Key technical aspects and vascular access safety in membrane-based therapeutic plasma exchange for the pediatric population

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Abstract

Introduction: Therapeutic plasma exchange (TPE) is a widely used extracorporeal blood purification procedure. While its principles are similar across age groups, the technical complexity and risks are heightened in pediatric patients due to unique technical considerations. This study assessed the safety regarding both technical and clinical complications of vascular access and membrane-based TPE filters in a pediatric population at a single center.
Material and methods: This retrospective cohort study reviewed charts of patients undergoing TPE at a level 3 referral center over 25 years.
Results: The study involved 178 patients undergoing a total of 740 procedures during 214 sessions, predominantly using femoral vascular access. The median duration of the entire TPE sessions (treated as a surrogate for catheter lifespan) was 118.5 hours. Technical complications occurred in 20.8% of procedures (31.6% of events), while clinical complications occurred in 4.2% (4.7% of events). Technical complications were nearly five times more frequent than clinical complications, with technical events being 6.7 times more common. The proportion of patients experiencing clinical complications was 15.2%. Logistic regression demonstrated that each additional day of catheter placement increased the probability of technical complications by 3%. Additionally, each year of patient age decreased the likelihood of clinical complications by 8.9%, while fresh frozen plasma (FFP) supplementation within a session increased the probability of clinical complications by 21.6%.
Conclusions: Prolonged catheter use increases technical events, while FFP supplementation elevates catheter-related clinical complication risk. Advancing patient age reduces the likelihood of clinical complications, underscoring age-specific safety considerations in pediatric TPE.

Key words: children, filter, central catheter, therapeutic plasma exchange, technical adverse effects, clinical adverse effects.

Introduction

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification procedure employed in clinical settings. It functions on the principle of eliminating dissolved pathogenic entities, such as autoantibodies or immune complexes, from the blood plasma while simultaneously replenishing essential plasma components. This technique is applied across a broad spectrum of medical disciplines, particularly in neurology, hematology, rheumatology, metabolic disorders, nephrology, and selected aspects of toxicology [1].

The fundamental principles of TPE are consistent between adults and children; however, several technical distinctions exist, including the establishment of vascular access, differences in volume of distribution, and increased vascular complications associated with smaller blood vessels. Additionally, the lack of patient cooperation during the procedure contributes to the overall risk and technical complexity, making this form of therapy more challenging in children than in adults [2]. Although there are studies on the clinical indications and complications associated with this technique in the pediatric population, research focusing solely on technical issues in this field remains somewhat scarce. Hence, we decided to analyze our 25-year experience with TPE in children, with a particular emphasis on vascular access, filter issues, and anticoagulation challenges in this heterogeneous patient population.

The objective of this study was to assess the safety of vascular access, including central venous catheters (CVC), filters, anticoagulation, and the performance of membrane technique components in TPE conducted over a 25-year period in a pediatric population with neurological and non-neurological conditions at a single tertiary referral hospital.

Material and methods

This study is a retrospective chart review of patients who were deemed eligible for the TPE procedure due to neurological and non-neurological conditions, performed at the Pediatric Nephrology and Hypertension Clinic in (blinded for review) between January 1998 and December 2022. The non-neurological group included patients from the intensive care, pediatric nephrology, and pediatric hematology departments.

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 and TPE charts 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 four-week interval between each procedure. If the interval between TPE procedures was four or more weeks, then the TPE sessions were considered separate. This is related to the maximum duration of use for an acute dual-lumen catheter.

Due to the inability to obtain precise data regarding the time of implantation of the dual-lumen CVC for TPE, for statistical purposes in this review, the duration of the session was adopted as a surrogate for the lifespan of the given catheter. If a single TPE procedure was conducted within a given session, the duration of that procedure was considered equal to the CVC utilization time.

For statistical calculations, anthropometric data (age, body mass, height, and corresponding percentile values) recorded at the beginning of the given TPE session were considered. The categorization of indications for performing TPE for each patient was determined according to the most recent guidelines of the American Society for Apheresis (ASFA) [3].

The decision to determine eligibility of a patient for treatment using the TPE method was made based on the primary diagnosis by the specialist neurologist, nephrologist, intensivist, or pediatric hematologist, while the decision regarding the placement of an acute dual-lumen catheter and its size was made after consultation between the nephrologist and an experienced surgeon. Dual-lumen catheters ranging from 8 F to 12.5 F were individually adapted to the child's morphology and body weight according to literature recommendations [4, 5].

Therapeutic plasma exchange procedures were carried out using the filtration method in accordance with the prevailing guidelines, using the following types of machines and filters: 1) Hospal machine with PSN1, Hemaflex BT 900, and PF1000N filters (years: 1998-2008); 2) Prisma machine with PF1000N and PF2000N filters (years: 2009-2015); and 3) Prisma Flex machine with PF1000N filters (from 2016 onwards). The sizes of the specific filters were chosen according to the child's body mass in line with the medical product's characteristics.

The TPE procedures were performed according to our center's protocol, which included, among other elements, the establishment of appropriate vascular access for age (i.e., catheter size and location), priming and anticoagulation of the circuit, laboratory tests, and continuous monitoring of the patients (including hemoglobin oxygen saturation, heart rate, and blood pressure values) during the TPE procedure [5, 6].

As supplements, fresh frozen plasma (FFP), 5% human albumin (HA) solution, 6% hydroxyethyl starch (HES) solution, and crystalloids were used.

The type and configuration of supplements used depended on both the clinical condition of the patient and the timeline in which the treatment was administered [5–7]. The nephrology specialist planned and supervised the course of the TPE procedures in coordination with the team of specialists managing the patient's care.

The initial total plasma volume (TPV) to be exchanged (estimated plasma volume status – EPV) was calculated based on the patient's hematocrit (Hct) level and body weight using the Kaplan formula: EPV = [0.065 × body weight (kg)] × [1 – Hct] [3, 5]. Unfractionated heparin was used for anticoagulation, with an initial dose of 50–70 IU/kg body weight followed by a continuous intravenous infusion (and/or boluses) of unfractionated heparin at a dose of 10–30 IU/kg/hour, with dosing adjusted to achieve a therapeutic activated clotting time (ACT) between 180 and 240 seconds [6]. The analysis included, among other factors, the number of performed plasmapheresis procedures and technical aspects of the TPE process such as blood flow rate, duration of each procedure, size of the dual-lumen catheter, type of filter, initial dose of anticoagulant, ACT values, as well as clinical and technical complications resulting from the used vascular access and membrane technique, and the actions taken in response to the observed complications.

Statistical analysis

Statistical analysis was performed using MATLAB software (The MathWorks Inc., 2022b; MATLAB version 9.13.0 (R2022b), Natick, Massachusetts, USA). Data were presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR). Distribution normality was assessed using the Shapiro-Wilk test. Depending on the distribution of the variables, the following tests were employed: Student's *t*-test, Wilcoxon rank-sum test, Fisher's exact test or McNemar's test for matched samples, and Pearson's linear correlation. For multivariate analysis, a generalized multivariate linear model (GLM) with backward elimination was used. Receiver operating characteristic (ROC) analysis was also performed, providing the relevant parameters. A *p*-value of less than 0.05 was pre-determined as the threshold for statistical significance.

Results

The study cohort consisted of 178 patients who collectively underwent 740 procedures during 214 sessions.

The neuroimmunological population (NE) consisted of 4 subgroups: 1) acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain-Barré syndrome, GBS): 65 children, 65 sessions, 247 TPE procedures, averaging 3.8 procedures per patient; 2) polyneuropathy (PN): 5 children, 5 sessions, 19 TPE procedures, averaging 3.8 procedures per patient; 3) myasthenia gravis (MG): 8 patients, 13 sessions, 56 TPE procedures, averaging 1.63 sessions per patient and 7 procedures per patient; 4) multiple sclerosis (MS): 3 children, 24 sessions, 38 TPE procedures, averaging 8 sessions per patient and 12.67 procedures per patient. In total, the neuroimmunological group included 81 patients; 360 therapeutic plasma exchanges were performed during 107 sessions.

The non-neuroimmunological population (non-NE) consisted of patients from the 7 main diagnostic fields: 1) pediatric intensive care unit (PICU) patients: 13 children, 13 sessions, 30 TPE procedures, averaging 2.3 procedures per patient; 2) toxicological patients: 21 children, 21 sessions, 39 TPE procedures, 3.3 procedures per patient; 3) hematology: 12 children, 13 sessions, 42 TPE procedures, 3.5 procedures per patient; 4) nephrology – rapid progressive glomerulonephritis: 11 children, 13 sessions, 71 TPE procedures, 6.5 procedures per patient; 5) nephrology – systemic lupus erythematosus: 13 children, 15 sessions, 70 TPE procedures, 5.4 procedures per patient; 6) nephrology – focal segmental glomerulosclerosis: 4 children, 6 sessions, 28 TPE procedures, 7 procedures per patient; 7) nephrology – thrombotic microangiopathy: 23 children, 26 sessions, 100 TPE procedures, 4.4 procedures per patient. In total, the non-neuroimmunological group included 97 patients; 380 therapeutic plasma exchanges were performed during 107 sessions.

Detailed epidemiological data on the studied population of NE and non-NE patients, as well as the composition and doses of used supplements, are included in Table I and Supplementary Table SI. Regarding epidemiological data, only body mass in the NE group was significantly higher. In the non-NE group, procedures using FFP were performed significantly more often (88.2% vs. 76.1%), but the dose was significantly smaller (30 vs. 33.6 ml/kg) than in the NE group. Similarly, the duration of TPE procedures and the rate of supplement exchanges did not differ.

In both patient groups, the femoral vascular access was predominant (in the NE group 86.9% vs 60.7% in the non-NE group). Due to potential complications (including pneumothorax and vascular narrowing), at our center, the use of short-term subclavian vein access is avoided. CVCs were mostly inserted in the femoral vein, which is the preferred site of insertion in acute hemodialysis/TPE due to a smaller number of complications [8]. Detailed data regarding vascular access, its location, and size are included in Supplementary Table SII.

Table I. Epidemiological data of the studied population, doses of supplements used, and technical data of TPE procedures: NE subgroup (81 patients, 107 sessions, 360 TPEs), non-NE subgroup (97 patients, 107 sessions, 380 TPEs), entire studied population (178 patients, 214 sessions, 740 TPEs). Data are presented as medians with interquartile ranges (IQR), *p*-value – Wilcoxon test

Parameter	NE subgroup	Non-NE subgroup	*P*-value	All studied population
Characteristics of studied population and TPE procedures				
Age [months]	166.0 (104.0)	120.00 (104.38)	NS	138.00 (105.00)
Body mass [kg]	44.5 (30.0)	32.00 (32.40)	NS	38.00 (32.00)
Body mass [%]	29.0 (58.0)	50.00 (58.00)	NS	39.00 (60.00)
Height [cm]	160.00 (43.00)	138.25 (45.00)	0.043	146.00 (47.50)
Height [%]	45.00 (42.00)	40.00 (60.75)	NS	40.50 (52.00)
Dosages of supplements				
FFP [ml/kg]	33.6 (17.7)	30.00 (24.88)	0.008	32.00 (20.20)
5% Albumin [ml/kg]	38.5 (28.2)	33.33 (23.52)	0.012	36.23 (26.72)
6% HES [ml/kg]	25.6 (15.6)	25.42 (13.34)	NS	25.53 (15.67)
Crystalloid fluids/Ringer [ml/kg]	12.5 (8.3)	10.42 (7.55)	0.009	11.63 (8.99)
Total exchanged plasma volume [ml/kg]	73.1 (23.1)	70.16 (28.31)	0.025	72.12 (25.81)
FFP/total exchanged plasma volume	0.5 (0.1)	0.44 (0.22)	NS	0.46 (0.17)
FFP/5% Albumin	1.1 (0.8)	1.00 (0.85)	0.002	1.00 (0.86)
FFP/6% HES	1.1 (0.7)	1.08 (0.80)	NS	1.10 (0.70)
20% Albumin [ml/kg]	2.1 (0.9)	1.75 (1.35)	0.056	2.13 (1.23)
Technical aspects of procedures				
QB [ml/kg/min]	2.00 (1.3)	2.17 (1.52)	0.022	2.12 (1.48)
Duration of TPE procedure [min]	155.00 (90.00)	150.00 (80.00)	NS	155.00 (90.00)
Duration of TPE session [hours]** (all catheters)	145.00 (184.50)	49.00 (224.44)	0.027	118.50 (215.00)
Duration of TPE session [hours]** (excluding permanent catheters)	143 (168.8)	46.5 (188.7)	0.003	99 (192.9)
Supplement exchange flow rate [ml/kg/hour]	28.3 (21.6)	28.49 (20.68)	NS	28.37 (21.11)
Heparin initial dose [mg/kg]	0.30 (0.29)	0.27 (0.25)	< 0.001	0.29 (0.29)
Dosage of calcium supplementation [ml/kg] (only for TPE with FFP)	1.64 (0.81)	1.45 (1.04)	0.003	1.54 (0.92)

*FFP – fresh frozen plasma, HES – hydroxyethyl starch, NE – neuroimmunological population, QB – blood flow velocity, TPE – therapeutic plasma exchange. *Data pertain to the first TPE in a given session, **surrogate for catheter usage time; for single TPE sessions, the time corresponds to the duration of the specific TPE.*

Dysfunction of the catheter was defined as a failure to attain sufficient extracorporeal blood flow for an efficient procedure. An exit site infection (ESI) was defined as signs of inflammation in the area surrounding the catheter exit site and/or the presence of exudate that proves to be culture-positive.

Detailed information regarding catheter-related technical and clinical complications, interventions conducted in response to them, and issues related to the filter, machine, and reasons for premature termination of the TPE procedures are included in Tables II–IV.

Comparing the studied populations, in the NE group, a statistically significant 2.3-fold higher incidence of TPE with technical complications (29.4% vs. 12.6%) and a 2.4-fold higher rate of technical complication events (45.3% vs. 18.7%) were noted (including a 2-fold higher rate of procedures on reversed lines and a 3.4-fold greater incidence of malfunctions in the arterial part of the catheter) compared to the non-NE population.

However, the incidence of TPE with clinical complications (3.9% vs. 4.5%) and the percentage of patients with clinical complications (13.6% vs. 16.5%) were comparable between the groups.

Interestingly, it was found that in the NE group there was a statistically significant 1.7-fold higher percentage of patients requiring intervention due to technical and clinical complications related to vascular access (29.6% vs. 17.5%); a 1.8-fold higher rate of TPE with technical complications related to the filter (6.7% vs. 3.7%); a 1.8-fold higher rate of adverse events (AEs) related to the filter (11.7% vs. 6.6%); a 2.75-fold higher rate of TPE

Table II. Catheter-related technical and clinical complications in NE and non-NE populations. NE subgroup (81 patients, 107 sessions, 360 TPEs), non-NE subgroup (97 patients, 107 sessions, 380 TPEs), entire studied population (178 patients, 214 sessions; 740 TPEs). Data are presented as the number of events and percentages; *p*-value – one-sided Fisher's exact test

Catheter-related technical complications	**NE subgroup, *n* (%)**	**Non-NE subgroup, *n* (%)**	***P*-value**	**All studied population, *n* (%)**
No. of TPEs with technical complication (% vs. no. of TPEs)	106 (29.4)	48 (12.6)	< 0.001	154 (20.8)
No. of particular technical AEs (% vs. no. of TPEs)				
Insufficient blood intake – malfunction in the arterial part of the catheter	89 (24.7)	28 (7.3)	< 0.001	117 (15.8)
Reversed lines	68 (18.9)	35 (9.2)	< 0.001	103 (13.9)
Insufficient blood return – malfunction in the venous part of the catheter	5 (1.4)	5 (1.3)	NS	10 (1.4)
Thrombosis within the catheter	1 (0.3)	1 (0.3)	NS	2 (0.3)
Spontaneous catheter repositioning	0	1 (0.3)	NS	1 (0.1)
Catheter leakage	0	1 (0.3)	NS	1 (0.1)
No. of all technical AEs (% vs. no. of TPEs)	163 (45.3%)	71 (18.7%)	< 0.001	234 (31.6%)
Catheter-related clinical complications				
No. of TPEs with clinical complications (% vs no. of TPEs)	14 (3.9)	17 (4.5)	NS	31 (4.2)
No. of particular clinical AEs (% vs no. of TPEs)				
Thrombosis in the vessel with the catheter in place	6 (1.7)	5 (1.3)	NS	11 (1.5)
Bleeding at the implantation site	2 (0.6)	8 (2.1)	NS	10 (1.4)
Catheter exit site infection	3 (0.8)	3 (0.8)	NS	6 (0.8)
Pain at the catheter implantation site	4 (1.1)	2 (0.5)	NS	6 (0.8)
Edema of the extremity with the catheter	1 (0.3)	1 (0.3)	NS	2 (0.3)
No. of all catheter-related clinical AEs (% vs no. of TPEs)	16 (4.4)	19 (5)	NS	35 (4.7)

AEs – adverse events, NE – neuroimmunological population, TPE – therapeutic plasma exchange.

Table III. Medical interventions required for catheter-related technical and clinical complications in NE and non-NE populations. NE subgroup (81 patients, 107 sessions, 360 TPEs), non-NE subgroup (97 patients, 107 sessions, 380 TPEs), entire studied population (178 patients, 214 sessions; 740 TPEs). Data are presented as the number of events and percentages; *p*-value – one-sided Fisher's exact test

Type of intervention (% vs. no. of TPEs)	**NE subgroup, *n* (%)**	**Non-NE subgroup, *n* (%)**	***P*-value**	**All studied population, *n* (%)**
Low molecular weight heparin	8 (2.2)	5 (1.3)	NS	13 (1.8)
Surgical pressure dressing	1 (0.3)	8 (2.1)	0.023	9 (1.2)
Topical antibiotic	3 (0.8)	3 (0.8)	NS	6 (0.8)
Additional peripheral vascular access	0	5 (1.3)	0.035	5 (0.7)
Urokinase/Taurolock (administered via catheter)	3 (0.8)	1 (0.3)	NS	4 (0.5)
rTPA/Actylise (intravenous)	2 (0.6)	1 (0.3)	NS	4 (0.5)
Flushing the catheter with saline	3 (0.8)	1 (0.3)	NS	4 (0.5)
Administration of analgesic medication	2 (0.6)	2 (0.5)	NS	4 (0.5)
Changing the position of the extremity	2 (0.6)	1 (0.3)	NS	3 (0.4)
Removal of a single suture and adjustment of the catheter	2 (0.6)	0	NS	2 (0.3)
Cooling dressing	2 (0.6)	0	NS	2 (0.3)
Transfer of the patient to the ICU	1 (0.3)	0	NS	1 (0.1)
Catheter replacement	1 (0.3)	0	NS	1 (0.1)
Surgical vessel suturing under general anesthesia	1 (0.3)	0	NS	1 (0.1)
Total no. of interventions (% vs. no. of TPEs)	31 (8.6)	27 (7.1)	NS	58 (7.8)
Total no. of patients with catheter-related interventions (% vs. no. of patients)	24 (29.6)	17 (17.5)	0.019	41 (23)

AEs – adverse events, ICU – intensive care unit, NE – neuroimmunological population, rTPA – recombinant tissue-type plasminogen activator, TPE – therapeutic plasma exchange.

Table IV. Technical difficulties related to the filter, machine, and causes of premature termination of the TPE in NE and non-NE populations. NE subgroup (81 patients, 107 sessions, 360 TPEs); non-NE subgroup (97 patients, 107 sessions, 380 TPEs), entire studied population (178 patients, 214 sessions; 740 TPEs). Data are presented as the number of events and percentages; *p*-value – one-sided Fisher's exact test

Technical AEs related to filters and machine	NE subgroup, *n* (%)	Non-NE subgroup, *n* (%)	*P*-value	All studied population, *n* (%)
No. of TPEs with technical AEs related to filters (% vs. no. of TPEs)	24 (6.7)	14 (3.7)	0.047	38 (5.1)
No. of particular AEs related to filters (% vs. no. of TPEs)				
Filter clotting	16 (4.4)	13 (3.4)	NS	29 (3.9)
Filter replacement	16 (4.4)	8 (2.1)	0.056	24 (3.2)
Increased pressure on the filter without clotting	6 (1.6)	4 (1.1)	NS	10 (1.3)
Capillary rupture in the filter	4 (1.1)	0	0.056	4 (0.5)
Total no. of filter-related AEs (% vs no. of TPEs)	42 (11.7)	25 (6.6)	0.011	67 (9.1)
No. of TPEs with technical AEs related to machines (% vs. no. of TPEs)	3 (0.8)	0	NS	3 (0.3)
No. of TPEs prematurely terminated (% vs No. of TPE)	16 (4.4)	6 (1.6)	0.018	22 (3)
No. of particular AEs related to prematurely terminated TPE (% vs no. of TPEs)				
Filter malfunction	12 (3.3)	6 (1.6)	NS	18 (2.4)
CVC malfunction	7 (1.9)	0	0.006	7 (1)
CVC-related clinical complications	1 (0.3)	0	NS	1 (0.1)
Machine failure	1 (0.3)	0	NS	1 (0.1)
Damaged FFP bag	1 (0.3)	0	NS	1 (0.1)
Total no. of AEs related to prematurely terminated TPE (% vs. no. of TPEs)	22 (6.1)	6 (1.6)	0.001	28 (3.8)

AEs – adverse events, CVC – central venous catheters, FFP – fresh frozen plasma, NE – neuroimmunological population, TPE – therapeutic plasma exchange.

with premature termination (4.4% vs. 1.6%); and a 3.8-fold higher rate of AEs related to premature termination of TPE (6.1% vs. 1.6%) compared to the non-NE group.

In the analysis of the study population concerning the administration of FFP during TPE, it was found that the group receiving FFP (FFP1) exhibited a significantly higher incidence of TPE with technical events (23% vs. 10.7%; a 2.1-fold increase) and clinical events (4.9% vs. 0.8%; a 6.1-fold increase). Additionally, the occurrence of clinical complications was 7 times higher in the FFP1 group compared to those not receiving FFP (FFP0, 5.6% vs. 0.8%).

In the FFP1 group, a statistically significant 2.4-fold higher incidence of TPE with any event (clinical and technical) related to vascular access was also observed (27.9%) compared to the FFP0 group (11.5%, $p < 0.05$; one-sided Fisher's test). The analyzed data therefore indicate that the use of FFP contributes to a higher percentage of clinical AEs in this group of patients.

Detailed information on catheter-related technical and clinical complications, challenges related to the filter, machine, and causes of premature termination of the TPE procedure in the FFP1 and FFP0 subgroups is included in Tables V and VI.

In the entire studied population, the incidence of TPE with technical complications was 20.8% (154/740), and the rate of all technical complication events was 31.6% (234/740); this equates to 0.9 TPEs with a technical complication and 1.3 technical complication events per patient. Meanwhile, the incidence of TPE with clinical complications was 4.2% (31/740), and the rate of all clinical complication events was 4.7% (35/740); the percentage of patients with clinical complications was 15.2% (27/178), and the rate of all clinical complication events in the studied population was 19.7% (35/178). Therefore, in the studied population, the frequency of TPE with technical complications is nearly 5 times greater than that with clinical complications (20.8% vs. 4.2%, $p < 0.05$); similarly, the frequency of technical events is 6.7 times greater than that of clinical events (31.6% vs. 4.7%, $p < 0.05$).

The median duration of entire TPE sessions (which in this study serves as a surrogate for catheter lifespan) was nearly three times longer in the NE group compared to the non-NE group (145 vs.

Table V. Catheter-related technical and clinical complications in FFP1 and FFP0 populations. FFP1 population: 609 TPEs, FFP0 population: 131 TPEs. Data are presented as the number of events and percentages; *p*-value – one-sided Fisher's exact test

Catheter-related technical complications	**FFP1 subgroup, *n* (%)**	**FFP0 subgroup, *n* (%)**	***P*-value**
No. of TPEs with technical complication (% vs. no. of TPEs)	140 (23)	14 (10.7)	0.001
No. of particular technical AEs (% vs. no. of TPEs)			
Insufficient blood intake – malfunction in the arterial part of the catheter	89 (14.6)	28 (21.4)	0.040
Reversed lines	81 (13.3)	22 (16.8)	NS
Insufficient blood return – malfunction in the venous part of the catheter	8 (1.3)	2 (1.5)	NS
Thrombosis within the catheter	2 (0.3)	0	NS
Spontaneous catheter repositioning	1 (0.2)	0	NS
Catheter leakage	1 (0.2)	0	NS
No. of all technical AEs (% vs. no. of TPEs)	182 (29.9)	52 (39.7)	0.020
Catheter-related clinical complications			
No. of TPEs with clinical complications (% vs no. of TPEs)	30 (4.9)	1 (0.8)	0.017
No. of particular clinical AEs (% vs no. of TPEs)			
Thrombosis in the vessel with the catheter in place	10 (1.6)	1 (0.8)	NS
Bleeding at the CVC implantation site	10 (1.6)	0	NS
Catheter exit site infection	6 (1)	0	NS
Pain at the catheter implantation site	6 (1)	0	NS
Edema of the extremity with the catheter	2 (0.3)	0	NS
No. of all catheter-related clinical AEs (% vs. no. of TPEs)	34 (5.6)	1 (0.8)	0.008

AEs – adverse events, FFP – fresh frozen plasma, TPE – therapeutic plasma exchange.

Table VI. Technical difficulties related to the filter, machine, and causes of premature termination of the TPE in FFP1 and FFP0 populations. FFP1 population: 609 TPEs, FFP0 population: 131 TPEs. Data are presented as the number of events and percentages; *p*-value – one-sided Fisher's exact test

Technical AEs related to filters and machine	**FFP1 subgroup, *n* (%)**	**FFP0 subgroup, *n* (%)**	***P*-value**
No. of TPEs with technical AEs related to filters (% vs no. of TPEs)	20 (3.3)	18 (13.7)	< 0.001
No. of particular AEs related to filters (% vs no. of TPEs)			
Filter clotting	14 (2.3)	15 (11.4)	< 0.001
Filter replacement	12 (2)	12 (9.2)	< 0.001
Increased pressure on the filter without clotting	7 (1.1)	3 (2.3)	NS
Capillary rupture in the filter	3 (0.5)	1 (0.8)	NS
Total no. of filter-related AEs (% vs. no. of TPEs)	36 (5.9)	31 (23.7)	<0.001
No. of TPEs with technical AEs related to machines (% vs. no. of TPEs)	2 (0.3)	1 (0.8)	NS
No. of TPEs prematurely terminated (% vs. no. of TPEs)	12 (2)	10 (7.6)	0.002
No. of particular AEs related to prematurely terminated TPE (% vs no. of TPEs)			
Filter malfunction	11 (1.7)	7 (5.3)	0.026
CVC malfunction	3 (0.5)	4 (3.1)	0.021
CVC-related clinical complications of TPE	1 (0.2)	0	NS
Machine failure	0	1 (0.8)	NS
Damaged FFP bag	1 (0.2)	0	NS
Total no. of AEs related to prematurely terminated TPE (% vs. no. of TPEs)	16 (2.6)	12 (9.2)	0.001

AEs – adverse events, CVC – central venous catheters, FFP – fresh frozen plasma, TPE – therapeutic plasma exchange.

49 hours). Across the entire studied population, it averaged 118.5 hours. It is important to underline that in cases where a patient was diagnosed with severe kidney injury or end-stage kidney disease (ESKD) (7 nephrological patients, in 7 sessions) or when a longer period of TPE was planned in advance (2 neurological patients in 2 sessions), a permanent catheter was electively used. Nevertheless, narrowing the studied population to acute catheters only, their usage time was also 3.1 times longer in the NE population compared to the non-NE population, with the median usage time for these catheters in the entire population being 99 hours.

Furthermore, the incidence of TPE with any clinical and technical event related to vascular access was significantly higher, by 1.9 times in the NE group (33.3%) compared to the non-NE group (17.1%). Across the whole study population, this rate was 25%. Thus, the significantly longer duration of catheter use in the NE group may influence the higher number of technical AEs and the proportion of events related to the filter in this group of patients.

Furthermore, a multivariate logistic regression analysis of the entire sessions on the occurrence of catheter-related technical complications in a given TPE session showed that belonging to the NE group increased the probability of a technical complication by 2.4 times (2.1 for acute catheters only), and each day the catheter was in place increased the probability of a technical complication by 3% (6% for acute catheters only). Moreover, a multivariate logistic regression analysis of the entire sessions on the occurrence of catheter-related clinical complications in a given TPE session indicated that each additional year of the patient's life decreased the probability of a clinical complication by 8.9% (9.1% for acute catheters only), and each additional FFP procedure during the session increased the probability of a clinical complication by 21.6% (20.8% for acute catheters only) (Table VII).

Additionally, an analysis of area under the ROC curves (AUROCs) conducted for entire TPE sessions (summing the number of AEs occurring in each session) revealed that the AUROC for the selected cut-off value of 5 days of catheter lifespan for the occurrence of any catheter-related technical AEs was 71% (likelihood ratio (LR): 2.16; sensitivity: 76.5%; specificity: 64.7%; 95% CI: 65.26–76.65, p-value < 0.05), indicating good predictive value. This model suggests a 71% probability that the model will correctly distinguish between a technical AE and no event.

Similarly, an analysis of AUROCs conducted for entire TPE sessions (summing the number of AEs occurring in each session) showed that the AUROC for the selected cut-off value of 5 days of catheter lifespan for the occurrence of TPE with any vascular access-related technical event was 71.3% (LR: 2.15; sensitivity: 79.9%; specificity: 62.9%; 95% CI: 65.29–77.34, p-value < 0.05), also indicating good predictive value. This model suggests a 71.3% probability that the model will correctly distinguish between a technical AE and no event. The AUROC values for the above data, extracted only for the subpopulation of acute catheters, were below 70%; therefore, they were not included in this paper.

Discussion

Therapeutic plasma exchange remains a widely used treatment modality for various diseases in children by removing plasma containing patho-

Table VII. Multivariable logistic regression evaluating the influence of selected variables on occurrence of a technical and clinical complication during a given TPE divided into all and only acute catheters; OR values for selected factors; 95% CI intervals for OR values; *p*-value

Parameter	Age [years]		Use of FFP (1/0)*		Affiliation with the NE subgroup (1/0)		Days since catheter placement	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
All catheters								
Technical complication	–	–	–	–	2.396 (1.347–4.263)	0.003	1.030 (1.003–1.057)	0.029
Clinical complication	0.911 (0.840–0.988)	0.024	1.216 (1.016–1.456)	0.033	–	–	–	
Acute catheters only								
Technical complication	–	–	–	–	2.090 (1.175–3.718)	0.012	1.060 (1.015–1.108)	0.008
Clinical complication	0.909 (0.839–0.986)	0.021	1.208 (1.012–1.442)	0.037	–	–	–	

*CI – confidence interval; independent variables, FFP – fresh frozen plasma, NE – neuroimmunological population, OR – odds ratio, TPE – therapeutic plasma exchange. *Presented as the number of FFP1 TPEs within a given session.*

genic agents. While the principles of TPE are similar in adults and children, there are several technical differences that may affect the overall efficacy and safety of this treatment in the pediatric population.

One of these factors is CVC, which in the pediatric population is usually performed by an interventional radiologist under direct visualization and often under general anesthesia.

In this study, technical AEs related to CVC were analyzed, including the necessity of conducting the procedure using reversed lines (which affects the procedure's efficacy), incidents involving difficulties in blood withdrawal and return (indicating malfunction of the arterial and venous parts of the catheter, respectively), thrombosis within the catheter, spontaneous catheter repositioning, and catheter leakage.

Adverse events of a clinical nature related to the CVC were also scrutinized, including thrombosis in the vessel with the catheter in place, edema of the extremity with the catheter, catheter ESI, isolated pain at the catheter implantation site, and bleeding at the implantation site of the CVC. Additionally, AEs related to the filters themselves were analyzed, such as episodes of clotting, ruptures, the necessity for replacement, and increased pressure on the filter without clotting. The severity of these AEs was indirectly assessed by analyzing the type and number of interventions required for the aforementioned AEs. Furthermore, the frequency and causes of premature termination of the TPE procedure were evaluated.

In this population, due to the specific characteristics of the pediatric population, the femoral access was the most commonly selected access site (73.8%). In the literature, femoral catheter placement is reported at levels ranging from 5.9% to 80% [8–14].

In this study, catheter-related technical malfunctions were recorded in 230 out of 740 TPE sessions (31.1%), with the two most frequently reported catheter-related technical complications being arterial catheter malfunction (15.8%) and the necessity to conduct the procedure using reversed lines (13.9%). Other noted complications were very rare (0.1–1.4% per TPE).

Additionally, after excluding AE related to procedures performed on reversed lines, the rate of technical events was reduced to 17.7% (131/740) per TPE. In the literature, reports on access malfunction vary widely, ranging from 1.2% to 38.8% per TPE [13, 15–21]. This discrepancy may result from differences in the definition of catheter malfunction used in different centers and statistical calculation methods.

In this study, each type of AE was recorded separately; thus, during a single TPE session, both an arterial catheter malfunction and a procedure conducted on reversed lines could be documented.

Catheter leakage is reported in the literature at a level of 2% per TPE [20] and 5% per patient [22], while catheter thrombosis is reported at 1.6% per TPE [15] and at levels ranging from 10% [14] to 17.4% [10] per patient. In the studied population, catheter leakage was observed in 1 case (0.1% per TPE), while catheter thrombosis occurred in only 2 patients (1.1%) and in 0.3% per procedure.

The two most frequently documented clinical complications were thrombosis in the catheterized vessel (1.5%) and bleeding at the implantation site of a double-lumen catheter (1.4%). Other recorded clinical complications were even rarer (0.3–0.8% per TPE). In the literature, catheter-related thrombosis is noted at levels of 0.08% [1] to 0.4% [16] per TPE and at levels of 1.7–6.25% per patient [8, 16, 22, 23].

In contrast, bleeding at the implantation site of a double-lumen catheter aligns with data from the literature, which describes it at levels of 0.25% to 3% per TPE [1, 8, 17, 24].

Pain at the catheter implantation site was observed in 6 cases (0.8% per TPE) in this study, whereas the literature notes 'abnormal sensation' in 0.25% per TPE [1].

In the literature, the rate of catheter-related infections (bacteremia/catheter-related sepsis) is documented at 4.8–17% of patients [8, 16, 25–27] and at 0.25–2.1% per procedure [1, 16, 26]. In this study, no AEs in the form of bacteremia or catheter-related sepsis were recorded. This could be attributed to the fact that children at risk of systemic infection (e.g., PICU patients, nephrological, or hematological patients) were treated with systemic antimicrobial therapy due to their underlying disease, which a priori complicates the analysis of such data.

In this study, complications such as pneumothorax (reported in the literature at 0.9% of patients [25]) and premature catheter disconnection (reported in the literature at 1.8% per TPE [20]) were not observed. However, one case of spontaneous catheter repositioning was documented (0.1% per TPE).

The two most common medical interventions related to catheter-associated technical and clinical complications in the studied population were the systemic administration of low-molecular-weight heparin (1.8%) and the application of a surgical compression dressing (1.2%). The rate of other interventions did not exceed 1% per TPE.

The two most frequently documented technical complications related to the filter were clotting within the filter (3.9%) (reported in the literature at 19.6% per TPE [25]) and the need for filter replacement (3.2%).

The rate of prematurely terminated TPE sessions due to various causes in this study was 3% (filter-related issues: 2.4%; vascular access-related technical issues: 1%). Data reported in the literature range from 4.4 to 7% [22, 28].

Machine-related problems over a 25-year period were recorded at a rate of 0.3% per TPE, whereas the literature reports this complication at a level of 18.6% per TPE [29].

The median duration of entire TPE sessions (which, in this study, serves as a surrogate for catheter lifespan) in the studied population was 118.5 hours (equivalent to 4.9 days), with a range from 0.75 hours to 1732 hours (including permanent catheters), and 100 hours (4.2 days) with a range up to 767 hours (32 days) when permanent catheters were excluded. In the literature, the mean catheter lifespan is reported as ranging from 1 to 27 days, with an average of 8.1 ±6.4 days [8].

Analysis of the studied population revealed that a longer duration of catheter lifespan (in the NE group) may be associated with a higher number of catheter-related technical AEs and an increased percentage of filter-related AEs, as each additional day of catheter lifespan increased the odds of a technical complication by 3%. Furthermore, it was observed that after five days of catheter lifespan, the probability of experiencing any catheter-related technical AE or a TPE session with any technical event rose to 71%.

The use of FFP was found to contribute to a higher percentage of catheter-related clinical AEs, as each additional FFP procedure during a session increased the odds of a clinical complication by 21.6%. Additionally, it was observed that each additional year of the patient's age reduced the odds of a clinical complication by 8.9%, which is consistent with reports in the literature stating that catheter-related problems are significantly associated with younger age [15].

Comparing technical complications of TPE in the literature is challenging due to differences in methods of analysis depending on the author. Percentages are calculated relative to the total number of TPEs, the number of patients, or the total number of recorded complications. Therefore, in this study, the focus was placed on comparing selected groups of complications, presenting them in a systematic manner as the number of TPEs with a given complication and as the number of AEs relative to the total number of TPEs. For selected clinical complications, they were also presented relative to the number of patients.

Additionally, the study examined the influence of factors such as patient age, body weight, duration of the treatment session (used as a surrogate for CVC lifespan), the use (or non-use) of FFP during TPE, and group assignment (NE or non-NE) on the analyzed complications.

For the evaluation of procedural and patient safety, we primarily recorded technical and clinical access-related and filter-related problems. In the studied population, the percentage of patients with clinical complications was 15.2%, which is consistent with data reported in the literature [26]. All of these AEs were mild in severity and could be managed with standard methods. It is also noteworthy that no severe AE related to the TPE procedure or CVC that resulted in patient death was recorded. The obtained data indicate a very good safety profile for the TPE procedure at our center.

The membrane-based technique might also play a role in the incidence of technical complications during TPE. Webb *et al*. compared membrane TPE (mTPE) and centrifugal TPE (cTPE) in 105 patients under 21 years of age and reported higher machine-related complications (17.4%) in mTPE compared to 7.1% in cTPE, as well as higher rates of circuit clotting (6.7%) vs. none in cTPE. However, they found no significant differences in patient complications between the techniques [30]. Similar findings regarding lower clotting rates in cTPE were described by Kielstein *et al*. [31].

An important limitation of the obtained results is the fact that this study is retrospective and single center, spanning 25 years, during which the technical conditions of the procedures evolved, including changes in machines, filters, supplements, and CVCs. However, complications during TPE sessions are typically well documented in our center, as they often require procedural adjustments or additional medication. We are also aware of the bias affecting the results of catheter-related complications, stemming from the fact that 4.2% of sessions involved TPE procedures on a permanent catheter. Nevertheless, as we did not want to exclude these TPEs from the database due to other valuable data subjected to analysis, we assumed that these proportions were relatively small in the whole dataset and would not have a significant impact on the overall results. Furthermore, in the multivariate logistic regression analyses, data for permanent and acute catheters were analyzed separately.

Nonetheless, to the best of our knowledge, this study represents the most extensive patient database from a single tertiary referral center in Central and Eastern Europe, spanning such a prolonged period, and meticulously evaluating the technical safety of the TPE membrane procedures in children.

As Meyer and Wong stated, there are striking differences in the rates of complications between published research on the safety of TPE in children. They also suggested that the inclusion criteria and analytical approaches might significantly differ, emphasizing the need for prospective, collaborative clinical trials, which could portray the true incidence of AE in pediatric TPE procedures [32].

The obtained data support the conclusion that in the membrane TPE technique, technical complications predominate, while clinical complications are relatively rare and mild, and in our study, complications were manageable with standard interventions, with their likelihood decreasing with the patient's age.

Importantly, the data highlight key factors that can further enhance safety: awareness of potential complications allows for better preparation and response; careful selection of candidates – particularly those with known risk factors – may help avoid unnecessary risk by incorporating alternative therapies. Additionally, a longer duration of catheter lifespan is associated with a higher number of catheter-related technical AEs and an increased percentage of filter-related AEs, whereas the use of FFP contributes to a higher percentage of catheter-related clinical AEs.

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Ethical approval

The local ethics committee approved the study – approval number 118.6120.187.2023.

Conflict of interest

The authors declare no conflict of interest.

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