BMC Nephrology

RESEARCH Open Access

Three decades of experience with therapeutic apheresis at a tertiary academic center: review of indications, clinical practice, special age groups and complications

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Abstract

Introduction We performed a comprehensive retrospective analysis of 30-year therapeutic apheresis (TA) activity and practices at one a national apheresis center in Slovenia to describe trends and main TA characteristics.

Methods We retrospectively reviewed the medical records of all TA procedures from 1986 to 2016 and extracted indications, vascular access, number of procedures and complications. We compared two time periods (1986–2000 vs. 2001–2016) and analyzed two age subgroups (children and elderly). For the most recent patient cohort (2010 to 2016) we retrieved additional parameters pertaining to each TA procedure.

Results The whole cohort included 1,132 patients who underwent a total of 14,082 apheresis procedures. Central venous catheters were predominantly used, with a trend toward greater use of arterio-venous fistulas in the later period. The number of procedures increased over time. The use of lipid apheresis was stable, and the use of immunoadsorption declined in recent years. The use of apheresis for some indications increased, whereas other indications remained stable over the years. The comparison of the two time periods revealed increased utilization of the TA, increasing patient age, and a shift in vascular access type. In pediatric and elderly patient populations, the indications differed substantially. Chronic apheresis was utilized in a distinct subset of patients. Our analysis confirmed that TA was generally safe and had a low incidence of complications. The most common adverse events were hypotension and mild allergic reactions. Only 0.6% of the procedures were stopped because of a complication.

Conclusion Our study provides valuable insights into TA practices over three decades. This finding underscores the importance of vascular access in apheresis treatment and reaffirms the safety profile of TA across different age groups. Our center's collaborative approach to providing TA under nephrologist supervision has proven effective in managing changes in the field of apheresis and ensuring patient safety.

Keywords Plasmapheresis, Apheresis, Therapeutic plasma exchange, Complications, Indications

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Introduction

Therapeutic apheresis includes several different extracorporeal procedures, in which patient blood is nonselectively or selectively purified from presumably pathogenic components, e.g. therapeutic plasma exchange (TPE), immunoadsorption, and lipid apheresis, to name just a few [1]. The basic principle behind apheresis treatment is (un)selective removal of large plasma components (antibodies, immune complexes, lipoproteins and other macromolecules), which are considered pathogenic in specific diseases. Despite this simple concept, some of its mechanisms of action are pleomorphic [2], and possible adverse effects are sometimes not fully appreciated, e.g., the removal of concomitantly used medications [3–5]. Nevertheless, apheresis is an invaluable therapeutic option for certain diseases and a second line treatment for many others [6]. The field of apheresis medicine is evolving and apheresis can also be used for some emerging indications, which should be recognized in the clinical setting. It is therefore not surprising that category 3 (optimum role not established) is the most common category in the American Society for Apheresis guidelines [6]. Apheresis can be considered whenever a suspected pathogenic substance in plasma has a relatively long half-life; it cannot be removed with medications, hemodialysis or hemoadsorption, and it can be presumed that its clearance would improve the disease course [7–9]. Some examples of newer indications include treatment for propofol infusion syndrome [10], nephrogenic systemic fibrosis [11], immune-related adverse events associated with immune checkpoint inhibitors [12] and severe, extremely preterm preeclampsia [13–16].

Although apheresis is an evolving and multidisciplinary field, large registry reports [17] or single-center analyses are relatively rare. We believe that a description of historical and recent clinical practice is important for reflecting on apheresis practices and advancements in the field. Furthermore, such analyses can provide data on small subpopulations (e.g., children and elderly individuals [18]), as well as on the incidence of complications, which is important to support the subjective feeling of clinicians that apheresis is a very safe treatment, e.g., it is also used during pregnancy. Furthermore, analysis of adverse effects related to replacement solution, e.g., fresh frozen plasma (FFP), can drive changes in its use, for example, using fibrinogen concentrate instead of FFP [19], when it is used solely to prevent consumption coagulopathy.

Therefore, the aim of our study was to provide a comprehensive analysis of therapeutic apheresis in a tertiary academic hospital over 30 years. We reviewed indications and clinical practice and put special attention to adverse effects, marginal age groups and changes in practice patterns that occurred during this period.

Methods

Study design and data collection

This was a retrospective study of all apheresis procedures, performed at our center from 1986 to 2016. Our center was a national referral center until a few years ago and is still one of the only two centers performing therapeutic apheresis for a population of 2 million. Importantly, we also host a national kidney transplant center. We used patient and apheresis records to collect clinical data, which were anonymized prior to statistical analysis. Data acquisition included crucial information regarding each course of apheresis treatment (patient sex, age, date of first procedure, diagnosis, referral department, type and number of procedures, date of last procedure, venous access, hepatitis/HIV status). We later categorized the referral wards and diagnoses to make comparisons possible. We considered each patient unique, and "a course of apheresis treatments" was a course of apheresis procedures performed for the same indication in a closed time span. We arbitrarily defined "chronic apheresis" treatment as treatment lasting for more than 3 months. We decided to compare two 15-year periods (1986–2000 and 2001–2016) to evaluate the evolution of practice in our center and allow for statistical comparison.

Furthermore, for the more recent subgroup of patients in the period from 2010 to 2016, the retrieval of specific additional parameters pertaining to each apheresis procedure was possible: ambulatory or in-hospital setting, type of replacement fluid, anticoagulation and medications given during the procedure. Complications during apheresis that were recorded were classified as: allergic reactions (urticaria or anaphylaxis), hypotension (defined as a blood pressure drop of >40 mmHg or a systolic blood pressure <90 mmHg with a concomitant drop of >20 mmHg), therapy for hypotension, arrythmia confirmed by electrocardiogram, nausea, resuscitation, and death. We did not record the volume of treated plasma.

Apheresis treatments

Our TPE protocol included the exchange of 1–2 plasma volumes. Hemofiltration solution with albumin added to a final concentration of approx. 30 g/l was used as the replacement fluid. When indicated by an indication for TPE (e.g., thrombotic thrombocytopenic purpura (TTP)) or when bleeding complications were anticipated (e.g., pre/postsurgery or invasive procedures) or when fibrinogen was <1.0 g/l or <1.5 g/l with a significant bleeding risk present (e.g., after recent kidney biopsy or lumbar puncture)), FFP was used as a sole replacement solution or in combination with an albumin solution (10–20 ml/kg body weight).

It was common practice in our center to obtain central venous access for apheresis. In a minor proportion of

patients, arterio-venous fistula was present and successfully used, together with peripheral veins.

There was no upper age limit to apply apheresis in our center.

Statistical methods

The data are presented via descriptive statistics: i.e., means and ranges or relative proportions, as appropriate. Missing data were not imputed; due to the nature of data collection the missing data was rare, therefore, for clarity, we omitted the number (percent) of missing data in the tables. For between-group comparisons, Student's t-test and the chi-square test were used. A p value of < 0.05 was interpreted as statistically significant. We used Microsoft Excel to organize the data and R (version 4.4.3) [20] for visual representations and statistical analyses.

Results

Patients

We included 1,132 patients who underwent an overall of 14,082 apheresis procedures within 1,344 different apheresis courses. The median age of the patients was 50 (IQR 38–65) years, and 47% were females. The median number of procedures per course of apheresis treatment was 6 (IQR 3–10), and each course lasted for a median of 13 days (IQR 3–26).

The number of apheresis procedures performed clearly increased over the three decades, as apheresis gained recognition and acceptance among other specialties. Most commonly, patients were hospitalized in departments of nephrology (26%), neurology (25%), and in intensive care units (10%) at the initiation of apheresis treatment. A minority of patients (3%) started apheresis in the outpatient setting.

Among patients 3.6% were hepatitis B antigen positive and 1.5% were hepatitis C antibody positive. All patients had their viral status checked prior to starting apheresis treatment, positive patients were isolated, and no known transmission occurred.

Vascular access

At the initiation of the apheresis course, the most common vascular access was a central venous catheter (CVC, 57%), followed by a combination of a catheter and peripheral venous access (27%), whereas arteriovenous fistula (6%) was relatively rare; in 13% the access was other/unknown. Changes over time are shown in Fig. 1. In the first period, a central venous catheter and a peripheral vein were mostly used, whereas in the later period, peripheral access was abandoned, and a CVC was used most frequently. The arterio-venous fistula was predominantly used in patients with preexisting fistulas, who

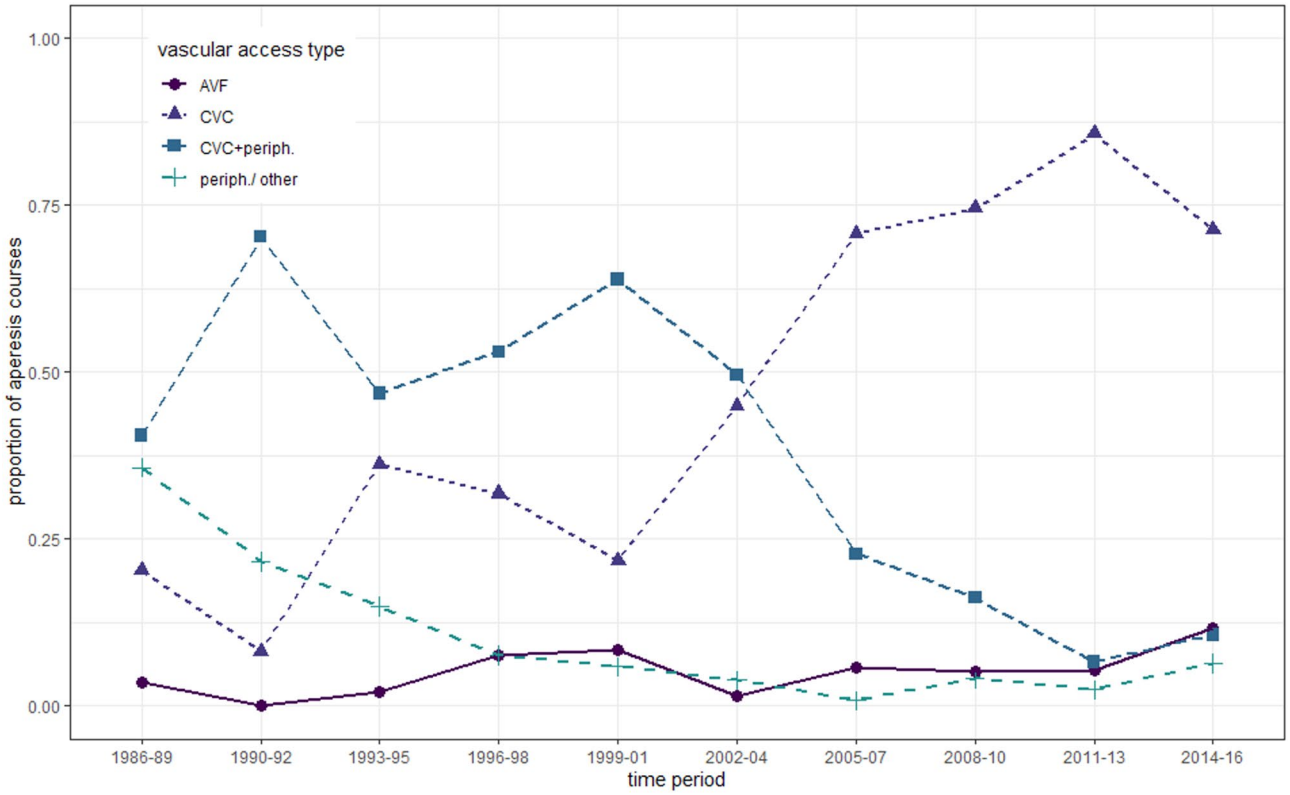

Fig. 1 Vascular access used at the initiation of apheresis treatment. (CVC = central venous catheter, AVF = arteriovenous fistula, periph. = peripheral venous access)

were treated for humoral rejection of kidney transplants or recurrent focal segmental glomerulosclerosis. The use of an arterio-venous fistula was convincingly increasing in the later period, when the prevalence of kidney transplant patients increased in our center. Furthermore, there were a few patients for whom an arterio-venous fistula was constructed for the purpose of chronic apheresis treatment.

Types of apheresis procedures

We analyzed different types of apheresis procedures used at our institution. The number of TPE procedures increased over time, especially in the recent years, and TPE was also the most common apheresis modality overall. We observed an increase in the use of immunoadsorption between the years 2001 and 2004, after which it was introduced, with a moderate concomitant drop in TPE, as they were used for similar indications. The use of low-density lipoprotein (LDL) apheresis was initiated in 1990 and the number of procedures was relatively stable over time (see Fig. 2).

Indications for apheresis

The breakup of indications for apheresis treatment courses revealed that the use of apheresis for some indications increased, whereas other indications have remained stable over the years (see Fig. 3).

Hypertriglyceridemic pancreatitis was increasingly recognized as a potentially "treatable" disease in the past two decades, so the number of patients increased; however, in recent years (not included in this analysis), we have changed clinical practice on the basis of negative results from our randomized trial [21]. Humoral rejection of transplanted organs (almost exclusively kidneys) was more common after the acceptance of our transplant center into Eurotransplant in 2000 [22], which considerably increased the number of kidney transplant patients in Slovenia, resulting also in more rejections. On the other hand, the number of procedures performed for TTP/(atypical) hemolytic uremic syndrome ((a)HUS))/thrombotic microangiopathy, myasthenia gravis, and Guillain-Barré syndrome were stable. The number of patients treated for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis increased after 2010, probably because of increased recognition of this disease as an indication for apheresis. The number of patients treated for systemic lupus erythematosus was low and stable.

Comparison of the 1986–2000 and 2001–2016 periods

The whole period of data collection was divided into two 15-year periods to evaluate the evolution of practice in our center and allow for statistical comparison. Both the overall number of patients treated and the number of procedures performed increased significantly in

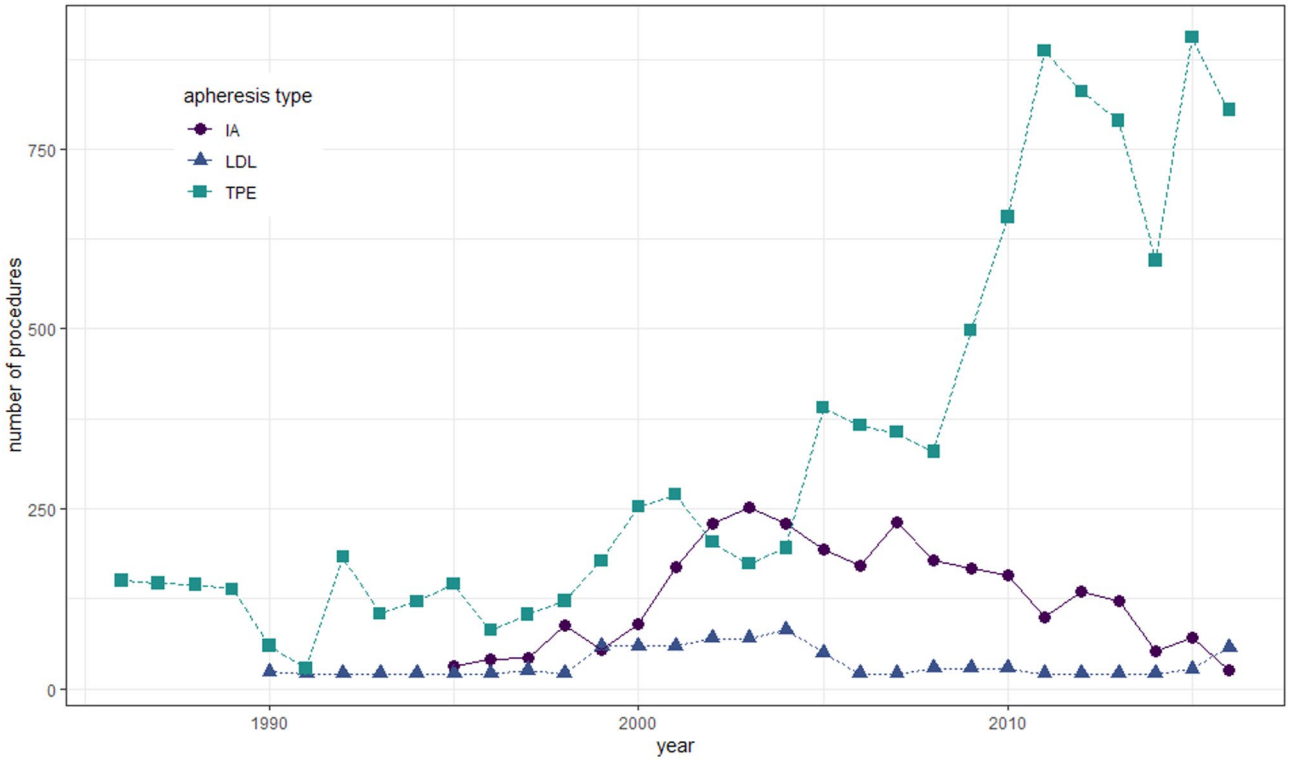

Fig. 2 Number of apheresis procedures performed, stratified by apheresis modality, over time. (LDL – LDL apheresis, IA – immunoadsorption, TPE – therapeutic plasma exchange)

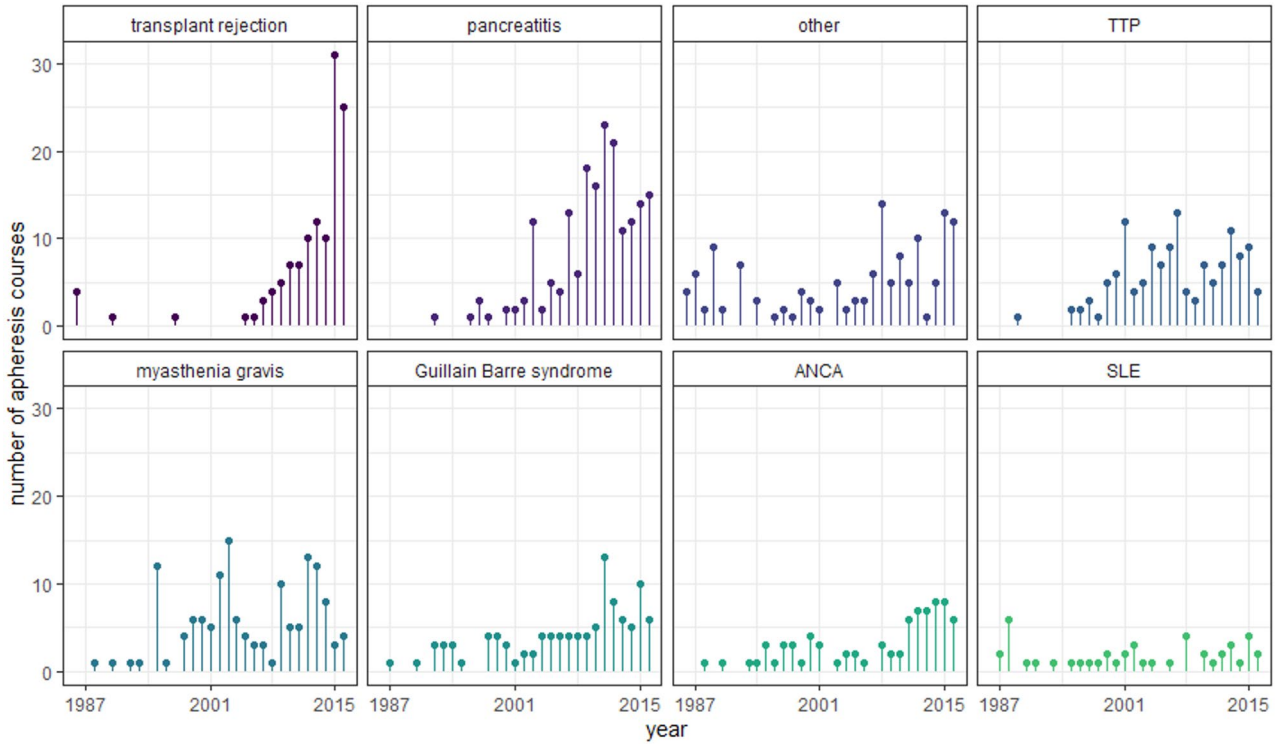

Fig. 3 Breakup of indications for apheresis treatment over time. (TTP = thrombotic thrombocytopenic purpura, ANCA = antineutrophil antibody associated vasculitis, SLE = systemic lupus erythematosus)

Table 1 Patients' and apheresis procedures' characteristics in two time periods (1986–2000 vs. 2001–2016). Data are shown as number (percent)

	1986–2000[1]	2001–2016[1]	*p*-value[2]
Apheresis courses	318	1026	/
Female gender	48%	47%	0.600
Age (years)	44 (28–62)	51 (39–65)	< 0.001
Procedures per patient	6 (3–10)	6 (3–11)	0.800
Courses of treatments			
• TPE	• 270 (85%)	• 880 (86%)	0.770
• IA	• 32 (10%)	• 92 (9%)	0.631
• LDL	• 5 (2%)	• 10 (1%)	0.561
• other/combined	• 11 (3%)	• 42 (4%)	0.731
Vascular access at first procedure (%)			
• CVC	• 75 (24%)	• 695 (68%)	< 0.001
• CVC + peripheral	• 167 (52%)	• 192 (19%)	< 0.001
• AVF	• 13 (4%)	• 70 (7%)	0.101
• other	• 63 (20%)	• 69 (6%)	< 0.001
Viral hepatitis			
• HBV	• 11 (3.5%)	• 37 (3.6%)	> 0.9
• HCV	• 2 (0.6%)	• 18 (1.8%)	0.200

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

PEX: plasma exchange, IA: immunoadsorption, LDL: LDL apheresis, CVC: central venous catheter, AVF: arterio-venous fistula, HBV: hepatitis B virus, HCV: hepatitis C virus

the second period, whereas the number of procedures per patient did not change. There was an increase in the median age of patients in the second period, with a comparable sex structure (see Table 1). Notably, the number of procedures per patient was stable and there were no notable differences in the types of procedures used; however, the use of vascular access (during the first procedure) changed dramatically, with a reduction in the use of peripheral veins and increased use of catheters.

Apheresis in children

During the observed period of 30 years, 74 children (< 18 years old) were treated with 83 courses of apheresis. The median age of the children was 14 (IQR 8–17) years, and there was an equal distribution of both sexes (48% girls). The most common indications for apheresis were (a) HUS (12%), followed by TTP (12%), Guillain-Barré syndrome and acute liver failure (both 10%). The most common vascular access method used was a central venous catheter (68%), followed by a catheter, combined with a peripheral vein (13%), and an AVF (8%). The total number of procedures performed in children was 1,706. The median number of procedures per course of treatment was 9 (IQR 6–15) over a median duration of 17 (IQR 6–43) days.

Apheresis in elderly patients

We treated 286 elderly patients (≥65 years) with 329 courses of apheresis and a total number of 2,595 procedures. The most common indications for apheresis were myasthenia gravis (20%), Guillain-Barré syndrome and ANCA-associated vasculitis (13%) as well as (a)HUS/TTP (10%). The median age of the elderly patients was 73 (IQR 69–77) years, and there was an equal distribution of both sexes (50% females). 62% started apheresis with a central venous catheter, 30% with a CVC and a peripheral vein and less than 2% with an AVF. Among the elderly patients, 119 patients older than 75 years (median 77 years, IQR 76–80 years) were included; these patients underwent 141 courses with a total of 1,002 procedures. Their characteristics did not differ substantially. There was a median of 6 (IQR 4–10) procedures per apheresis course performed over a median of 14 (IQR 7–26) days.

Chronic apheresis (> 3 months of treatment)

We arbitrarily defined a chronic apheresis as any treatment course that was longer than 90 days. This cut-off was partly based on the fact that the distribution of the apheresis treatment duration dropped sharply around 90 days interval and that no apheresis treatment in the intensive care unit was longer than 90 days (see Supplementary Fig. S1). We treated 109 patients who underwent apheresis treatment for more than 3 months. The patients' median age was 49 (IQR 40–61) years, and 62% were females. Those patients were most commonly treated for myasthenia gravis (30%), primary focal segmental glomerulosclerosis (13%), cryoglobulinemia (12%), and chronic inflammatory demyelinating polyneuropathy (8%). This group of patients underwent 5,386 procedures, with a median of 25 (IQR 15–57) procedures per treatment course. The median treatment course duration was 309 days (IQR 133–1,099). Almost half (49%) of the patients on chronic apheresis were treated with immunoadsorption or LDL apheresis, which enabled the longest interval between procedures.

Complications during apheresis (2010–2016 period)

We analyzed complications during all apheresis procedures performed in a subgroup of patients, treated between 2010 and 2016. We collected detailed patient and treatment data for 4,880 apheresis procedures performed during 589 apheresis treatment courses in 531 patients (median age 51 (IQR 40–65) years, 47% females). Most procedures (90%) were performed in hospitalized patients. There were 4,579 TPE procedures, 226 immunoadsorption procedures and 75 LDL apheresis procedures (94%, 4.6% and 1.5%, respectively). In TPE, an albumin solution was used as a replacement fluid in 56% of the procedures, whereas FFP was used as a full (24%) or partial (20%) replacement volume in the remaining procedures. Regarding anticoagulation during apheresis procedures, regional citrate anticoagulation (RCA) was used in 87% of the procedures, and the other procedures were performed with systemic heparin anticoagulation. In terms of initial vascular access, 75% of procedures were performed via CVCs, 12% via AVFs, 8.8% via CVCs and peripheral veins, 4% via peripheral veins only, and a small proportion otherwise (e.g., via extracorporeal membrane oxygenation (ECMO)).

We analyzed a predefined set of adverse events that were usually documented in patients' apheresis records; the results are shown in Tables 1, 2 and 3. The most frequently observed complication during apheresis treatment was hypotension, which occurred in 126 (2.6%) procedures. Hypotension was more common during LDL

Table 2 Frequency of adverse events during 4,880 apheresis procedures (in 2010 to 2016 period)

Adverse event	*N* (%)
Allergy	109 (2.2%)
• Anaphylaxis	9 (0.2%)
• Rash/urticaria	100 (2.0%)
Hypotension	126 (2.6%)
Nausea	41 (0.8%)
Hypocalcemia	63 (1.3%)
Procedure stopped due to adverse event	29 (0.6%)
• Anaphylaxis	6 (0.1%)
• Hemolysis	5 (0.1%)
• Hypotension	2 (< 0.1%)
• Other	13 (0.3%)
• Resuscitation	2 (< 0.1%)
• Death	1 (< 0.1%)

Table 3 Adverse events, stratified by procedure type (2010 to 2016 period)

Adverse event	TPE, *N* = 4,579[1]	LDL, *N* = 75[1]	IA, *N* = 226[1]	*p*-value[2]
Allergy	106 (2.3%)	1 (1.3%)	2 (0.9%)	0.412
Allergy – type:				0.244
• Anaphylaxis	8 (0.2%)	0 (0%)	1 (0.4%)	
• Rash/urticaria	98 (2.1%)	1 (1.3%)	1 (0.4%)	
Hypotension	106 (2.3%)	11 (15%)	9 (4.0%)	**< 0.001**
Nausea	27 (0.6%)	4 (5.3%)	10 (4.4%)	**< 0.001**
Hypocalcemia	61 (1.3%)	0 (0%)	2 (0.9%)	0.740
Procedure stopped	20 (0.4%)	2 (2.7%)	5 (2.2%)	**0.002**
Reason for stopping:				**< 0.001**
• Anaphylaxis	6 (0.1%)	0 (0%)	0 (0%)	
• Hemolysis	4 (< 0.1%)	0 (0%)	1 (0.4%)	
• Hypotension	0 (0%)	2 (2.7%)	0 (0%)	
• Other	8 (0.2%)	0 (0%)	3 (1.3%)	
• Resuscitation	1 (< 0.1%)	0 (0%)	1 (0.4%)	
• Death	1 (< 0.1%)	0 (0%)	0 (0%)	

[1] n (%)

[2] Fisher's exact test

TPE: therapeutic plasma exchange; LDL: LDL apheresis; IA: immunoadsorption

apheresis (15% of procedures) and less common when the replacement fluid used during TPE was FFP (1.8% of procedures).

Allergic reactions were recorded during 109 (2.2%) procedures and were more common during TPE with FFP used as a replacement solution (5% of procedures). Allergic reactions were described mainly as transient rash (urticaria), whereas true anaphylactic reactions were very rare and occurred in only in a small number of procedures (9 procedures, 0.2% of all procedures), but were more common during TPE with FFP (6 procedures, 0.3% of all procedures with FFP as part of replacement solution; see Table 4). Interestingly, the allergic reaction recured in only 12 courses of apheresis treatment. It should be noted that it was our clinical practice to prescribe preventive antihistaminic in patients after first allergic reaction and that some patients were also receiving corticosteroids for their primary disease.

There were 63 cases (1.3%) of severe hypocalcemia (defined as ionized calcium < 0.85). As expected, they were more common if FFP was used as part of the substitution fluid (40 cases, 2% of procedures with FFP) and when RCA was used (62 cases, 1.5% of procedures with RCA). Nausea was recorded in only 41 cases (0.8%), and it seemed to be more common during immunoadsorption and LDL apheresis (5.3% and 4.4% of procedures, respectively).

In 29 cases (0.6%), the procedure was stopped because of a complication. The number is small, but it seems that immunoadsorption and LDL apheresis procedures were stopped more frequently (immunoadsorption in 5 cases (2.2% of immunoadsorption procedures), LDL in 2 cases (2.7% of LDL procedures), $p < 0.001$), whereas TPE was only stopped in 19 cases (0.4% of TPE procedures). We recorded 2 resuscitations and 1 death during an apheresis procedure, which was not necessarily related to the procedure itself (the cause of resuscitation/death could not be determined from apheresis records).

A comparison of complications in elderly patients (aged ≥ 65 years) and younger patients (see Table 5), revealed a significantly lower incidence of allergic reactions in elderly (0.8% vs. 2.8% of procedures), but a greater risk of hypotension during apheresis (4% vs. 2.1% of procedures). Other adverse events occurred with similar frequencies in elderly and younger patients.

Table 4 Adverse events, stratified by the use of FFP during apheresis (2010 to 2016 period). The group without FFP includes also apheresis procedures without a replacement solution (IA and LDL)

Adverse event	Procedures with FFP, *N* = 2,018[1]	Procedures without FFP, *N* = 2,862[1]	*p*-value[2]
Allergy	100 (5.0%)	9 (0.3%)	**< 0.001**
Allergy – type:			**< 0.001**
• Anaphylaxis	6 (0.3%)	3 (0.1%)	
• Rash/urticaria	94 (4.7%)	6 (0.2%)	
Hypotension	37 (1.8%)	89 (3.1%)	**0.006**
Nausea	12 (0.6%)	29 (1.0%)	0.115
Hypocalcemia	40 (2.0%)	23 (0.8%)	**< 0.001**
Procedure stopped	14 (0.7%)	13 (0.5%)	0.267
Reason for stopping:			0.253
• Anaphylaxis	5 (0.2%)	1 (< 0.1%)	
• Hemolysis	2 (< 0.1%)	3 (0.1%)	
• Hypotension	0 (0%)	2 (< 0.1%)	
• Other	5 (0.3%)	6 (0.2%)	
• Resuscitation	1 (< 0.1%)	1 (< 0.1%)	
• Death	1 (< 0.1%)	0 (0%)	

[1] n (%)

[2] Pearson's Chi-squared test; Fisher's exact test

FFP: fresh frozen plasma

Table 5 Adverse events, stratified by age group

Adverse event	Age < 65 years, *N* = 3,591[1]	Age ≥ 65 years, *N* = 1,289[1]	*p*-value[2]
Any event	249 (6.9%)	93 (7.2%)	0.735
Allergy	99 (2.8%)	10 (0.8%)	**< 0.001**
Allergy – type:			**< 0.001**
• Anaphylaxis	9 (0.3%)	0 (0%)	
• Rash/urticaria	90 (2.5%)	10 (0.8%)	
Hypotension	74 (2.1%)	52 (4.0%)	**< 0.001**
Nausea	32 (0.9%)	9 (0.7%)	0.515
Hypocalcemia	43 (1.2%)	20 (1.6%)	0.334
Procedure stopped	21 (0.6%)	6 (0.5%)	0.620
Reason for stopping:			0.644
• Anaphylaxis	5 (0.1%)	1 (< 0.1%)	
• Hemolysis	4 (0.1%)	1 (< 0.1%)	
• Hypotension	2 (< 0.1%)	0 (0%)	
• Other	9 (0.3%)	2 (0.2%)	
• Resuscitation	1 (< 0.1%)	1 (< 0.1%)	
• Death	0 (0%)	1 (< 0.1%)	

[1] n (%)

[2] Pearson's Chi-squared test; Fisher's exact test

Discussion

In this report, we present three decades of experience with therapeutic apheresis at a tertiary center, which represents one of a few large cohort studies in the field of apheresis [17, 23, 24]. Some of the changes in clinical practice patterns are described as well as an analysis of apheresis in children and elderly individuals and treatment complications in a large subgroup of procedures.

Changes in epidemiology & indications

In our cohort, the indications for therapeutic apheresis changed substantially over time (see Fig. 3). There was a large increase in the use of apheresis for the treatment of antibody-mediated rejection (AMR) of transplanted kidneys (only rarely heart transplants) and hypertriglyceridemic pancreatitis. The increase in AMR as an indication followed a few years after the increase in the number of

kidney transplants performed in Slovenia after joining Eurotransplant [22]. Interestingly, the increase in AMR is in contrast to the findings of another published report [25]. Apheresis requirements in kidney transplantation might decrease in the future, owing to new treatments [26]. The increase in hypertriglyceridemic pancreatitis as an indication can be explained by increased awareness after we performed our initial analysis of this subgroup [27], although a steep decline is expected in the future, as our small randomized study revealed a very limited advantage of apheresis over conservative treatment [21]. The number of patients treated for (a)HUS/TTP also increased somewhat, probably due to better recognition of aHUS in past years. However, this could also be considered surprising, as the shift from clinical to laboratory diagnosis (with the use of ADAMTS levels and activity) should decrease the overall use of apheresis [28]. The majority of neurological indications were stable over time in our cohort. On the other hand, we have only a few patients on lipid apheresis, which might be underused, as noted by a report from a dedicated center in Germany [29, 30]. However, the sporadic nature of less-prevalent diseases and/or conditions prevents the analysis of subtle changes in general. Despite the long observation time and relatively large patient cohort, the number of changing indications for rare disorders (highlighted in the recent guidelines [6]) is not fully reflected in our review. Inclusion into multi-center registries would be necessary to capture the true incidence, implementations, and outcomes of therapeutic apheresis in these cases.

There is a great need to increase awareness of the role of apheresis therapy among collaborating specialties. In our center, apheresis is performed under the supervision of a nephrologist, but the indication is established in cooperation with other specialists, who treat specific conditions. It was shown that dedicated centers have a larger number of treated patients. This implies that patients at peripheral centers might be deprived of apheresis treatment even for established indications [29].

Trends in vascular access for apheresis

One important but often neglected technical aspect of apheresis treatment is the way in which vascular access is obtained. It is generally assumed, that a central venous access is needed. A retrospective study from 1989 questioned the need for a central venous catheter, since more than 60% of TPE procedures were performed with peripheral access only [31]. Similarly, a cohort study from the field of neurology reported the use of a peripheral access in 73% of cases [32], and a hematology-based apheresis center reported 41% [33]. As many complications during apheresis are a direct consequence of obtaining or maintaining a central venous access [34], achieving a peripheral-access driven apheresis could be a part of a strategy to reduce complications [35, 36]. Our data on vascular access are incomplete, as we recorded only vascular access at the first apheresis procedure, but they nevertheless showed the opposite trend of increasing use of central catheters. Notably, the recommendations of the ASFA working group for the preferred use of peripheral access in apheresis acknowledge its inferiority in membrane-based apheresis owing to longer procedure times and higher blood flow requirements [36] and the fact that our center uses membrane-based apheresis exclusively. Furthermore, as nephrologists, we advocate against the use of peripheral veins in the subgroup of patients with chronic kidney disease, as they should be preserved for vascular access for future hemodialysis in this population.

On the other hand, for successful chronic treatment with apheresis (e.g., lipid apheresis or as a maintenance treatment for some neurologic conditions), a peripheral access is often considered almost obligatory and peripheral access is indeed more commonly used in chronic apheresis [37]. In our opinion, for patients requiring apheresis as a long-term (e.g., more than 6 months) or even "indefinite" treatment (e.g., lipid apheresis), the construction of an AVF should be considered, except when the procedures are performed infrequently (e.g., immunoadsorption). Data on AVF use in apheresis are scarce, but the use of AVF used for apheresis often seems limited, possibly due to the absence of hypervolemia, which is associated with chronic kidney disease. Existing AVFs can always be used in kidney graft recipients, when available [38].

Safety of apheresis procedures

Overall, apheresis is generally considered a very safe treatment. Our data on a large subset of almost 5,000 procedures confirm this impression. The most common adverse events were hypotension and mild allergic reactions. Comparison with data from the literature are problematic, as the evaluation and grading of adverse effects are not consistent. A review of the available reports highlights great differences in center-reported adverse events, ranging from 2.3 to 6.9% [17, 18, 23, 24, 39] or even higher in the elderly population [18]. The variability stems from patient selection, treatment modalities, data acquisition, reporting, and possibly other factors. The structure of our data did not allow for grading of adverse event severity. However, a surrogate of severity could be the incidence of procedures that are stopped, which is very rare (0.6%), although there could be some interference with technical issues. Death occurred in only one procedure, in line with long-standing safety from lethal consequences [40].

With respect to procedure type, LDL apheresis was associated with more hypotension and premature

procedure termination (which was also the case for immunoadsorption; see Table 3). The higher incidence of hypotension in LDL is well-known as recently reviewed by Mickiewicz et al. [41] and likely reflects bradykinin reactions [42]. Notably, our patients did not undergo LDL apheresis, if they were receiving angiotensin converting enzyme inhibitor (ACEi) treatment.

Furthermore, when FFP is used as a substitution fluid, allergic reactions and hypocalcemia are more common, which was confirmed in our population (Table 4). This is likely due to the immunogenic characteristics of donor-derived plasma and the additional amount of citrate delivered to the patient. Hypotension, on the other hand, was more common when albumin was used as a replacement. Frequent TPE leads to the depletion of coagulation factors, with the subsequent need to use FFP as part of the replacement solution. One possible alternative is the use of purified fibrinogen concentrate, which might prevent allergic reactions. We have some preliminary experience with this [19], but a RCT would be necessary to prove superior safety and equal efficacy of fibrinogen concentrate vs. FFP used for correction of consumption coagulopathy.

It may be difficult to fully estimate the frequency of electrolyte disorders as an adverse effect, but a low frequency of severe hypocalcemia indicates good safety. Notably, we routinely use calcium substitution in our TPE with regional citrate anticoagulation, which has also been the preferred anticoagulation method in recent years [43].

Therapeutic apheresis in special age groups

Apheresis can be safely performed in pediatric patients [44]. In our center, we also treated a substantial number of pediatric patients, the majority of them for (a)HUS/TTP and Guillain-Barré syndrome. The pediatric population has specific challenges, and the number of pediatric patients treated with apheresis is generally very low. The main indications for performing apheresis occur infrequently in the pediatric population, but apheresis remains crucial in some severe cases.

Elderly patients also represent a special and growing subgroup of patients. Our center's experience is similar to other published data [18]; however, in contrast to the former study, where complications were more common in the elderly population, our data show that the overall incidence of complications is similar to that in the younger population (Table 5). Interestingly, the nature of the complications in the elderly group was different: they tended to have fewer allergic reactions, but more frequent hypotension. This is not surprising, as immunosenescence is well-documented, whereas cardiovascular comorbidities and the autonomous disfunction predispose patients to more frequent hypotension.

Strengths and limitations

One of the strengths of our analysis is that our center is a referral center for most of the country and therefore covers a defined population on a continuous basis; therefore, conclusions on the changes in practice can be drawn. Furthermore, we performed a per-procedure review of adverse events for a cumulative period of 17 years and these data were conclusive. The study is, nevertheless, retrospective in nature, with often incomplete records, which is inferior to prospective registries. Furthermore, our cohort might be biased toward treating disorders related to nephrology, neurology and rheumatology due to somewhat poorer collaboration with other specialties.

Conclusion

Therapeutic apheresis is an established and recognized therapy for many conditions and current retrospective study of 30-year long period emphasizes the proven efficiency and a low adverse effect profile. Despite changing indications and clinical practice, apheresis remains a significant tool and is irreplaceable even under certain conditions because of its fast action and nonspecific removal of pathogenic molecules. However, the field of apheresis is evolving as newer and more selective treatments are continuously being developed. We need to evaluate apheresis efficiency on a regular basis and raise awareness of the existing and possibly new and underrecognized indications. Some advances in the implementation of apheresis have been made in recent years, including improvements in vascular access for chronic apheresis and strategies to avoid FFP. Although apheresis presents some additional challenges in very young or very old patients, it is very safe even in these populations.

Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ANCA	Antineutrophil antibody associated vasculitis
AMR	Antibody-mediated rejection
ASFA	American Society For Apheresis
AVF	Arteriovenous fistula
(a)HUS	Atypical hemolytic uremic syndrome
CVC	Central venous catheter
ECMO	Extracorporeal membrane oxygenation
FFP	Fresh frozen plasma
IA	Immunoadsorption
IQR	Interquartile range
LDL	Low-density lipoprotein
RCA	Regional citrate anticoagulation
SLE	Systemic lupus erythematosus
TA	Therapeutic apheresis
TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-026-04750-2.

Supplementary Material 1: Supplementary Fig.1. Distribution of therapeutic apheresis duration (days) per treatment course

Acknowledgements
We would like to express our gratitude to Alenka Jerman, who has helped in collecting data from our archived health records.

Author contributions
AJ and VP designed the study. AJ acquired the data and performed the statistical analysis. AJ, MA, AŽČ, DF, JG, AMP, BM, RP, KR, BVT, MZ, and VP interpreted the results. AJ wrote the manuscript draft. All the authors revised and approved the final manuscript.

Funding
The study was partially funded by University Medical Center Ljubljana, research grant no. 20220095.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study conforms to the provisions of the Declaration of Helsinki and was approved by the National Medical Ethics Committee (Ref. No. 0120–441/2022/3).

Consent for publication
All personal data were anonymized before the publication. The need for informed consent was waived by the National Medical Ethics Committee (Ref. No. 0120–441/2022/3).

Competing interests
The authors declare no competing interests.

Received: 28 July 2025 / Accepted: 6 January 2026
Published online: 13 January 2026

References

1. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American society for apheresis guidelines. Hematol Am Soc Hematol Educ Program. 2012;2012:7–12. https://doi.org/10.1182/asheducation-2012.1.7.
2. Strauchmann J, et al. Lipoprotein apheresis reduces biomarkers of plaque destabilization and cardiovascular risk. J Clin Apheresis. 2014;29(5):235–42. https://doi.org/10.1002/jca.21311.
3. Ibrahim RB, Balogun RA. Medications and therapeutic apheresis procedures: are we doing our best? J Clin Apheresis. 2013;28(1):73–7. https://doi.org/10.1002/jca.21261.
4. Krzych ŁJ, Czok M, Putowski Z. Is antimicrobial treatment effective during therapeutic plasma exchange? Investigating the role of possible interactions. Pharmaceutics. 2020 Apr;12(5):395. https://doi.org/10.3390/pharmaceutics12050395.
5. Mahmoud SH, Buhler J, Chu E, Chen SA, Human T. Drug dosing in patients undergoing therapeutic plasma exchange. Neurocrit Care. 2021 Feb;34(1):301–11. https://doi.org/10.1007/s12028-020-00989-1.
6. Connelly-Smith L, 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 ninth special issue. J Clinical Apheresis. 2023 Apr;38(2):77–278. https://doi.org/10.1002/jca.22043.
7. Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis. 2008 Dec;52(6):1180–96. https://doi.org/10.1053/j.ajkd.2008.02.360.
8. Cervantes CE, Bloch EM, Sperati CJ. Therapeutic plasma exchange: core curriculum 2023. Am J Kidney Dis. 2023 Apr;81(4):475–92. https://doi.org/10.1053/j.ajkd.2022.10.017.
9. Williams ME, Balogun RA. Principles of separation: indications and therapeutic targets for plasma exchange. CJASN. 2014 Jan;9(1):181–90. https://doi.org/10.2215/CJN.04680513.
10. Levin PD, Levin V, Weissman C, Sprung CL, Rund D. Therapeutic plasma exchange as treatment for propofol infusion syndrome. J Clin Apher. 2015 Oct;30(5):311–13. https://doi.org/10.1002/jca.21376.
11. Poisson JL, Low A, Park YA. The treatment of nephrogenic systemic fibrosis with therapeutic plasma exchange. J Clin Apher. 2013 Aug;28(4):317–20. https://doi.org/10.1002/jca.21253.
12. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021 Dec;39(6):4073–126. https://doi.org/10.1200/JCO.21.01440.
13. Gubensek J, Ponikvar R, Premru Srsen T, Fabjan Vodusek V, Moertl MG, Lucovnik M. Therapeutic plasma exchange and dextran-sulfate plasma adsorption as extracorporeal treatments of extremely preterm preeclampsia with fetal growth restriction. J Clin Apheresis. 2021;36(4):595–605. https://doi.org/10.1002/jca.21899.
14. Gubenšek J, Ponikvar R, Premru T, Sršen V, Fabjan Vodušek MG, Moertl, Lučovnik M. Treatment of preeclampsia at extremely preterm gestation with therapeutic plasma exchange. Clin Nephrol. 2021 Suppl;96(1):101–6. https://doi.org/10.5414/CNP96S18.
15. Thadhani R, et al. Removal of soluble Fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. J Am Soc Nephrol. 2016 Mar;27(3):903–13. https://doi.org/10.1681/ASN.2015020157.
16. Winkler K, et al. Treatment of very preterm preeclampsia via heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) apheresis: the Freiburg preeclampsia H.E.L.P.-Apheresis study. Pregnancy Hypertens. 2018 Apr;12:136–43. https://doi.org/10.1016/j.preghy.2018.04.007.
17. Stegmayr B, et al. Using the world apheresis association registry helps to improve the treatment quality of therapeutic apheresis. TMH. 2021;48(4):234–9. https://doi.org/10.1159/000513123.
18. Basic-Jukic N, Brunetta B, Kes P. Plasma exchange in elderly patients. Therapeutic Apheresis Dialysis. 2010 Apr;14(2):161–5. https://doi.org/10.1111/j.1744-9987.2009.00793.x.
19. Zrimsek M, Gubensek J, Marn Pernat A. A pilot study on the replacement of fibrinogen with fibrinogen concentrates during therapeutic plasma exchange with mild to moderate bleeding risk—a comparison with fresh frozen plasma and albumin replacement. J Clin Med. 2024 Jan;13(24). https://doi.org/10.3390/jcm13247662.
20. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2024. R Core Team, Vienna, Austria. [Online]. Available: https://www.R-project.org/.
21. Gubensek J, et al. Comparable triglyceride reduction with plasma exchange and insulin in acute pancreatitis - a randomized trial. Front Med (Lausanne). 2022;9:870067. https://doi.org/10.3389/fmed.2022.870067.
22. Kandus A, Buturović Ponikvar J, Mlinšek G, Oblak M, Arnol M. Kidney transplantation in Slovenia from 1970 to 2015. Therapeutic Apheresis Dialysis. 2016;20(3):229–33. https://doi.org/10.1111/1744-9987.12428.
23. Mörtzell M, Henriksson, et al. Adverse events in apheresis: an update of the WAA registry data. Transfus Apher Sci. 2016 Feb;54(1):2–15. https://doi.org/10.1016/j.transci.2016.01.003.
24. Basic-Jukic N, Kes P, Glavas-Boras S, Brunetta B, Bubic-Filipi L, Puretic Z. Complications of therapeutic plasma exchange: experience with 4857 treatments. Therapher Dial. 2005 Oct;9(5):391–95. https://doi.org/10.1111/j.1744-9987.2005.00319.x.
25. Brunetta Gavranić B, Bašić-Jukić N, Kes P. Changes in indications for therapeutic plasma exchange over the last 27 years in croatia: therapeutic plasma exchange in Croatia. Therapeutic Apheresis Dialysis. 2011 Dec;15(6):587–92. https://doi.org/10.1111/j.1744-9987.2011.00986.x.
26. Doberer K, et al. CD38 antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation. 2021 Feb;105(2):451–57. https://doi.org/10.1097/TP.0000000000003247.
27. Gubensek J, et al. Treatment of hyperlipidemic acute pancreatitis with plasma exchange: a single-center experience. Ther Apher Dial. 2009 Aug;13(4):314–7. https://doi.org/10.1111/j.1744-9987.2009.00731.x.
28. Martin IW, Katus MC, Martin C-LB, Szczepiorkowski ZM, Gorham JD, Dunbar NM. Rapid ADAMTS13 availability impacts treatment for microangiopathic hemolytic anemia and thrombocytopenia. J Clin Apher. 2016 Oct;31(5):419–22. https://doi.org/10.1002/jca.21419.
29. Heigl F, et al. Lipoprotein apheresis in Germany - Still more commonly indicated than implemented. How can patients in need access therapy? Atheroscler Suppl. 2019 Dec;40:23–9. https://doi.org/10.1016/j.atherosclerosissup.2019.08.038.
30. Heigl F, et al. Indication and implementation of lipidapheresis, rheopheresis, or immunoadsorption (lessons learnt from Germany's largest apheresis center). Atheroscler Suppl. 2009 Dec;10(5):137–41. https://doi.org/10.1016/S1567-5688(09)71829-X.

31. Sutton D, Nair R, Rock G. Complications of plasma exchange. Transfusion. 1989 Feb;29(2):124–7. https://doi.org/10.1046/j.1537-2995.1989.29289146829.x.
32. Codron P, et al. Therapeutic plasma exchange in chronic dysimmune peripheral neuropathies: a 10-year retrospective study. J Clin Apher. 2017 Dec;32(6):413–22. https://doi.org/10.1002/jca.21530
33. Cid J, et al. The Barcelona hospital Clínic therapeutic apheresis database. J Clin Apher. 2018 June;33(3):259–64. https://doi.org/10.1002/jca.21587.
34. Couriel D, Weinstein R. Complications of therapeutic plasma exchange: a recent assessment. J Clin Apheresis. 1994;9(1):1–5. https://doi.org/10.1002/jca.2920090102.
35. Golsorkhi M, Azarfar A, Abdipour A. Vascular access in therapeutic apheresis: one size does not fit all. Therapeutic Apheresis Dialysis. 2022;26(4):694–16. https://doi.org/10.1111/1744-9987.13799.
36. Barth D, et al. Peripheral vascular access for therapeutic plasma exchange: A practical approach to increased utilization and selecting the most appropriate vascular access. J Clin Apheresis. 2020;35(3):178–87. https://doi.org/10.1002/jca.21778.
37. Doherty DJ, Pottle A, Malietzis G, Hakim N, Barbir M, Crane JS. Vascular access in lipoprotein apheresis: a retrospective analysis from the uk's largest lipoprotein apheresis centre. J Vasc Access. 2018 Jan;19(1):52–7. https://doi.org/10.5301/jva.5000755.
38. Vajdič Trampuž B, Arnol M, Gubenšek J, Ponikvar R, Buturović J, Ponikvar. A national cohort study on Hemodialysis arteriovenous fistulas after kidney transplantation - long-term patency, use and complications. BMC Nephrol. 2021 Oct;22(1):344. https://doi.org/10.1186/s12882-021-02550-4.
39. Kundrapu S, Datla S, Griffin V, Maitta RW. Adverse events during apheresis: a 10-year experience at a tertiary academic medical center. J Clin Apher. 2019 Oct;34(5):528–36. https://doi.org/10.1002/jca.21706.
40. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. Am J Kidney Dis. 1994 June;23(6):817–27. https://doi.org/10.1016/s0272-6386(12)80135-1.
41. Mickiewicz A et al. Long-term lipoprotein apheresis in the treatment of severe familial hypercholesterolemia refractory to high intensity statin therapy: three year experience at a lipoprotein apheresis center. Cardiol J. 2020 Jan;26(6):669–79. https://doi.org/10.5603/CJ.a2018.0100.
42. Krieter DH, et al. Contact activation in low-density lipoprotein apheresis systems. Artif Organs. 2005 Jan;29(1):47–52. https://doi.org/10.1111/j.1525-1594.2004.29007.x.
43. Antonic M, Gubensek J, Buturovic-Ponikvar J, Ponikvar R. Treatment efficacy and safety during plasma exchange with citrate anticoagulation: a randomized study of 4 versus 15% citrate. Artif Organs. 2016 Apr;40(4):368–75. https://doi.org/10.1111/aor.12559.
44. Sirignano RM, Paden ML, Fasano R, Meyer EK. Epidemiology of therapeutic apheresis with a multidisciplinary approach at a high volume pediatric center. J Clin Apher. 2018 June;33(3):297–302. https://doi.org/10.1002/jca.21604.

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