Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2020; 42 (1): 14-26

Research Article / Araştırma Makalesi

Therapeutic Plasma Exchange Indications, Complications and Responses : A Single Center, Retrospective Analysis.

Terapötik Plazma Değişimi Endikasyonları, Komplikasyonları ve Yanıtları; Tek Merkez, Retropsektif Analiz Sonuçları

[1]Bugra Ozkan, [2]Hava Uskudar Teke, [3]Dondu Uskudar Cansu, [4]Garip Sahin

[1]Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[2]Division of Hematology, Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[3]Division of Rheumatology, Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey
[4]Division of Nephrology, Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract: Therapeutic plasma exchange (TPE) is a process that allows high molecular weight substances to be removed from plasma. Therapeutic plasma exchange is widely used in many diseases in the practice of internal medicine. Current guidelines on this process have been published in recent years due to increased awareness and accessibility. The most common and most comprehensive of these is the American Apheresis Society (ASFA) guideline. In this study, we retrospectively determined the demographic data, underlying diseases, biochemical parameters, volume and type of replacement fluid, complications developed during and after the procedure, additional treatments, need for dialysis, and the number of sessions for patients who underwent therapeutic plasma exchange for any reason in the internal medicine clinic aimed to reveal aspects that can be improved in clinical practice. In the study, 117 patients between 2007 and 2016 were evaluated retrospectively. Of all cases, 63 (53.8%) were female. At the time of diagnosis, the mean age of the patients was 52.15 ± 16.8 (20-88) years. The most common indications for TPE were thrombotic thrombocytopenic purpura (TTP) and ANCA-associated vasculitis. Fresh frozen plasma and albumin were the most commonly used replacement fluids. Catheter related complication rate was 5.1%. The rate of complication related to TPE during TPE was 19.6%. No fatal reactions to TPE treatment were observed. There was a significant relationship between alkaline phosphatase (ALP) and mortality when the relationship between the laboratory data and the mortality rate of the patients with TTP was considered (p = 0.002). There was a significant correlation between chlorine and hematocrit and mortality in ANCA-associated vasculitis patients (p = 0.029 and p= 0.037, respectively). For the purpose of estimating mortality, further work is needed to confirm the validity of these laboratory data. As a result; TPE is a useful, easy and effective life saving treatment with few side effects.
Keywords: therapeutic plasma exchange, TTP, ANCA-associated vasculitis, mortality

Özet: Terapötik plazma değişimi (TPD) plazmadan yüksek molekül ağırlıklı maddelerin uzaklaştırılmasını sağlayan bir işlemdir. Terapötik plazma değişimi işlemi iç hastalıkları pratiğinde birçok hastalıkta yaygın olarak kullanılmaktadır. Bu işlem ile ilgili son yıllarda farkındalığın ve ulaşılabilirliğin artmasına bağlı olarak güncel kılavuzlar yayımlanmaktadır. Bunlardan en genel geçer ve kapsamlı olanı Amerikan Aferez Cemiyeti (ASFA)'nin yayımladığı kılavuzdur. Bu çalışmada, iç hastalıkları kliniğinde herhangi bir nedenle terapötik plazma değişimi yapılan hastaların demografik verilerini, altta yatan hastalıklarını, biyokimyasal parametrelerini, replasman sıvısının volümü ve tipini, işlem sırasında ve sonrasında gelişen komplikasyonları, ek tedavileri, diyaliz ihtiyacı olup olmadığını, seans sayılarını retrospektif olarak belirleyerek klinik pratikte geliştirilebilecek yönleri ortaya koyabilmek amaçlandı. Çalışmada 2007 ve 2016 yılları arasındaki, 117 hasta retrospektif olarak değerlendirildi. Tüm olguların 63 (%53,8)'ü kadın, 54 (%46,2)'ü erkekti. Tanı anında hastaların yaş ortalaması 52,15 ± 16,8 (20-88) yıl idi. En sık TPD endikasyonu TTP ve ANCA ilişkili vaskülit idi. Taze donmuş plazma ve albümin en sık kullanılan replasman sıvılarıydı. Katater ilişkili komplikasyon oranı %5,1 idi. TPD süresince TPD ilişkili komplikasyon oranı %19,6 idi. TPD işlemi ile ilgili herhangi bir fatal reaksiyona rastlanılmadı. TTP tanılı hastaların başvuru anındaki laboratuvar verileri ile mortalite arasındaki ilişkiye bakıldığında ALP ve mortalite arasında anlamlı bir ilişki bulundu (p= 0.002). ANCA ilişkili vaskülit hastalarında ise klor ve hematokrit ile mortalite arasında anlamlı bir ilişki bulundu (sırasıyla p = 0.029, p= 0.037). Mortaliteyi tahmin etmede kullanım amacıyla, bu laboratuvar verilerinin teyidi için ileri çalışmalara ihtiyaç vardır. Sonuç olarak; TPD, çok az yan etki ile faydalı, kolay ve etkili bir hayat kurtaran tedavi yöntemidir.
Anahtar Kelimeler: terapötik plazma değişimi, TTP, ANCA ilişkili vaskülit, mortalite

ORCID ID of the authors: B.O. 0000-0002-5614-8333, H.Ü.T. 0000-0002-4434-4580, D.Ü.C. 0000-0001-6543-3905 G.S. 0000-0003-0567-0866

Received 22.09.2018 ***Accepted*** 01.10.2018 ***Online published*** 02.10.2018

Correspondence: **Hava USKUDAR TEKE**- Division of Hematology, Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey, e-mail: havaus@yahoo.com

Cite this article as:
Ozkan B, Uskudar Teke H, Uskudar Cansu D, Sahin G. Therapeutic Plasma Exchange Indications, Complications and Responses in Internal Medicine Patients: A Single Center, Retrospective Analysis, Osmangazi Journal of Medicine , 2020;42(1):14-26
***Doi**: 10.20515/otd. 462835*

1. Introduction

Therapeutic plasma exchange (TPE) is a process which allows removal of high molecular weight substances from the plasma (eg immunocomplexes, endotoxins, myeloma light chains, lipoproteins, cryoglobulins). During the procedure, the patient's blood is passed through a medical device and the plasma is separated and replaced with combinations of colloid (albumin and / or plasma) or crystalloid / colloid solution. In addition to elimination of high molecular weight substances by plasma exchange, replacement of missing essential factors is also provided. TPE is indicated in addition to classical medical treatment in various nephrological, hematologic, rheumatologic, neurological, oncologic and multisystem diseases [1, 2]. Before TPE treatment entered clinical practice, the mortality of many related diseases was high. However, with TPE treatment, these mortality and morbidity rates have improved significantly [3-5]. The indication for TPE is often based on the definitions in the guidelines of the American Society of Apheresis (ASFA) [6, 7].

Apheresis, derived from a word that means separating or removing it by force in Greek. Apheresis was first tested on dogs in 1666 by Dr. Richard Lower [8]. Therapeutic plasma exchange was first applied in France in 1902 and in Russia in 1914 [9]. In the treatment of hyperviscosity syndrome in 1960, the use of TPE by Solomon and Fahey is acceptable as the starting point of the nearest TPE we are using today [10]. There is naturally more than one subtype of apheresis treatment applied in diseases in which pathophysiology is different and many different branches are concerned. Basically, application logic is similar, but various subdivisions are available in the literature, depending on who, how and for what purpose [6, 7].

The aim of this study was to evaluate the demographic data, underlying diseases, biochemical parameters, volume and type of replacement fluid, complications during and after the procedure, additional treatments, need for dialysis and number of sessions retrospectively for patients who underwent therapeutic plasma exchange for any reason in the internal medicine clinic and to reveal the aspects that can be improved in clinical practice.

2. Materials and Methods

Patients

In this study, data of 117 patients who had undergone TPE for University Hospital Department of Internal Medicine between January 1, 2007 and January 1, 2016 were examined after the approval of the local ethics committee.

During the first phase of the study, the records of the patients who underwent apheresis for any reason during the specified dates were examined at the University Medical Faculty Blood Center Apheresis Unit. Only those who applied TPE were recorded from these patients, patients who had undergone other procedures were excluded. patients who were in the pediatric age group and/or who were treated outside of internal medicine were not included in the study.

The retrospective data of patients deemed appropriate for inclusion in the study were recorded in the apheresis unit records, archives and electronic files. For each patient; demographic data (age, gender), indications for TPE and ASFA category, comorbid conditions, TPE onset and ending dates, duration of hospitalization, number and frequency of TPE sessions, additional immunosuppressive and/or chemotherapeutic drugs, concurrent hemodialysis need and persistence, the replacement fluid and volume used, the response to TPE, the route of vein used for TPE, and whether there were complications related to the route of vein, complications related to TPE procedure were recorded. The laboratory data included pre- and post- TPE, complete blood counts (CBC), creatinine, sodium, potassium, chlorine, calcium, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin and erythrocyte sedimentation rate were evaluated. Finally, information from the

archive file and electronic records was searched whether the patients were living or not. The records of all patients in the hospital information management system have been reviewed in order to confirm the information in the files or to complete the missing information.

Statistical Evaluation

Analysis of the data was done with the IBM SPSS 21.0 package program. The summary values for the quantitative variables were given as mean ± standard deviation or median (Q1-Q3). The summary values of the qualitative variables are shown as frequency and percentage. Normal distribution of quantitative variables was investigated by Shapiro-wilk test. Paired t test was used for dependent groups with normal distribution and Wilcoxon test was used for dependent groups without normal distribution. Independent groups with normal distribution were compared with independent samples by T test, Mann-Whitney U test was used for non-normal distribution. The statistical significance was accepted as $p < 0.05$.

3. Results

The data of 117 patients who met the inclusion criteria were retrospectively evaluated. Of all cases, 63 (53.8%) were female. At the time of diagnosis, the mean age of the patients was 52.15 ± 16.8 (20-88) years. The mean duration of TPE was 16,31 ± 18,7 (1-96) days. The mean duration of hospitalization was 29.74 ± 20.0 (0-101) days. The most common comorbid disease was hypertension in 40 (34.2%) of the patients. The demographic data of the examined patients are given in Table 1. The laboratory values of the patients on admission to the hospital are shown in Table 2.

When we look at the diagnosis with TPE indications; 35 (29.9%) patients had TTP, and 17 (14.5%) patients had ANCA associated vasculitis. Laboratory data of these two groups of patients are given in Table 3.

Table 1. Demographic data of TPE cases

Feature		Total (n=117)
Gender n, %	Female	63(%53.8)
	Male	54 (%46.2)
Age (mean ± sd, min.-max.) / year		52.15± 16.8 (20-88)
TPE duration (mean ± sd, min.-max.) / day		16.31± 18.7 (1-96)
Length of stay (mean ± sd, min.-max.) / day		29.74± 20.0 (0-101)
Number of TPE sessions (mean ± sd, min.-max.)		9.95± 10.0 (1-61)
TPE replacement fluid volume per session (mean ± sd, min.-max.)/unit		8.91± 2.4 (4-16)
Comorbidity n, %		
Hypertension		40 (%34.2)
Diabetes mellitus		20 (%17.1)
Chronic renal failure		20 (%17.1)
Coronary artery disease		13 (%11.1)
Hypothyroidism		13 (%11.1)
Cerebrovascular disease		9 (%7.7)
Atrial Fibrillation		7 (%6.0)
Chronic obstructive pulmonary disease		7 (%6.0)
Other		55 (%47.0)

TPE; Therapeutic plasma Exchange

Table 2. Laboratory data of TPE cases

Laboratory parameters	n	mean ± sd, (min.-max.)
Leukocyte (10^3/uL)	110	9,52 ± 6,16 (0,1-34,5)
Neutrophil (10^3/uL)	110	7,53 ± 5,76 (0,0-31,0)
Hemoglobin (g/dL)	110	9,19 ± 1,95 (5,1-15,9)
Hematocrit (%)	110	26,77 ± 6,25 (5,9-46,2)
Platelets (10^3/uL)	110	126,35 ± 153,64 (3-1035)
MPV (fL)	110	8,71 ± 1,46 (4,8-12,7)
Creatinine (mg/dL)	110	2,54 ± 2,54 (0,2-14,3)
Sodium (mEq/L)	110	137,75 ± 4,70 (126-158)
Potassium (mEq/L)	110	4,36 ± 0,71 (3,0-6,3)
Chlorine (mEq/L)	110	102,21 ± 5,55 (88-119)
Calcium (mg/dL)	110	8,52 ± 1,07 (6,0-15,6)
Total protein (g/dL)	95	6,49 ± 1,84 (3,7-13,6)
Albumin (g/dL)	98	3,30 ± 0,82 (1,3-5,6)
AST (U/L)	99	97,34 ±257,77 (9-2016)
ALT (U/L)	99	67,01 ± 191,96 (1-1722)
ALP (U/L)	92	239,62 ±624,86 (27-6037)
GGT (U/L)	91	68,81 ± 99,53 (4-676)
LDH (U/L)	96	1448,56 ± 1384,92 (270-10380)
Total bilirubin (mg/dL)	105	2,45 ± 4,62 (0,2-27,8)
Indirect bilirubin (mg/dL)	105	1,24 ± 1,62 (0,1-9,9)
ESR (mm/h)	68	63,66 ± 42,57 (1-148)

MPV; mean platelet volume, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma-glutamyl transferase, LDH; lactate dehydrogenase, ESR; erythrocyte sedimentation rate

Table 3. Laboratory data of patients with TTP and ANCA associated vasculitis

Laboratory data at the time of admission	TTP			ANCA associated vasculitis		
	n	mean.±sd, (min.-max.)	Median (Q1-Q3)	n	mean.±sd, (min.-max.)	Median (Q1-Q3)
Leukocyte (10^3/uL)	33	9,30±5,14 (2,1-28,6)	8,70 (6,55-10,50)	17	12,46±7,12 (4,9-34,5)	11,3 (7,5-14,5)
Neutrophil (10^3/uL)	33	6,99±4,79 (1,6-26,6)	5,80 (4,30-8,25)	17	10,78±6,70 (3,7-31,0)	9,7 (5,7-12,7)
Hemoglobin (g/dL)	33	9,18±2,04 (5,1-13,9)	9,40 (7,60-10,30)	17	8,64±1,34 (6,6-11,0)	8,5 (7,4-9,3)
Hematocrit (%)	33	26,57±6,00 (15,0-40,4)	26,0 (22,3-29,3)	17	25,97±4,43 (19,0-34,0)	25,6 (22,3-28,5)
Platelets (10^3/uL)	33	47±63 (3,0-295,0)	18 (11-58)	17	253±160 (11,0-585,0)	235 (129-354)
MPV (fL)	33	8,67±1,79 (5,3-12,7)	8,7 (7,0-9,6)	17	8,75±1,08 (6,8-10,9)	8,8 (8,0-9,6)
Creatinine (mg/dL)	33	1,95±2,37 (0,4-11,6)	0,9 (0,8-2,0)	17	3,84±2,11 (0,5-6,8)	3,7 (1,8-5,9)
Sodium (mEq/L)	33	139±5,28 (128-158)	140 (136-142)	17	136±4,14 (129-142)	137 (133-140)
Potassium (mEq/L)	33	4,11±0,66 (3,0-5,8)	4,0 (3,6-4,4)	17	4,80±0,80 (3,1-5,3)	4,7 (4,2-5,4)
Chlorine (mEq/L)	33	104±4,68 (88-111)	106 (102,5-108)	17	99±6,61 (89-119)	98 (95-102)
Calcium (mg/dL)	33	8,59±1,07 (6,0-11,3)	8,50 (8,05-9,25)	17	8,28±0,54 (7,4-9,0)	8,3 (7,8-8,7)
Total protein (g/dL)	30	6,53±1,27 (3,9-10,0)	6,50 (5,9-7,1)	12	5,87±1,42 (3,7-8,2)	5,8 (4,6-6,9)
Albumin (g/dL)	31	3,77±0,82 (2,1-5,6)	3,70 (3,3-4,4)	13	2,79±0,59 (2,1-4,0)	2,7 (2,3-3,1)
AST (U/L)	32	53±41,84 (17-206)	40 (22,5-65,0)	12	36±30,62 (10-99)	23 (14-61)
ALT (U/L)	32	38±38,36 (5-188)	22 (16,2-45,7)	12	30±36,38 (1-114)	16 (8-51)

ALP (U/L)	30	190±124,33 (45-558)	153 (117,5-245,7)	12	183±98,30 (56-330)	158 (101-292)
GGT (U/L)	30	37±31,11 (7-120)	23 (16,7-58,5)	12	90±84,70 (16-274)	64 (26-121)
LDH (U/L)	31	1610±768,53 (315-4110)	1739 (1032-2123)	12	617±182,01 (383-879)	595 (450-825)
ESR (mm/h)	25	39±28,81 (1-101)	39 (13-51)	10	71±39,93 (19-142)	66 (45-101)

TTP; Thrombotic thrombocytopenic purpura, ANCA; anti-neutrophil cytoplasmic antibody, ALT; alanine aminotransferase, AST; aspartate aminotransferase; MPV; mean platelet volüme, ESR; erythrocyte sedimentation rate

Other few indications for TPE are; hemolytic uremic syndrome (HUS), atypical HUS, autoimmune hemolytic anemia, rapid progressive glomerulonephritis, multiple myeloma, waldenström macroglobulinemia, systemic lupus erythematosus, acute liver failure, ABO incompatible stem cell transplantation, thyrotoxicosis, pre-renal transplantation, cryoglobulinemia, hyperbilirubinemia, chronic liver failure, pure red cell aplasia, IgA nephropathy, henoch-schönlein purpura vasculitis, antiphospholipid antibody syndrome. There were 47 patients with TTP, HUS and atypical HUS. 46 (%97,9) of these patients had microangiopathic hemolytic anemia (MAHA), 45(%95,7) had thrombocytopenia, 14 (%29,8) had fever, 15 (%31,9) had neurological signs, and 26 (%55,3) had azotemia.

117 patients' diagnoses, responses to treatment, and TPE -related complications are given in Table 4.

Table 4. Data of patients according to primary disease

TPE reason	n, %	Additional treatment (n)	Results (n)				TPE related complications (n)	H/D (n)
			PR	CR	No response	No data		
TTP	35 (%29,9)	Methylpred (26) Rituximab (10) Cyclophosphamide (2)	16	9	8	2	No (25) Hypocalcemia / Arrhythmia (1) Allergy (2) Hypofibrinogenemia (7)	No(28) Permanent (6) Temporary (1)
HUS	3 (%2,6)	Methylpred (2)	1	0	2	0	No (2) Hypofibrinogenemia (1)	Permanent (1) Temporary (2)
Atipical HUS	9 (%7,7)	Methylpred (6) Eculizumab (4) Cyclophosphamide (1)	4	1	4	0	No (8) Hypofibrinogenemia (1)	No (2) Permanent (5) Temporary (2)
AIHA	4 (%3,4)	Methylpred (3)	1	2	1	0	No (2) Hypotension / Syncope (1) Hypofibrinogenemia (1)	No (2) Permanent (1) Temporary (1)
RPGN	1 (%0,9)	Methylpred (1) Cyclophosphamide (1)	1	0	0	0	No (1)	No (1)
MM	9 (%7,7)	Methylpred (5) Cyclophosphamide (3)	1	2	5	1	No (9)	No (7) Permanent (2)
WMG	5 (%4,3)	Methylpred (1) Cyclophosphamide (1)	0	2	1	2	No (5)	No (5)
ANCA Vasculitis	17 (%14,5)	Methylpred (17) Cyclophosphamide (16)	7	2	8	0	No (12) Hypocalcemia / arrhythmia (1)	No (4) Permanent (11)

							Allergy (1) Hypotension / Syncope (1) Leukopenia (2)	Temporary (2)
SLE	1 (%0,9)	Methylpred (1) Clophosphamide (1)	1	0	0	0	Hypofibrinogenemia (1)	No (1)
Acute Liver Failure	1 (%0,9)		1	0	0	0	Hypocalcemia / Arrhythmia (1)	No (1)
ABO İncompatible Stem Cell Transplant	7 (%6,0)	Methylpred (3) Cyclophosphamide (2)	0	7	0	0	No (7)	No (7)
Thyrotoxicosis	5 (%4,3)		3	1	1	0	No (5)	No (5)
Other	20 (%17,1)	Methylpred (13) Cyclophosphamide (5) Rituximab (1)	5	4	10	1	No (18) Hypocalcemia / Arrhythmia (1) Hypofibrinogenemia (1)	No (14) Permanent (3) Temporary (3)

Methylpred; metilprednizolon, PR; Parsiyel response, CR; Complete response , H/D; hemodialysis, TPE; therapeutic plasma exchange, TTP; thrombotic thrombocytopenic purpura, HUS; hemolytic uremic syndrome, AIHA; autoimmune hemolytic anemia, RPGN; rapid progressive glomerulonephritis, MM; multiple myeloma, WMG; waldenstrom macroglobulinemia, ANCA; anti-neutrophil cytoplasmic antibody, SLE; systemic lupus erythematosus,

The number of TPE patients per day was 100 (85.5%). In 93 (79.4%) of the patients, fresh frozen plasma and albumin were used together. In 12 (10.3%) patients only fresh frozen plasma was used, in 12 (10.3%) patients, data were not available for the replacement fluid used.

75 (64.1%) patients are known to have a catheter site. Of these, 47 (40.2%) were juguler, 18 (15.4%) were femoral and 7 (6.0%) were subclavian catheter. 111 (94.9%) patients had no catheter related complications. 5 (4,2%) patient bleeding, and 1 (0,9%) patient thrombus was detected. 111 (94.9%) patients did not have catheter infection. Six (5,1%) of the patients had evidence of catheter-related infection.

When the final status of the patients was evaluated, 55 (47%) were still living and 62 (53%) were ex. As a result of the information obtained from the hospital archive files and electronic files, 33 (28%) patients were found to be exitus. It was determined that 4 (12%) of these patients were ex during TPE, others were at any time after TPE treatment. 25 (76%) of these 33 patients had sepsis, 4 (12%) had cardiopulmonary arrest, 2 (6%) had adult respiratory distress syndrome (ARDS), 1 (3%) had gastrointestinal system (GIS) bleeding, and 1 (3%) had multiple organ failure. In order to obtain information about the life status of the other patients, a questionnaire was made from the hospital information management system and 29 (25%) patients were found to have died out due to an unknown reason outside the hospital.

When there is a relationship between mortality and laboratory data of patients with TTP, which is the most common TPE indication in our study, there was no statistically significant difference between the parameters except alkaline phosphatase ($p > 0.05$). The median value of alkaline phosphatase at the time of presentation of surviving TTP patients was 135 (76.5-172.2) U/L. The median value of patients in the exitus condition was 226 (155.7-344.2) U/L. There was statistically significant difference between two values ($p = 0.002$).

When there is a relationship between mortality and laboratory data of patients with ANCA associated vasculitis, which is the second most common TPE indication in our study, there was no statistically significant difference between the parameters except hematocrit and chlorine ($p > 0.05$). The median value of hematocrit at the time of presentation of surviving ANCA associated vasculitis patients was 28,58 % ± 4,07. The median value of patients in the exitus condition was 24,14 % ± 3,85. There was statistically significant difference between two values ($p = 0.037$). The median value of chlorine at the time of presentation of surviving ANCA associated vasculitis patients was 95,29 ± 3,98 mEq/L. The median value of

patients in the exitus condition was 102,20 ± 6,73 mEq/L. There was statistically significant difference between two values (p = 0.029).

4. Discussion

TPE is widely used in many diseases in the practice of internal medicine. Current guidelines on this process have been published in recent years due to increased awareness and accessibility. The most common and most comprehensive of these is the ASFA guide [11]. There is also a national apheresis guide published by the Turkish Apheresis Society in our country [12]. In our study, it is seen that the majority of patients who underwent TPE in clinical practice of internal diseases were patients with TTP (29.9%) and ANCA related vasculitis (14.5%). There are different data in the literature depending on the planning scheme of the studies and the patient population of the centers. In order to have more healthy information in this regard, further studies are needed in which all apheresis centers in Turkey are included in a single information management system and an evaluation is made under these data.

It is known that female gender is more prevalent in TTP, which constitutes the majority of TPE indications in our study [13-16]. TTP and ANCA-associated vasculitis are more common in the 4th and 5th decades in the population [16, 17]. In our study, it was seen that the number of female patients (63, 53.8%) was higher than the number of male patients (54, 46.2%). The mean age of the patients in our study was 52.1 ± 16.8. The reason for this difference between genders is thought to be due to the high number of patients with TTP, and the age average is similar to the literature.

Patients who underwent TPE for any reason in the internal medicine clinic were included to study. These patients formed a heterogeneous community. Because of this heterogeneity; it was thought that the duration of TPE ranged from 1 to 96 days and the length of hospitalization ranged from 0 to 101 days. On the other hand, there has not been any literature information in recent years. In a study of Kim et al. involving 52 patients, 353 TPE sessions were performed and the median number of sessions per patient was found to be 5 (1-32) [14]. In a study of Samanci et al. inolving 110 patients, 734 TPE sessions were performed and the average number of sessions per patient was 6.6 ± 4.3 (1-25) [1]. Yilmaz et al. in a study of 330 patients in the intensive care unit in 10 years reported that a total of 1188 TPE sessions were performed. In this study, no average value per patient was given, but 83.7% of patients were reported to be receiving 1 to 5 TPE sessions [18]. A total of 1164 TPE sessions were performed in our study and the average number of sessions per patient was found to be 9,95 ± 10,0 (1-61). From this point of view, we found that our study was somewhat higher in terms of mean value and a wider range of TPE treatment was performed and was not similar to the literature. This is thought to be due to heterogeneity in our patients.

Plasmapheresis as a medical procedure is not an uncomplicated procedure. Severe and life-threatening complications can be seen between 0.025% and 4.75% [19, 20]. When isolated deviations from normal values in laboratory tests such as reduced hemoglobin, thrombocytopenia, hypokalemia, hypofibrinogenemia are included, it is thought to be between approximately 25% and 40% of the total incidence of complications [21-23]. There are studies in the literature where plasmapheresis-related complications are widely analyzed and presented [22, 24]. In a study involving 370 TPE procedures performed by Wojciech Szczeklik et al. in 54 intensive care patients in 2013, 88.9% had no complications. Life-threatening complications in this study were shock (%1,08), arrhythmia requiring pharmacologic therapy (0.81%) and haemolysis (0.27%). Not life-threatening complications were; hypotension (7,30%), arrhythmia (2,7%) requiring fluid therapy or spontaneous resolution, anxiety and agitation (1,35%), chills and paresthesia (1,08%), allergic reaction (0,81%), lower extremity pain (0,81%), fever (0,54%), abdominal pain (0,54%) and eyelid tremor (0,27%). [25]. In another study performed by Benitez et al. in 20 intensive care patients in 2005, the most

common complications were; hypocalcemia (50%), hypotension (42,1%), coagulopathy (35%), hypokalemia (29%), rash (20%), process related infections (18%) and fever (10%). There were no fatal reactions associated with TPE in this study [26]. In our study, no complication was observed in the majority of patients (80.3%) when the complication rates were considered during TPE procedure, while mild complications were seen in the remaining patients. These complications include; hypofibrinogenemia (10,3%), hypocalcemia (3,4%), allergy (2,6%), hypotension / syncope (1,7%) and leukopenia (1,7%). Exitus occurred in only 4 cases during TPE, and the cause of exitus was found to be related to primary disease in these patients. No fatal reactions to TPE treatment were observed. From this point of view, our study was found to be consistent with the literature. It should be kept in mind that the complication rates may be higher and some slight signs of mild reactions may not be kept.

In the study of Samancı et al., 2 (100%) patients with paraneoplastic neurological syndrome, 8 (72,7%) patients with HUS, 11 (64,7%) patients with RPGN, 2 (50%) patients with MM, 1 (50%) patient with SLE, 7 (26.9%) patients with renal transplant, 9 patients (50%) with ANCA associated vasculitis were required to have hemodialysis as well as plasmapheresis at the time of admission. [1]. In this study, TPE and hemodialysis procedures were performed on successive days and 23.1% of patients with renal transplant, 35.3% of patients with RPGN, 36.4% of patients with HUS, 16.7% of patients with ANCA-associated vasculitis, all patients with paraneoplastic neurological syndrome, 50% of patients with SLE, 16.7% of patients with FSGS, and 25% of patients with MM were found to be hemodialysis-dependent [1]. In our study, it was seen that 40 (34.2%) patients needed hemodialysis and 29 (24.8%) of all patients, this hemodialysis requirement became permanent. In subgroups, 28 (80%) of our patients with TTP, one of the two most common indications for TPE, did not require hemodialysis and were temporary in 1 of the hemodialysis patients and permanent in 6 remaining patients. When we looked at ANCA-associated vasculitis, which was the second most common indication, 4 (23.5%) patients did not need hemodialysis and 13 (76.5%) patients needed hemodialysis. Hemodialysis is permanent in 11 of these patients. It is thought that the need for hemodialysis is higher in our patients with ANCA-associated vasculitic disease, while the low plasma plasmapheresis response should be considered as a factor.

TTP, is a systemic disease characterized by platelet aggregation and thrombi that leads to occlusion in the microvascular circulation of the body [16]. This disease is closely related to HUS, sometimes overlapping and more broadly, these diseases are defined as thrombotic microangiopathy [27]. As a classical pentad; fever, hemolytic anemia, thrombocytopenia, renal insufficiency, neurological findings are not universal and highly variable [3, 28]. Some older studies have reported that between 5% and 40% of classical pentad is diagnosed at the time of diagnosis [29]. Fever is uncommon and reported to occur in only 24% of patients with TTP in a randomized controlled trial [3]. The HUS and atypical HUS are also a group of thrombotic microangiopathy and additionally include renal impairment and failure [30]. In a retrospective multicentre study involving 163 patients with TTP diagnosed by Korkmaz et al. thrombocytopenia 163 (100%), MAHA 163 (100%), neurological abnormalities 135 (83%), renal insufficiency 128 (79%), fever 145 (89%) were reported. In this study, the number of patients including 4 of the 5 criteria was 17 (10.4%) and including 3 of the 5 criteria was 17 (10.4%). The classic pentad was only 10 cases (6.1%) [13, 15, 31]. In our study, 47 patients with TTP, HUS and atypical HUS; microangiopathic hemolytic anemia were found in 46 (97.9%), thrombocytopenia 45 (95.7%), fever 14 (29.8%), neurological findings 15 (31.9%) and azomemia 26 (55.3%). Examination of the file of 1 patient without microangiopathic hemolytic anemia revealed that the data of the registered laboratory could not be reached. In the same way, 2 patients without thrombocytopenia were not able to access laboratory data. In fact, when we excluded these patients, we found that MAHA and thrombocytopenia were found in all patients.

Fever, neurological findings and azotemia were variable rates. The variability in neurological findings is thought to be due to the inadequacy of file recordings. While the frequency of MAHA and thrombocytopenia is similar to the literature, our other findings are different.

In the literature, it is suggested that plasma exchange should be used to until improve the patient's current clinic level or acute status, especially microangiopathic haemolytic states such as TTP, atypical HUS [6, 7, 12]. In our study, 100 (85.5%) patients were TPE every day during the acute phase of the disease, in the following days the transaction frequency was gradually reduced. In this respect, our study was found to be consistent with the literature. In some patients, it is not possible to make a definite diagnosis with the present clinical and laboratory signs and symptoms; but it is vital that the therapeutic plasma exchange process required by the nature of the disease is not delayed. We also found that patients with this condition were also present, these patients were diagnosed on the one hand and the therapeutic plasma exchange process was started as soon as possible. However, in the following days, a small number of these mentioned patients have been removed from the pre-diagnosis at the time of admission, and when it is understood that the therapeutic plasma exchange process is not needed, the process is terminated. As new developments occur in the diagnosis, the amount of unnecessary therapeutic plasma exchange operation will decrease in a serious way.

It is recommended in the literature to use fresh frozen plasma and/or albumin depending on the indication for TPE treatment [3, 31-35]. In a study by Stefanello et al. in 2014, cryoprecipitate-poor plasma and fresh frozen plasma were compared in newly diagnosed TTP patients. More TPE sessions, higher plasma exposures, and acute exacerbations were seen at higher levels in the cryoprecipitate-poor plasma. Therefore, it has been reported that it should not be used in primary care [36]. In a retrospective study of Kaya and his colleagues in neurological diseases; In the TPE procedure, 66% of the patients had albumin and 34% of fresh frozen plasma [37]. In a study performed by Erkurt et al. in hematologic diseases in 2013, it was stated that fresh frozen plasma was used in all 44 patients as TPE replacement fluid [38]. In our study, records of TPE replacement fluid were not available in 12 of 117 patients; 93 (79.4%) of the patients were using fresh frozen plasma with albumin and 12 (10.3%) patients were using only fresh frozen plasma. Plasma use was compatible with the literature, but albumin was found to be overused. The rate of albumin use in internal medicine applications is lower in the literature. In this respect, our study was not compatible with the literature.

Sufficient venous flow must be provided for the success of the TPE procedure. The preferred way of vascular access varies from hospital to hospital. Peripheral venous use can reduce TPE -related morbidity, but the peripheral antecubital venous used for this purpose must be sufficiently wide, otherwise, a central venous route should be preferred. In most US healthcare facilities, central venous tracts are seen to be used predominantly [39]. In the study Kaya and his colleagues performed in 2013, 66% of the patients used central venous catheters and 34% used peripheral venous pathways [37]. Guptill et al. found that 75% of the patients preferred peripheral venous lineage [39]. In our study, the central venous route was used in the majority of patients (64.1%). However, in 42 (35.9%) patients, no record was found. In these patients, it was thought that large peripheral arterial routes were used but no notes were placed in the file.

A study of McGuckin et al. in patients with TTP who underwent TPE procedure in 2013, reported no catheter-related infection or thrombosis [40]. In the study of Samancı et al. 1 (0.9%) hematoma was seen as catheter related complication and no catheter-related infection [1]. In the study of Eren et al., No catheter-related complication was found in any patient [2]. In our study, catheter-related complications were found to be very rare, similar to the literature. Only 5 patients (4.3%) had hemorrhage and 1 patient (0.9%) had thrombosis; catheter related complications were not observed in the remaining 111

(94.9%) cases. Likewise, catheter-related infection was very rare and 111 (94.9%) patients did not have any infection. It has been thought that the maximum attention to antisepsis during the time from the insertion of the vessel line used for TPE treatment to the completion of the treatments is thought to provide a low rate of catheter-related infection in our study. It is desirable to reduce all complications to zero. For this; it is very important to place the vessel to the experienced hands in case of imaging as needed, pay attention to the antisepsis throughout the entire hospital stay, and remove the catheter when it is not necessary.

Various studies investigating the risk factors for mortality in TTP are available in the literature. In an earlier study that Pereira et al. did; there was a relationship between response and age, stupor or coma, delay in TPE procedure, plasma fibrinogen level, but was not to early death or survival status and only could be considered as a preliminary variable. There was no correlation between laboratory data and mortality in this study [41]. An earlier study by Patton et al. reported that serum LDH level and thrombocyte count in the third day of TPE process, were associated with survival [42]. In an earlier study by Hollenbeck et al., no significant predictor of mortality was found [43]. A 24-year study of 178 patients by Levandovsky et al. in 2008 found that the best predictive factor for mortality was the underlying serious disease. What is interesting in this study is that the presence of renal insufficiency is associated with a reduction in relapse risk [44]. In a study performed by Goel et al. in TTP patients treated with TPE in 2016, platelet transfusion, intracranial haemorrhage, arterial thrombosis, myocardial infarction, ischemic stroke, age greater than 60 years, and renal insufficiency as risk factors [45]. When we look at the literature, there is no definite laboratory data suggesting that there may be a relationship between TTP and mortality. When we examined patients with TTP in our study, we found a significant relationship between the ALP value at the time of admission and mortality. The result is that mortality is higher in patients with high ALP values. However, there is a need for randomized controlled trials with higher patient numbers to arrive at a definite conclusion.

There are various data on mortality in the literature on ANCA-associated vasculitis. In a study performed by Hogan et al, pulmonary haemorrhage, c-ANCA positivity in place of p-ANCA, use of corticosteroid alone instead of cyclophosphamide combination was associated with mortality [46]. In a recent study performed by Weiner et al, advanced age, high creatinine, low BVAS score were associated with high mortality rates. In the same study, high creatinine level at diagnosis was found to be the only significant predictive factor for renal survival [47]. In a study performed by Qing-ying et al. in patients diagnosed with 398 ANCA-associated vasculitis in 2014, advanced age, pulmonary involvement, and initial renal function were associated with all-cause mortality at admission. During follow-up, secondary infections were also associated with all-cause mortality [48]. In our study, when patients with ANCA-associated vasculitis were examined, there was a significant relationship between hematocrit value and mortality at admission. It was concluded that mortality was higher in patients with low hematocrit values. Another significant difference in the same patient group was the chlorine value of the applicant. According to this, high mortality was observed at high chlorine level. It seems that there is a need for randomized controlled studies with higher patient numbers to confirm the information that is generated about these two parameters and to reach a definite result.

Reported case-fatality rate for TPE is reported to be around 3-5 (0,03-0,05%) at 10,000 [22, 49]. Since 1989, there are more than 50 deaths associated with TPE, respiratory and cardiac complications are the most common causes [50]. Cardiac arrhythmias are frequently observed, especially when plasma is used. Suspected etiology is thought to be a reduced ionized calcium concentration but the cause-and-effect relationship has not yet been proven. Among respiratory deaths; Symptoms of ARDS and non-cardiogenic pulmonary edema have only recently been observed in death, and these patients are receiving plasma

infusion also. Anaphylaxis, vascular complications, hepatitis, sepsis and thrombosis are the other less frequent causes of death [51]. In our study, no fatal reaction to TPE treatment was found. There were 33 patients with known death cause. 25 (76%) of these patients had sepsis, 4 (12%) cardiopulmonary arrest, 2 (6%) ARDS, 1 (3%) GIS bleeding, 1 (3%) multiple organ failure. It is known that sepsis is common among the causes of death in intensive care patients. The most common reason for this is plausible. Although catheter-related infection is uncommon, intensive care has a predisposition to septicemia due to the nature of the diseases and the intensity of interventional procedures. Secondly, cardiopulmonary arrest is thought to reflect cardiac arrhythmia or myocardial infarction. The data in this area is insufficient and it is thought that the records should be kept more carefully. In patients with TPE, a greater number of patients and multicentre studies are needed to investigate the causes of mortality.

5. Conclusion

There are several guidelines for apheresis in our country and in the world. In these guidelines, the TPE procedure was found to have a very wide range of diagnosis and life-saving if applied quickly in the right indications. There is a need to establish a national and international therapeutic apheresis network. Also, further research is needed to determine response criteria for diseases.

Complications for TPE are quite rare and TPE procedure is reliable. Nevertheless, care should be taken to minimize the complications and the registration system should be updated. The necessary precautions should be taken to minimize catheter-related problems and controlled studies are needed to confirm the laboratory data provided in this study in order to be used in predicting mortality.

REFERENCES

1. Sengul Samanci N, Ayer M, Gursu M, et al. Patients treated with therapeutic plasma exchange: a single center experience. *Transfus Apher Sci*. 2014;51:83-9.
2. Eren G, Çukurova Z, Kucur E, et al., Our Experience on Therapeutic Plasmapheresis Performed for A Variety of Clinical Indications in Our Intensive Care Unit *Turkiye Klinikleri J Med Sci* 2010;30:1683-9
3. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. 1991; 8;325:393-7.
4. Allford SL, Hunt BJ, Rose P, Machin SJ;Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology: Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol*., 2003. 120: p. 556-73.
5. Scully M, Hunt BJ, Benjamin S, et al., Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158: 323-35.
6. Szczepiorkowski ZM, Winters JL, Bandarenko N et al., Guidelines on the use of therapeutic apheresis in clinical practice evidence-based approach from the apheresis applications committee of the American Society for Apheresis. *J Clin Apher*. 2010;25:83-177.
7. Schwartz J, Winters JL, Padmanabhan A,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 sixth special issue. *J Clin Apher*. 2013;28:145-284.
8. Agishi, T., Spectrum of blood purification. *Prog Med*, 1985;134: 861-64.
9. Huestis, DW, Bove JR, Busch S. Practical blood transfusion. Little Brown and Company. 1981
10. Barnes A. Hemapheresis perspectives. Terapeutic Apheresis. Arlington, Virginia: American Association of Blood Banks, 1983: p. 1-13.
11. Shaz BH, Schwartz J, Winters JL. How we developed and use the American Society for Apheresis guidelines for therapeutic apheresis procedures. *Transfusion*, 2014;54: 17-25.
12. Toprak SK, İlhan O. Current Legislation in Therapeutic Apheresis and National Therapeutic Apheresis Guideline: Where Do We Stand in 2015? *Turkiye Klinikleri J Hematol-Special Topics* 2015;8:104-14
13. Korkmaz S, Keklik M, Sivgin S et al., Therapeutic plasma exchange in patients with thrombotic thrombocytopenic purpura: a

retrospective multicenter study. *Transfus Apher Sci*. 2013;48:353-8.
14. Kim JW, Kim I, Oh KH et al., Therapeutic plasma exchange in patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome: the 10-year experience of a single center. *Hematology*. 2011;16:73-9.
15. Miller DP, Kaye JA, Shea K, et al., Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. *Epidemiology*. 2004;15:208-15.
16. Kappler S, Ronan-Bentle S, Graham A. Thrombotic Microangiopathies (TTP, HUS, HELLP). *Emerg Med Clin North Am.* 2014;32:649-71.
17. Lane SE, Watts R, Scott DG. Epidemiology of systemic vasculitis. *Curr Rheumatol Rep*. 2005;7:270-5
18. Yilmaz AA, Can OS, Oral M, et al., Therapeutic plasma exchange in an intensive care unit (ICU): a 10-year, single-center experience. *Transfus Apher Sci.* 2011;45:161-6.
19. Gwathmey K, Balogun RA, Burns T.. Neurologic indications for therapeutic plasma exchange: 2011 update. *J Clin Apher*. 2012;27:138-45
20. Seck SM, Bertrand D, Boucar D. Current indication of plasma exchanges in nephrology: a systematic review. *Saudi J Kidney Dis Transpl*. 2011;22:219-24.
21. Kaplan, AA. A practical guide to therapeutic plasma exchange. 1999: Blackwell Science.
22. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. *Am J Kidney Dis*. 1994;23:817-27.
23. Passalacqua S, Staffolani E, Busnach G, et al., The Italian registry for therapeutic apheresis. A report from the apheresis study group of the Italian society of nephrology. *J Clin Apher*. 2005;20:101-6.
24. Bramlage CP, Schröder K, Bramlage P, et al., Predictors of complications in therapeutic plasma exchange. *J Clin Apher*. 2009;24:225-31.
25. Szczeklik W, Wawrzycka K, Włudarczyk A et al., Complications in patients treated with plasmapheresis in the intensive care unit. *Anaesthesiol Intensive Ther*. 2013;45:7-13.
26. Benítez C, Andresen M, Farías G, et al., Indications, adverse effects and results of plasmapheresis in critical care patients. *Rev Med Chil.* 2005;133:1441-8
27. Moake, JL. Thrombotic microangiopathies. *N Engl J Med.* 2002;347:589-600.
28. Kessler CS, Khan BA, Lai-Miller K. Thrombotic thrombocytopenic purpura: a hematological emergency. *J Emerg Med*. 2012;43:538-44.
29. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura: Report of 25 cases and review of the literature. Medicine (Baltimore). 1981;60:413-28.
30. Noris M, Remuzzi G. Hemolytic uremic syndrome. *J Am Soc Nephrol*. 2005;16:1035-50
31. George, JN. How I treat patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. *Blood.* 2000; 15;96:1223-9.
32. Haas M, Böhmig GA, Leko-Mohr Z, et al. Peri-operative immunoadsorption in sensitized renal transplant recipients. *Nephrol Dial Transplant.* 2002;17:1503-8.
33. Yin H, Hu XP, Li X, et al., Protein A immunoadsorption combined with rituximab in highly sensitized kidney transplant recipients. *Chin Med J (Engl).* 2009;122:2752-6.
34. Keskin A, Cagirgan S, Cetin M, Buyukkececi M. Thrombotic thrombocytopenic purpura: Report of 10 cases. *Turkish J. Med. Sci*, 1995. 24: 155–158.
35. Barz D. Budde U, Hellstern P. Therapeutic plasma exchange and plasma infusion in thrombotic microvascular syndromes. *Thromb Res.* 2002; 107 :23-7.
36. Stefanello B, De Paula EV, Andrade Orsi F et al. Safety and efficacy of cryoprecipitate-poor plasma as a replacement fluid for therapeutic plasma exchange in thrombotic thrombocytopenic purpura: A single center retrospective evaluation. *J Clin Apher*. 2014 ;29:311-5
37. Kaya E, Keklik M, Sencan M, et al. Therapeutic plasma exchange in patients with neurological diseases: multicenter retrospective analysis. *Transfus Apher Sci*. 2013;48:349-52
38. Erkurt MA, Kuku I, Kaya E, et al., Therapeutic plasma-exchange in hematologic disease: Results from a single center in Eastern Anatolia. *Transfus Apher Sci.* 2013;48:335-9
39. Guptill JT, Oakley D, Kuchibhatla M, et al. A retrospective study of complications of therapeutic plasma exchange in myasthenia. *Muscle Nerve.* 2013;47:170-6.
40. McGuckin S, Westwood JP, Webster H, et al. Characterization of the complications associated with plasma exchange for thrombotic thrombocytopaenic purpura and related thrombotic microangiopathic anaemias: a single institution experience. *Vox Sang*. 2014;106:161-6.
41. Pereira A, Mazzara R, Monteagudo J, et al. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: a multivariate analysis of factors predicting the response to plasma exchange. *Ann Hematol.* 1995;70:319-23.
42. Patton JF, Manning KR, Case D, Owen J. Serum lactate dehydrogenase and platelet count predict survival in thrombotic thrombocytopenic purpura. *Am J Hematol*. 1994;47:94-9.

43. Hollenbeck M, Kutkuhn B, Aul C, et al. Haemolytic-uraemic syndrome and thrombotic-thrombocytopenic purpura in adults: clinical findings and prognostic factors for death and end-stage renal disease. *Nephrol Dial Transplant.* 1998;13:76-81.
44. Levandovsky M, Harvey D, Lara P, Wun T. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS): a 24-year clinical experience with 178 patients. *J Hematol Oncol.* 2008 ;1;1:23.
45. Goel R, King KE, Takemoto CM, Ness PM, Tobian AA Prognostic risk-stratified score for predicting mortality in hospitalized patients with thrombotic thrombocytopenic purpura: nationally representative data from 2007 to 2012. *Transfusion.* 2016;56:1451-8.
46. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ., Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* 1996;7:23-32.
47. Weiner M, Goh SM, Mohammad AJ, et al. Outcome and treatment of elderly patients with ANCA-associated vasculitis. *Clin J Am Soc Nephrol.* 2015;10:1128-35.
48. Lai QY, Ma TT, Li ZY et al. Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 *Chinese patients. J Rheumatol*. 2014;41:1849-55.
49. Huestis D. Mortality in therapeutic haemapheresis. *Lancet.* 1983;1:1043.
50. Harris, T, Hillyer C. Technical manual. 2011.
51. Andre A Kaplan, Joy L Fridey. Therapeutic apheresis (plasma exchange or cytapheresis): Complications. www.uptodate.com ©2017 UpToDate