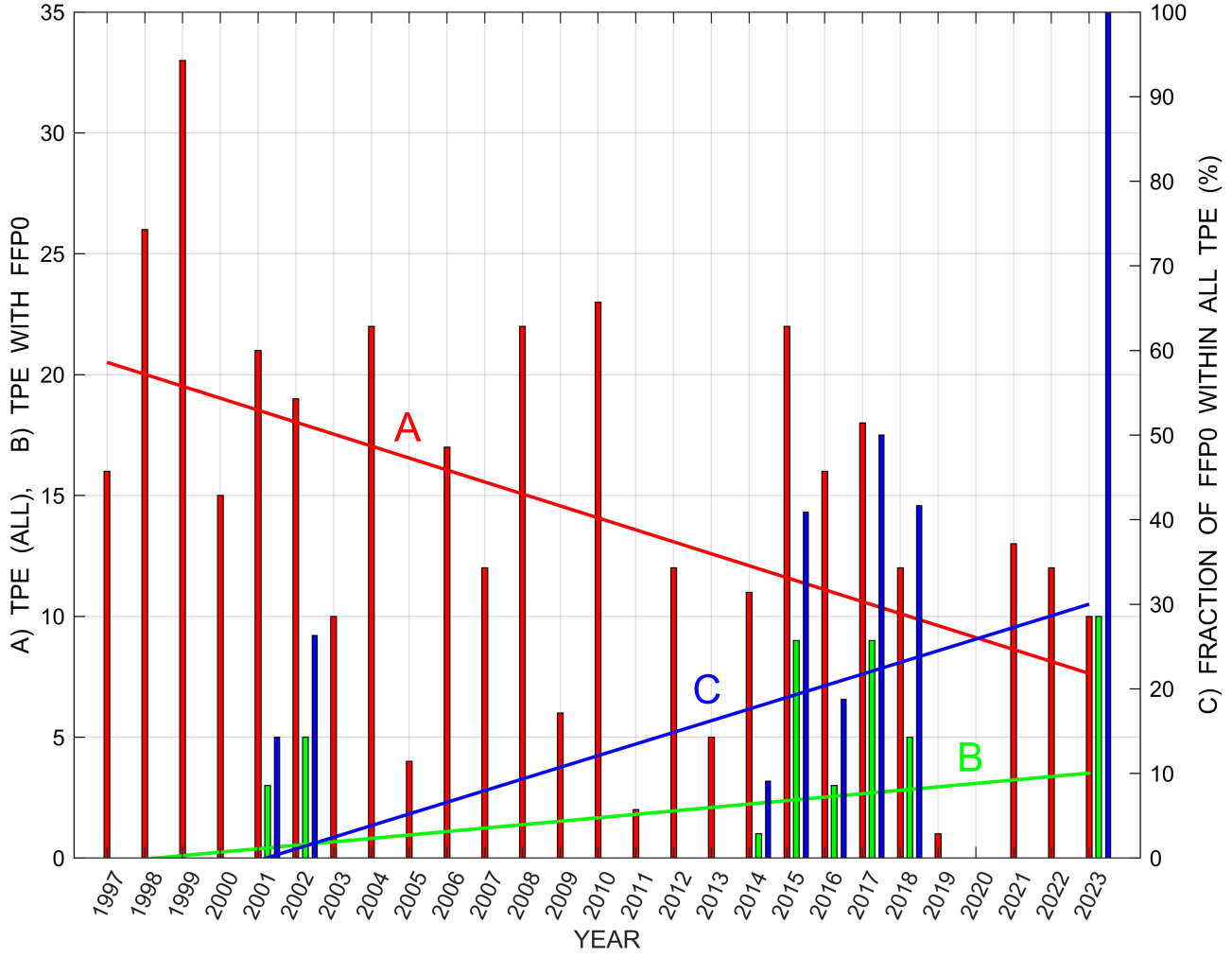

Figure 1 Number of all therapeutic plasma exchange (TPE) procedures in a given year (**A**), TPE procedures without fresh-frozen plasma (FFP0) (**B**), and the proportion of procedures FFP0 among all TPE procedures (**C**), from 1997 to 2023, with linear trend lines indicated.

https://doi.org/10.2147/IJNRD.S572328

Table 2 Clinical Characteristics of Patients During TPE Procedures

Patient Clinical Status (No. of Patients and % vs No. of TPE)	Non-Neph (46) TPE (111)	Neph (51) (TPE: 269)	Non-Neph vs Neph p-value (pF)	Total (97) TPE (380)
Good	31 (27.9%)	183 (68.1%)	<0.001	214 (56.3%)
Moderate	18 (16.2%)	30 (11.1%)	NS	48 (12.7%)
Serious	26 (23.4%)	20 (7.4%)	<0.001	46 (12.1%)
Critical	36 (32.5%)	36 (13.4%)	<0.001	72 (18.9%)
Good and moderate	49 (44.1%)	213 (79.2%)	<0.001	262 (69%)
Serious and critical	62 (55.9%)	56 (20.8%)	<0.001	118 (31%)
Conscious	76 (68.5%)	231 (85.9%)	<0.001	307 (80.8%)
Unconscious	35 (31.5%)	38 (14.1%)	<0.001	73 (19,2%)
No. of patients (%) requiring RRT during TPE (% vs No. of patients)	22 (47.8%)	33 (64.7%)	NS	55 (56.7%)
Survival up to 3 months after TPE (% vs No. of patients)	34 (73.9%)	46 (90.2%)	0.032	80 (82.5%)

Notes: Data are presented as number of TPE and appropriately defined percentage; p-value – one-sided Fisher test (pF); CT – data used within the same contingency table as in the previous line.
Abbreviations: TPE, therapeutic plasma exchange; RRT, Renal Replacement Therapy; Neph, nephrological; non-Neph, non-nephrological; NS, nonsignificant.

FFP0 groups, while efficacy was evaluated by comparing the semi-quantitative treatment response between nephrology and non-nephrology patient groups.

Safety

In the studied population, TPE procedures using FFP1 were predominant (88.2%). The median FFP dose was 30 mL/kg, and the FFP/total exchange volume ratio was 0.4 (IQR 0.2). Comparable proportions of procedures with and without FFP were performed in both the Neph and non-Neph groups. However, across the entire population, TPE FFP1 procedures were performed 7.5 times more often, and this group experienced a 2.1-fold higher rate of TPE with at least one allergic adverse event (AAE), 6.4-fold more procedures with moderate adverse events (AE), and 13.2-fold more TPE requiring intervention compared to the FFP0 group.

Overall, 33.9% of TPE procedures were associated with a clinical AE (30.2% after excluding agitation and anxiety), including 21.6% with at least one AAE. The proportion of patients with any AE was 64.9% (63/97), and 58.8% (57/97) after excluding agitation and anxiety. Since some patients underwent both FFP1 and FFP0 procedures, patient-level comparison by FFP group was not performed (Table 3 and Supplementary Data Table 5S). Nevertheless, trend analysis for TPE FFP0 procedures between 1997 and 2023 presents that the number of TPE FFP0 procedures increased by an average of 0.14 per year (1.4 per decade), and the proportion of TPE FFP0 relative to all TPE procedures increased by an average of 1.4% per year (14% per decade).

Mortality

Overall mortality in the study group was 17 deceases (17.5%). In the non-Neph group, 12 deaths (26.1%) were recorded. Of these, 11 patients died due to MOF: secondary to cardiac disease (2 patients), Reye's syndrome (4), burns (1), sepsis (1), and oncological disease (3). One child died of the primary disease (amanitin poisoning). In the Neph group, 5 deaths (9.8%) occurred: 3 due to the underlying disease (nephropathy, oncological disease, TMA), 1 due to MOF in the course of TMA, and 1 due to TRALI associated with TMA.

Table 3 Evaluation of Safety and Adverse Events (AE) During TPE in the Study Population, Categorized by Procedures with FFP (FFP1) and without FFP (FFP0)

No. of TPE with AE	**FFP1 (335; 88.2%)**	**FFP0 (45; 11.8%)**	**p-value FFP1 vs FFP0 (pF)**	**Total TPE (380)**
No. of TPE with at least 1 AE (% vs total No. of TPE)	118 (35.2%)	11 (24.4%)	NS	129 (33.9%)
No of TPE with at least 1 AE excluding anxiety/agitation	106 (31.6%)	9 (20%)	NS	115 (30.2%)
No. of TPE with more than 1 AE	35 (10.4%)	5 (11.1%)	NS	40 (10.5%)
No. of TPE with more than 1 AE excluding anxiety/agitation	28 (8.4%)	5 (11.1%)	NS	33 (8.7%)
No. of TPE with at least 1 AAE	77 (23%)	5 (11.1%)	0.046	82 (21.6%)
No. of TPE with mild AE* (% vs no. of TPE with AE)	49 (41.5%)	10 (90.9%)	NS	59 (45.7%)
No. of TPE with moderate AE** (% vs no. TPE with AE)	69 (58.5%)	1 (9.1%)	0.001	70 (54.3%)
No. of specific AEs (% vs no. of TPE)	**FFP1 (335; 88.2%)**	**FFP0 (45; 11.8%)**	**p value FFP1 vs FFP0 (pF)**	**Total (380)**
Blood pressure decrease / hypotension	27 (8.1%)	3 (6.7%)	NS	30 (7.9%)
Shivers / sensation of cold	32 (9.6%)	1 (2.2%)	NS	33 (8.7%)
Skin allergic reaction	11 (3.3%)	1 (2.2%)	NS	12 (3.2%)
Nausea / vomiting	12 (3.6%)	2 (4.4%)	NS	14 (3.7%)
Dyspnea	7 (2.1%)	1 (2.2%)	NS	8 (2.1%)
Total AAE	**89 (26.6%)**	**8 (17.8%)**	**NS**	**97 (25.5%)**
Anxiety / Agitation	26 (7.8%)	2 (4.4%)	NS	28 (7.4%)
Abdominal pain	7 (2.1%)	0	NS	7 (1.8%)
Increased blood pressure	21 (6.3%)	4 (8.9%)	NS	25 (6.6%)
Back pain	4 (1.2%)	0	NS	4 (1.1%)
Headache	4 (1.2%)	0	NS	4 (1.1%)
Fever	5 (1.5%)	0	NS	5 (1.3%)
Muscle tremors / paraesthesia	7 (2.1%)	0	NS	7 (1.8%)
Arrythmia	5 (1.5%)	0	NS	5 (1.3%)
Others (paleness; photophobia)	2 (0.6%)	0	0.01	2 (0.5%)
Total no. of AE	**170 (50.7%)**	14 (31.1%)	**0.010**	**184 (48.4%)**
Total no. of AE excluding anxiety /agitation	**144 (43%)**	12 (26.7%)	**0.025**	**156 (41%)**

Notes: Data are presented as number and percentage vs number of TPE with AE. AEs resulting from underlying disease and complications related to vascular access were not included in the table. Bold formatting is used to separate section headers and to highlight subtotal and total rows. *Mild AE – no interventions required, **moderate AE – interventions required, but TPE continued.

Abbreviations: TPE, therapeutic plasma exchange; AE, adverse event; AAE, allergic AE; NS, nonsignificant.

Due to more severe baseline status, including a higher proportion of unconscious patients, the non-Neph group had a 2.7-fold higher mortality. Most MOF cases at TPE qualification (92.6%) occurred in this group. Of 39 TPE sessions during MOF, 12 ended in death (non-Neph: 11; Neph: 1). ICU admissions and ICU-based TPE were 2.1 and 3.2 times more frequent in the non-Neph group, respectively (Table 1).

In the non-survivor group, the proportion of sessions involving MOF was 4.1 times higher vs survivor group, while the survival probability with TPE during MOF was 56%. Detailed survival rates by subgroups are presented in Table 4.

Despite better survival in the Neph group, 3.6 times more survivors showed no clinical improvement, leading to end-stage kidney disease (ESKD) in 21.6% of cases. Overall improvement rates were similar between groups (Table 5). Each additional year of age increased survival odds by nearly 2% based on univariate logistic regression, while ICU stay, ASFA III indication, and PICU status reduced them by 73%, 76%, and 84%, respectively (Table 6).

Table 4 Comparison of the Survival vs Non-Survival Groups Based on Selected Parameters

Variable	**Non-Survival (17)**	**Survival (80)**	**pW**
Age [months]	65.0 (74.8)	134.8 (98.0)	0.003
Body mass [kg]	21.0 (13.1)	36.5 (32.9)	0.006
Height [cm]	110.5 (38.0)	141.5 (46.0)	0.005
Hospitalization [number of days]	19.0 (20.5)	33.5 (39.0)	0.056
No. of days in ICU (only if > 0)	9.0 (22.3)	9.0 (14.8)	NS
Days in ICU vs hospitalization days (only patients in ICU) [%]	100.0 (60.6)	30.0 (40.5)	0.003
No. of TPE sessions (% vs total session no.)	**17 (15.9%)**	**90 (84.1%)**	**pF**
No. of TPE with RRT	9 (52.9%)	48 (53.3%)	NS
No. of TPE sessions with MOF	17 (100.0%)	22 (24.4%)	<0.001
No. of TPE sessions in ICU	15 (88.2%)	39 (43.3%)	0.001
No. of TPE (% vs 380)	**48 (12.6%)**	**332 (87.4%)**	**pF**
No. of TPE in ICU	42 (87.5%)	102 (30.7%)	<0.001
No. of patients in subgroups	**Non-Survival (% vs 17)**	**Survival (% vs 80)**	**pF**
ICU (13)	9 (52.9%)	4 (5.0%)	<0.001
Toxicology (21)	1 (5.9%)	20 (25.0%)	NS
Haematology (12)	2 (11.7%)	10 (12.5%)	NS
RPGN (11)	0 (0.0%)	11 (13.7%)	NS
SLE (13)	0 (0.0%)	13 (16.3%)	NS
FSGS (4)	1 (5.9%)	3 (3.7%)	NS
TMA (23)	4 (23.5%)	19 (23.8%)	NS
ASFA categories	**Non-Survival (% vs 17)**	**Survival (% vs 80)**	**pF**
ASFA I	1 (5.9%)	14 (17.5%)	NS
ASFA II	2 (11.8%)	29 (36.2%)	0.041
ASFA III	11 (64.7%)	25 (31.2%)	0.011
ASFA IV	0	5 (6.3%)	NS
ASFA not classified	3 (17.6%)	7 (8.8%)	NS

Notes: Data are presented as medians and IQR (interquartile range), p-value Wilcoxon (pW), and absolute values with appropriately defined percentages, p-value one-sided Fisher test (pF). Bold formatting is used to separate section headers and to highlight subtotal and total rows.
Abbreviations: TPE, therapeutic plasma exchange; ICU, intensive care unit; MOF, multiple organ failure; RPGN, rapid progressive glomerulonephritis; SLE, systemic lupus erythematosus; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy; ASFA, American Society for Apheresis; NS, nonsignificant.

Table 5 Effectiveness of TPE Treatment According to ASFA Categories, General Groups, and Detailed Diagnostic Subgroups

	Complete Improvement (25)	Partial Improvement (40)	No Improvement (15)	Non-Survival (17)
ASFA I (15)	4 (26.7%)	8 (53.3%)	2 (13.3%)	1 (6.7%)
ASFA II (31)	13 (41.9%)	12 (38.7%)	9 (25%)	11 (30.6%)
ASFA III (36)	3 (8.3%)	13 (36.1%)	9 (25%)	11 (30.6%)
ASFA IV (5)	1 (20%)	4 (80%)	0	0
ASFA not classified (10)	4 (40%)	3 (30%)	0	3 (30%)
Non-Neph (46)	14 (30.4%)	17 (37%)	3 (6.5%)	12 (26.1%)
Neph (51)	11 (21.6%)	23 (45.1%)	12 (23.5%)	5 (9.8%)
p-value (pF)	NS	NS	0.019	0.032
All patients (97)	25 (25.8%)	40 (41.2%)	15 (15.5%)	17 (17.5%)

Notes: Data are presented as percentages vs no. of patients in the given group; p-value Fisher (pF).
Abbreviations: ASFA, American Society for Apheresis; Neph, nephrological; non-Neph, non-nephrological; NS, nonsignificant.

Table 6 Univariate Logistic Regression Analysis Evaluating the Influence of Selected Variables on Mortality in the Studied Population

Studied Variable	p-Value	OR	CI95
Age [years]	0.001	1.019	1.008–1.031
Body mass [kg]	0.008	1.053	1.013–1.095
Height [cm]	0.001	1.036	1.014–1.058
TPE procedure performed during ICU stay	0.031	0.268	0.081–0.888
ASFA III	0.009	0.234	0.078–0.697
Population of patients in ICU	0.004	0.155	0.044–0.544

Abbreviations: TPE, therapeutic plasma exchange; ASFA, American Society for Apheresis; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Efficacy

In the overall study population, complete clinical recovery was observed in 25.8% of patients; complete or partial improvement in 67%; while no improvement was noted in 15.5%. There were no differences in rates of complete or partial improvement between non-Neph and Neph groups (Table 5).

Improvement in eGFR was observed after TPE and at 3 months post-TPE in all Neph subgroups except FSGS. Data refer to values before the first TPE session and only included surviving patients who did not require RRT, either immediately after TPE or at 3-month follow-up. In the FSGS group, 3 patients developed ESKD post-TPE, and 1 died, therefore eGFR could not be assessed in that group.

In the entire Neph population, median eGFR increased 3.2-fold immediately after completing TPE and nearly 3.8-fold at 3 months. No significant difference was observed between the post-TPE and 3-month eGFR gains. Median eGFR values before TPE, after the procedure session, and 3 months post-TPE for the nephrology subpopulations are presented in Table 7.

Taking into account the whole study population, partial or complete improvement was achieved in 90.5% of toxicology cases; in the TMA group – 82.6%; and in the SLE group – 69.2%. In the hematology and RPGN groups,

Table 7 Change in eGFR Values Before and After TPE Procedures, and After a 3-month Follow-up in the Population That Survived

eGFR [mL/min] [Medians]	RPGN (11)	SLE (13)	FSGS (4)	TMA (23)	Total Nephrological Population (51); (TPE - 269)
eGFR before TPE [mL/min]	8.5 (12.0)	36.0 (34.9)	31.0 (66.8)	23.3 (58.5)	24.0 (38.8)
eGFR after TPE	52.1 (28.7)	68.5 (50.0)	27.0 (0.0)	98.0 (51.0)	77.0 (54.2)
eGFR 3 months after TPE	53.8 (26.1)	84.5 (44.0)	NA	99.5 (19.0)	90.0 (42.3)
No. of patients requiring RRT 3 months after TPE (ESKD) (% vs no. of patients)	5 (45.5%)	2 (15.4%)	3 (75%)	1 (4.3%)	11 (21.6%)
p-value before vs after TPE	0.004	0.023	NS	<0.001	<0.001
p-value before vs after 3 months	0.001	0.005	No data	<0.001	<0.001

Notes: Data are presented as medians and IQR (interquartile range), p-value Wilcoxon, and absolute values.
Abbreviations: TPE, therapeutic plasma exchange; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; RPGN, rapid progressive glomerulonephritis; SLE, systemic lupus erythematosus; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy; NS, nonsignificant.

no cases of complete improvement were observed, while in the FSGS group, no improvement was achieved in any patient. Table 6S in Supplementary Data presents TPE efficacy by diagnostic subgroup for the entire study population.

In the ASFA I group, immunosuppressive (IS) therapy was used in 80% of cases; in ASFA II – 48.4%; in ASFA III – 27.8%; and not at all in ASFA IV. This demonstrates a clear decline in IS use with decreasing TPE indication strength, consistent with the underlying disease mechanisms assigned to ASFA categories. Across the entire population, IS treatment was used in 39.2%. Thus, outcomes in ASFA I and II groups also reflect the effects of adjunctive therapies such as IS, intravenous immunoglobulin (IVIG), and glucocorticoids (GCs).

The use of GCs and IVIG was similar between Neph and non-Neph groups; however, IS therapy was used 7.7 times more frequently in the Neph group, reflecting the nature of the underlying nephrological conditions. Detailed data on GCs, IVIG, and IS use are presented in Table 8.

Table 8 Incidence of Glucocorticoids (GCs), Intravenous Immunoglobulins (IVIG), and Immunosuppressants (IS) Use According to ASFA Categories, in General Groups, and Detailed Diagnostic Subgroups (% Vs Number of Patients in the Group)

	GCs	IVIG	IS
ASFA I (15)	13 (86.7%)	4 (26.7%)	12 (80%)
ASFA II (31)	28 (90.3%)	2 (6.5%)	15 (48.4%)
ASFA III (36)	29 (80.6%)	14 (38.9%)	10 (27.8%)
ASFA IV (5)	3 (60%)	2 (40%)	0
ASFA not classified (10)	5 (50%)	3 (30%)	1 (10%)
Non-neph (46)	35 (70.1%)	15 (32.6%)	4 (8.7%)
Neph (51)	43 (84.3%)	10 (19.6%)	34 (66.7%)
p-value (pF)	NS	NS	<0.001
All patients (97)	78 (80.4%)	25 (25.8%)	38 (39.2%)

Abbreviations: ASFA, American Society for Apheresis; Neph, nephrological; non-Neph, non-nephrological; NS, nonsignificant; Pf, p-value Fisher.

Discussion

To the best of the authors' knowledge, only few studies on TPE have addressed populations outside of neurological patients or only focused on ICU patients. This study aimed to fill that gap by presenting epidemiological data on pediatric patients without neuroimmunological diseases.

Safety

Overall mortality in the studied population was 17.5%, but it was primarily related to critical condition of the patients and underlying diseases, not procedure-associated complications.

The non-Neph group had higher mortality rate compared to the Neph group, which likely reflects more severe baseline condition, more frequent ICU-based TPE, a higher proportion of ICU hospitalizations, and a greater incidence of MOF (confounding by indication). According to available literature, mortality rates among patients undergoing TPE vary significantly depending on the eligibility criteria for the procedure: lower rates are observed in nephrological patients – such as no deaths,[4,11] while higher rates are reported in ICU settings, up to 28.4%[12–15] and 33% in septic, adult plasmapheresis-treated patients.[16]

In our study, FFP was the primary replacement fluid. Its extended use in earlier years, before updated guidelines and albumin availability, likely explains the higher rate of allergic reactions, as FFP is a known individual risk factor for hypersensitivity.[17,18] Joseph et al reported allergic reactions in 13.4% of TPE with FFP, with none using albumin.[18] These findings highlight the importance of replacement fluid choice in reducing TPE-related complications.

The most common diagnosis in our cohort was TMA, and before advanced TMA diagnostics became available, TPE with FFP was administered in all non-STEC-HUS cases - accounting for 26.3% of TPE procedures. Other major indications for TPE FFP1 included MOF (10.3%), toxicological causes including amatoxin poisoning (10.3%), and hematological disorders (11%). These indications alone account for 57.9% of all TPE procedures in this study.

Nonetheless, due to AE associated with FFP, the use of TPE without FFP in our center was gradually introduced starting in 2001, especially after 2014. By 2023, 100% of TPE procedures were performed without FFP, a trend observed worldwide. This may be attributed to evolving treatment options and IS therapy protocols introduced over time such as the PEXIVAS trial, which showed that among patients with severe ANCA-associated vasculitis, TPE did not reduce the incidence of death or ESKD,[19] as well as advances in TMA diagnostics, which reduced the need for TPE with FFP.[20]

In the FFP1 group, the rates of AAE, moderate AEs requiring intervention, and interventions themselves were higher compared to FFP0 procedures, as seen in the literature.[17]

Although no severe AEs requiring premature termination of TPE were observed in the study population, one TMA patient died within 24 hours of completing TPE FFP1 due to TRALI. This occurred at a time when guidelines by The European Pediatric Study Group for HUS recommended FFP substitution upon diagnosis of aHUS.[21]

The incidence of allergic and severe reactions to FFP was reported in a systematic review and meta-analysis conducted by Saadah et al. Across various indications for transfusion, allergic reactions occurred at a rate of 92 per 100,000 units transfused, transfusion-associated circulatory overload (TACO) at 6 per 100,000 units, and TRALI at 1.8 per 100,000 units.[22]

The relatively high rate of TPE procedures and patients with AEs in this study, aside from FFP use, may also be attributed to other factors. One is the phenomenon of bioincompatibility, resulting from hypersensitivity to ethylene oxide (EtO), which was used to sterilize extracorporeal circulation lines and TPE filters during the early years of the study. Its clinical manifestations - such as hypotension, dyspnea, cough, vomiting, pruritus, urticaria, fever, headache, and confusion - closely resembled allergic reactions and could affect up to 15% of procedures.[23,24] It was only in later years that steam - and gamma radiation - sterilized components became available.

Another contributing factor to AAE may have been 6% hydroxyethyl starch (HES), which was frequently used in the early observation period of this study. This compound is known to potentially cause severe allergic reactions[25] and was used as a replacement fluid in various configurations during 176 TPE procedures (46.3%) due to lack of access to 5% albumin then.

Moreover, allergic reactions to albumin and heparin have been reported in the literature.[3]

It should also be considered that some AEs (eg, hypotension, nausea, vomiting, abdominal pain, headache) may have reflected the underlying disease or concurrent pharmacotherapy rather than the TPE itself.

Efficacy

In the non-Neph group, TPE procedures were conducted only for ASFA I–III indications, while in the Neph group, procedures were performed across all ASFA categories. However, only 41.3% of TPEs in the non-Neph group were for ASFA I–II indications, compared to 53% in the Neph group.

Among surviving Neph patients, the rate of no clinical improvement was 3.6 times higher than that in the non-Neph group. Thus, although the baseline condition in the non-Neph group was more severe, TPE was less frequently ineffective in this group.

Across the studied population, 67% showed complete or partial clinical improvement after treatment courses that included TPE. Since renal recovery in Neph patients likely reflected both TPE and frequent use of adjunctive IS therapy, the independent contribution of TPE cannot be fully determined.

TPE was found to be effective in various pediatric studies,[4,26–29] with eGFR increase at a rate of 50% of patients at a follow-up.[27]

In the overall cohort, the most common indication for TPE was TMA, with aHUS being the leading diagnosis, distribution similar to Mazahir et al.[5]

Among patients diagnosed with HUS/TTP, complete or partial remission was described in 91.6% of children in multi-center study by Paglialonga[4] and in 62% of children with atypical HUS in the analysis by Noris et al.[30] Efficacy is known to vary by underlying mutation or antibody profile: the highest efficacy (55%–80%) was achieved in cases with mutations in the genes encoding CFH, C3, THBD, or in the presence of antibodies against these proteins, whereas low efficacy was observed in the presence of a CFI mutation.[30]

The highest rates of clinical improvement were observed in the toxicology group (treated as ASFA II and III), the TMA group (treated as all ASFA categories except III), and the SLE group (ASFA II). Despite 54.5% of RPGN procedures being performed for ASFA I indications, no complete clinical improvement was achieved in this group.

Similarly, no improvement was observed in either the hematology group (with 75% ASFA III indications) or the FSGS group (ASFA III), where no patient experienced any clinical benefit. The FSGS subgroup was small (4), therefore, no conclusion on efficacy in FSGS affecting native kidney can be drawn, and the findings should be interpreted cautiously. Fencl et al observed, though on a small group of patients, that remission in native kidney in recurrent FSGS can be achieved on condition of early initiation of the TPE.[31] Current studies are investigating whether lipoprotein apheresis will prevent the progression of renal disease in drug-resistant nephrotic syndrome, based on a hypothesis that podocyte function can be affected by lipotoxic environment created by hypercholesterolemia.[32,33]

We acknowledge several limitations: retrospective, single-center design; 27-year observation period with evolving TPE protocols and equipment; heterogeneous study population especially in the Neph group; which necessitated reliance on semi-quantitative efficacy assessment and warrants cautious interpretation of efficacy outcomes given changing standards of care over time. Evaluation in TMA is particularly complex given advances in diagnostics and therapies, including anti-C5 monoclonal antibodies, which have replaced (in the majority of the cases) TPE in complement-mediated HUS.[20,34] Given the complexity of many cases - particularly ICU-based indications - decisions to initiate, continue, or discontinue TPE should be made through multidisciplinary discussion, disease severity, and available alternative therapies.

Despite its retrospective single-center design, this dataset may help inform pediatric apheresis practice by: (1) supporting patient selection, as outcomes differed by indication and baseline severity (with ICU/MOF and ASFA III associated with poorer survival), (2) guiding replacement fluid choice, given the higher AE/intervention rates observed with FFP and the shift toward FFP-free procedures when clinically appropriate, reserving FFP for indications requiring plasma factor replacement and (3) improving AE anticipation by identifying settings and procedures associated with higher complication risk, supporting tailored monitoring and preparedness in pediatric centers.

Further multicenter and prospective studies that enroll more homogeneous diagnostic populations and use standardized outcome definitions are needed to confirm our observations and to better delineate evidence-based indications for TPE in pediatric non-neurological conditions.

In Summary

TPE appears to be a safe and effective treatment, with the majority of patients experiencing complete or partial clinical improvement. The use of FFP as a replacement fluid during TPE was associated with a higher likelihood of AE and an increased need for clinical interventions.

In renal conditions, notable improvement in kidney function was observed following TPE. However, due to the nature of the underlying diseases, these patients more frequently required concurrent immunosuppressive therapy. Therefore, the clinical benefit of TPE in this population should be interpreted in the context of other standard treatments.

ICU stay and ASFA III or IV indication were independently associated with reduced survival odds in non-neurological indications.

In conclusion, TPE is an effective therapeutic option with a low rate of severe complications in pediatric renal and non-renal conditions. When performed in experienced and properly equipped centers, it is safe even for small children.

Ethics Statement

This study was approved by the Bioethics Committee of the Jagiellonian University, Cracow, Poland and was conducted in accordance with the principles of the Declaration of Helsinki. Participants privacy was protected by anonymizing all study data and handling it under strict confidentiality procedures.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing interests or personal relationships that could have appeared to in the work reported in this paper. The authors have no funding to disclose.

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