RESEARCH ARTICLE

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# Therapeutic Plasma Exchange: Indications and Outcomes. Single-Center Registry

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## ABSTRACT

***Introduction:*** **Therapeutic plasma exchange is used to manage immune-mediated diseases as early as 1970th. Nevertheless, the evidence beyond the therapeutic indication is still anecdotal and depends on observational data and national registries from different parts of the world. Aim of the Study: To review the use of therapeutic plasma exchange (TPE) to manage different conditions in the Dubai Hospital-nephrology department and benchmark against standard indications categories by American Society of Apheresis (ASFA) guidelines.**

***Methods:*** **The study included all adult patients who performed TPE in Dubai Hospital during 24 months period from January 2017 until December 2019. Patient demographics, indications, anticoagulation used, the number of sessions, duration of hospitalization, ICU admission, mortality outcome, and occurrence of procedure-related complications were included.**

***Results:*** **During the 24 months, 142 TPE sessions were performed for 33 registered patients (an average of 4.3 sessions/patient). The most common indications for TPE use in our registry were nephrology-related indications in 119 sessions (85%), while non-nephrology indications contributed for 21 sessions (15%). Among Nephrology related Indications, Thrombotic Thrombocytopenic purpura was the most common indication (47.8%), followed by post kidney transplantation (21%), while non-Nephrology-related indications were mainly for pancreatitis with Hypertriglyceridemia (9.2%). Complications arose in 2 sessions (1.4%), and mortality occurred in one (3%) critically ill patient related to non-procedure consequences and the severity of the underlying disease.**

***Conclusion:*** **Our registry data confirm the safety of therapeutic plasma exchange in a professional, well-equipped nephrology setting when used for proper evidence-based indications with a lower rate of morbidity and mortality.**

**Keywords:** Albumin, anticoagulation, fresh frozen plasma (FFP), therapeutic plasma exchange (TPE), thrombotic thrombocytopenic purpura (TTP).

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## I. Introduction

Plasmapheresis is a general word for any kind of apheresis, which removes plasma, while therapeutic Plasma exchange (TPE) involves the replacement of the removed plasma making large volume procedures possible. The typical goal is to exchange 1 to 1.5 times the estimated plasma volume per treatment [1], [2]. Therapeutic plasma exchange (TPE) has been used to manage immune-mediated diseases as early as 1970th, such as good pasture syndrome in 1975, systemic lupus erythematosus in 1976, and Thrombotic thrombocytopenic purpura in 1977 [3]-[7].

In use for over 50 years, the rationale for TPE remains based mainly on case series and retrospective studies [8]-[11]. In 1985, the American Medical Association (AMA) Council on Scientific Affairs reviewed all indications of therapeutic plasma exchange and categorized them into one of four categories based on the available evidence at that time:

I. Standard therapy, acceptable but not mandatory
II. Available evidence tends to favor efficacy: conventional therapy is usually tried first
III. Inadequately tested at this time
IV. No demonstrated value in controlled trials [12].

Lately, results from different randomized controlled trials, meta-analyses, and prospective studies have proven the efficacy of plasmapheresis in various renal and non-renal diseases. Among renal indications that have cumulative evidence is the Anti-glomerular basement membrane (Anti-GBM) disease, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, recurrent focal segmental glomerulosclerosis (FSGS) post kidney transplantation, and acute allograft rejection post kidney transplantation, and it

has provided insights into more rational use of this therapy [13]-[17]. In addition, the American Society of Apheresis recently published guidelines on the use of therapeutic plasma exchange in different disease conditions categorized to either standard therapy or adjunctive therapy or no rationale of service, depending on the strength of evidence accumulated in the past decade [18]. Nevertheless, in the new era of the COVID-19 pandemic, TPE gained a further reputation in managing severe resistant COVID cases by removing toxic cytokines, viral particles and restoring coagulation status, with favorable outcomes [19]-[21]. However, our study was done in the pre-COVID era; hence these cases were not included.

## II. Aim of the Study

We conducted this analysis to review the indications of the therapeutic plasma exchange (TPE) to manage different conditions at the nephrology department of Dubai Hospital and associated morbidity and mortality.

## III. Methods

This is a retrospective observational analysis done at the nephrology department of Dubai Hospital, one of the major tertiary hospitals of Dubai health authority, in the United Arab Emirates. The study included all patients above 14 years of age, who performed TPE in Dubai Hospital for 24 months period from January 2017 until December 2019, including demographics, indications, anticoagulation used, number of sessions, duration of hospitalization, ICU admissions, mortality outcome, and occurrence of procedure-related complications.

All data tabulated and indications categorized in accordance with American Society of Apheresis categories ASFA (2) and analyzed in SPSS 24 statistical software. Data presented as Mean ±SD or Median (range), number (percentage) according to data type and appropriateness.

## IV. Results

During the 24 months from January 2017 until December 2019, 33 patients underwent 142 sessions of plasma exchange with an average of 4.3 sessions /patient (1-18 sessions). The patients were predominantly male (18, 54%), with a median age of 37.15 (15-94). 36.5% (n=12) were younger than 30 years old, while 45.5% (n=15) and 18.2% (n=6) were between 30-50 years, and older than 50 years respectively.

### *A. Indications and Number of Sessions*

Table I and Fig. 1 show the indications of therapeutic plasma exchange categorized as per the American Society of Apheresis categories and the underlying grades of evidence. The most common indications for TPE use in our registry were the nephrology-related indications in 21 patients, who underwent 119 sessions (85%), while the non-nephrology indications contributed to the rest (12 patients, 21 sessions, 15%).

Thrombotic Thrombocytopenic purpura was the most common indication. 13 patients (39%) underwent 67(47.8%) sessions, followed by kidney transplantation related complications {n=3, 9%, had 30 sessions (21%)}, Systemic Lupus erythematosus (SLE) with rapidly progressive lupus for 3 patients (9% of the total population, had 12% sessions) and myeloma kidney in multiple myeloma. Non-Nephrology-related indications for TPE in our data included mainly pancreatitis secondary to Hypertriglyceridemia (30%, n=10), underwent 13 (9.2%) sessions, and toxic epidermal necrolysis and Gillian-Barre syndrome with 5 sessions each (3.57%). Table I shows the cases categories as per AFSA-categories and the underlying level of evidence for the use of therapeutic plasma exchange as part of therapeutic management. Table II shows the number of cases treated with TPE, the average number of sessions, duration of hospitalization, and age distribution. Fig. 1 shows general indications of TPE in our center during the study period.

TABLE I: TPE INDICATIONS, AGE, NUMBER OF SESSIONS AND HOSPITALIZATIONS

| ASFA Category and Level of Evidence | Indication (Number of cases) (%) | Age Median (Range) | No. of Sessions Median (range) | Hospital Duration Median (range) |
|---|---|---|---|---|
| Category I - 1A - Renal Indication | TTP/HUS 2 (6%) | 32 (6) | 5 (2) | 6.5 (50 |
| | TTP 8 (24.2%) | 31.5 (32) | 4 (17) | 8 (22) |
| | TTP /acquired 1 (3%) | 33 | 3 | 5 |
| | TTP/ Myelodysplatic Syndrome 1 (3%) | 94 | 5 | 20 |
| | TTP/REFRACTORY 1 (3%) | 50 | 4 | 5 |
| Category I - 1B - Neurology Indication | GUIANNE BARRE SYNDROME – (Acute Motor Sensory Polyneuropathy) 1(3%) | 9 | 5 | 9 |
| Category I - 1B - Renal Indication | Anti-GBM disease with crescentic GN 1 (3%) | 27 | 4 | 25 |
| Category I - 1B - Renal Indication | Post Kidney Transplant Recurrent FSGS 1(3%) | 24 | 14 | 52 |
| Category II- 2B - Renal Indication | Post kidney allograft rejection 1(3%) | 25 | 14 | 52 |
| Category IIB - Renal Indication | Myeloma kidney 1(3%) | 52 | 1 | 26 |
| Category IIC - Renal Indication | SLE 3 (9%) | 35 (19) | 5 (2) | 47 (40) |
| Category III - 1C - Hypertriglyceridemia With Pancreatitis | Acute Pancreatitis/Hypertriglyceridemia 7(27%) | 38 (21) | 1 | 6 |
| | Recurrent Pancreatitis/Hypertriglyceridemia 1(3%) | 41 (14) | 1 | 7 (7) |
| Category III - 2C - Renal Indication | FSGS 1(3%) | 28 | 2 | 3 |
| Category III - 2B | Toxic Epidermal Necrolyis 1(3%) | 15 | 5 | 4 |

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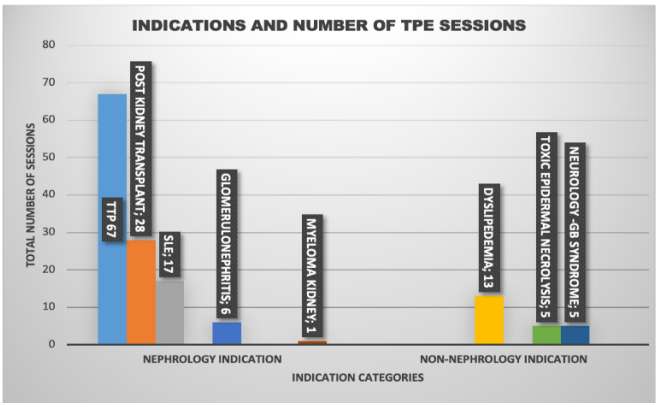


Fig. 1. Indications for TPE and number of sessions.

TABLE II: PATIENT'S DEMOGRAPHICS AND TPE SESSIONS

| Patient Characteristics | n=33 |
|---|---|
| Age in Years (Median) | 37.15(15-94) |
| sex | |
| Male | 18(54.54%) |
| Comorbid | |
| Hypertension | 6(18.18%) |
| Diabetes Mellitus | 10(30.30%) |
| Dyslipidemia | 8(24.24%) |
| SLE | 3(9%) |
| Breast Ca | 1(3.03%) |
| Polymyalgia rheumatica | 1(3.03%) |
| Indication of Plasmapheresis | |
| Thrombotic Microangiopathy | 13(39.39%) |
| Hypertriglyceridemia | 10(30.30%) |
| Post-transplant FSGS | 2(6.06%) |
| Acute Rejection | 1(3.03%) |
| SLE | 3(9.09%) |
| Multiple Myeloma | 1(3.03%) |
| Toxic Epidermonecrolysis | 1(3.03%) |
| GBS | 1(3.03%) |
| Anti GBM | 1(3.03%) |
| No of sessions/ admission | 2.90(1-8) |
| Replacement fluid | |
| Albumin | 15(48.4%) |
| FFP | 16 (51.6%) |
| Hospital stays in days (Median) | 14.96(1-60) |

### *B. Replacement Fluids*

Albumin alone was used in 15 cases (48.4%), while Albumin combined with fresh frozen plasma was used in 2 patients, and fresh frozen plasma alone was used as a replacement in 16 cases (51.6%). Table III compares both groups using either Albumin alone or FFP alone.

### *C. Vascular Access and Anticoagulation used*

Vascular access used was predominantly the temporary femoral catheter in 19 cases (58%), internal jugular catheter in 13 cases (39%), while AVF was used in one case only (3%). The anticoagulation used was predominantly the unfractionated heparin in 18 cases (55%), low molecular weight heparin in 6 cases (18%), and regional citrate anticoagulation in 2 patients (6%), while no anticoagulation was used in 7 patients (21%).

### *D. Other Therapies used in Conjunction with TPE*

Other therapies used in conjunction with the therapeutic plasma exchange in our registry included pulse steroids (in 3 cases, 9%) with thrombotic thrombocytopenic purpura (TTP) and transplant patients with recurrent FSGS. In addition, IVIG was used in 1 case with post kidney transplant antibody-mediated rejection, Rituximab (anti-CD 20 antibodies) in 2 cases (6%) with TTP, bortezomib in 1 case (3%) with refractory TTP and Mycophenolate mofetil in two cases (6%) with TTP.

### *E. Complications during the Procedure*

Complications occurred in 2 sessions out of 142 sessions (1.4%); allergic reaction to IVIG given after the session of TPE in post kidney transplant patient with acute allograft rejection and lastly volume overload, resulted from replacement fluid in a patient with acute pancreatitis and Hypertriglyceridemia.

TABLE III: COMPARASION OF BOTH GROUPS USING EITHER ALBUMIN OR FFP

| | Albumin (n=15, 48.39%) | FFP (n=16, 51.61%) | p-value |
|---|---|---|---|
| Age in Years (Median) | 34.2 (15-50) | 40.5 (24-94) | 0.228791 |
| Sex | | | |
| Male | Male=10 (66.66%) | 7 (43.75%) | 0.200089752 |
| Comorbid | | | |
| Hypertension | 6 (40%) | 3 (18.75%) | 0.192709582 |
| Diabetes Mellitus | 8 (53.33%) | 4 (25%) | 0.105551668 |
| Dyslipidemia | 6 (40%) | 1 (6.25%) | 0.024705382 |
| Indication of Plasmapheresis | | | |
| Hypertriglyceridemia | 9 (60%) | 1 (6.25%) | 0.001377606 |
| Thrombotic Microangiopathy | 0 | 13 (81.25) | <0.005 |
| Post-transplant FSGS | 2 (13.33%) | 0 | 0.157299 |
| Acute Rejection | 1 (6.66%) | 0 | 0.293778936 |
| SLE | 2 (13.33%) | 1 (6.25%) | 0.505008845 |
| Multiple Myeloma | 0 | 1 (6.25%) | 0.293778936 |
| Toxic Epidermonecrolysis | 1 (6.66%) | 0 | 0.293778936 |
| No: of sessions/ admission | 3.8 (1-14) | 4.75 (1-18) | 0.609389 |
| Hospital stay in days (Median) | 20.07 (4-60) | 10.5 (1-26) | 0.138865 |
| Complications | | | |
| Allergic reactions | 1 (6.66%) | 0 | 0.317311 |
| Fluid overload | 1 (6.66%) | 0 | 0.317311 |

TABLE IV: MORBIDITY AND MORTALITY IN PATIENTS WHO UNDERWENT TPE

| ICU Admissions and Mortality Reported | | | |
|---|---|---|---|
| INDICATION CATEGORY BY ASFA | | ICU admissions | Mortality |
| CATEGORY I - 1A - RENAL INDICATION | TTP- HEMOLYTIC UREMIC SYNDROME | 0 | 0 |
| | TTP | 2 (6%) | 1 (3%) |
| | TTP-ACQUIRED | 0 | 0 |
| | TTP-MYELODYSPLASTIC SYNDROME | 0 | 0 |
| | TTP-REFRACTORY | 0 | 0 |
| CATEGORY I - 1B - NEUROLOGY INDICATION | NEUROLOGY- GUILLAIN BARRE SYNDROME | 1 (3%) | 0 |
| CATEGORY I - 1B - RENAL INDICATION | GLOMERULONEPHRITIS-Anti-GBM disease | 0 | 0 |
| CATEGORY I -1B - RENAL INDICATION | KIDNEY TRANSPLANT-with RECURRENT FSGS | 0 | 0 |
| CATEGORY II- 2B - RENAL INDICATION | KIDNEY TRANSPLANT-ACUTE ALLOGRAFT REJECTION | 0 | 0 |
| CATEGORY IIB- RENAL INDICATION | MULTIPLE MYELOMA-MYELOMA KIDNEY | 0 | 0 |
| CATEGORY IIC - RENAL INDICATION | SLE | 2 (6%) | 0 |
| CATEGORY III - 1C - HYPERTRIGLYCERIDEMIA WITH PANCREATITIS | ACUTE PANCREATITIS- HYPERTRIGLYCERIDEMIA | 1 (3%) | 0 |
| | RECURRENT PANCREATITIS- HYPERTRIGLYCERIDEMIA | 1 (3%) | 0 |
| CATEGORY III - 2C- RENAL INDICATION | GLOMERULONEPHRITIS -FSGS | 0 | 0 |
| CATEGORY III - 2B | DERMATOLOGY-TOXIC EPIDERMAL NECROLYSIS | 1 (3%) | 0 |

### *F. Mortality*

TPE was done either in the nephrology ward (25 patients (75.8%)) or the intensive care unit (ICU) (8 patients, 24.2%) sittings, according to the patient condition before the procedure; however, it was performed in ICU setting not as procedure-related but as disease severity related. In our registry, mortality occurred in a single case (3%) with severe TTP related to critical illness (Table IV).

## V. Discussion

Therapeutic plasmapheresis is a process to remove pathological toxins from the body. With available upgraded machines, targeted selective pathological components can be removed, which results in a tremendous improvement in various disorders [22]. TPE is considered safe if performed by trained nurses [23], [24] and associated with occasional mild side effects. Though TPE is a high-risk procedure done in the ICU setting in most centers, in our center, TPE is performed in the general ward with expert hands, handling any expected complication carefully. In our study group, only two patients (1.4%) had an adverse impact during TPE, while [24] reported that 3% of TPE patients had adverse effects. The main indications of therapeutic plasma exchange in our study patients were Thrombotic microangiopathy, allograft dysfunction, systemic lupus erythematosus, and acute pancreatitis.

### *A. Thrombotic Microangiopathy (TMA)*

In our study, 39.39% (n=13) patients were suffering from TMA and received 67 sessions (47.8%) of plasma exchange in total, and replacement fluid was fresh frozen plasma in almost all cases. Their median hospital stay was 8.84 (1-23) days. These patients also received rituximab (n=2), methylprednisolone (n=2), bortezomib (n=1), mycophenolate mofetil (n=2) and cyclosporine (n=1). 6 (46.15%) patients improved clinically, and their median platelet count increased by 184 (58-364). The overall survival rate was 92.31%. There have been many studies appreciating the role of plasmapheresis in TMA. Reference [25] observed lower mortality rates (HR=0.034 and p=0.001) regardless of disease severity in patients with infection-associated TMA treated with plasma exchange. Reference [26] reported lower organ failure scores from day 3 to 9 and improved outcomes in secondary TMA patients treated with plasma exchange. Though studies have proved the positive effect of plasma exchange on secondary TMA, the strength of data is quite limited. Still, there is growing interest in changing the plasma milieu in cases of systemic inflammation, especially sepsis-induced multi-organ failure.

### *B. Hypertriglyceridemia complicated by Acute Pancreatitis*

30.30% (n=10) of patients received 13 sessions of TPE as they suffered from acute pancreatitis secondary to Hypertriglyceridemia. Their replacement fluid was Albumin, and their median hospital stay was 7.3 (2-14) days. Their median pre-TPE triglyceride levels were 3401 (989-4425), which improved to 475.6 (250-1494). All patients recovered fully, and none of them had complications related to plasma exchange. For hypertriglyceridemia-induced acute pancreatitis, the standard treatment is heparin, insulin, and plasmapheresis; however, studies advocate that those patients should be treated conservatively initially. Plasma exchange is an effective method to decrease triglycerides (Up to 70% with a single session) [27]-[30].

### *C. Systemic lupus erythematosus (SLE)*

Indications in SLE where plasma exchange might be beneficial are acute life-threatening manifestations and severe therapy-resistant manifestations, like refractory SLE renal disease, diffuse alveolar hemorrhage, neuropsychiatric SLE, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, hyperviscosity syndrome, and cryoglobulinemia. In our cohort, three SLE patients required 17 sessions of TPE. Indications were severe lupus nephritis with multi organs involvement (n=1), SLE with TTP (n=1), and lupus carditis (n=1); their hospital stay was longer because of the higher morbidity of the disease. There were no TPE-related complications observed. David Aguirre et al. observed that 62.12% of SLE patients improved after plasma exchange and found it safe and effective [31], while

Reference [32] treated 31 autoimmune disorder patients with plasma exchange, corticosteroids, immunosuppressive; however, the mortality was 35% despite TPE.

### *D. Renal allograft Rejection and FSGS*

Plasma exchange removes the preformed antibodies, so it is part of the standard treatment protocol for the treatment of Antibody-mediated rejection [33]. The most recent data depict that Antibody-mediated rejection (AMR) can be reversed safely and effectively with intensive therapy with TPE, IVIG, and adjustment of basal immunosuppression [34]-[36]. Furthermore, studies suggest that there are plasma-borne factors that increase glomerular permeability and cause focal segmental glomerulosclerosis (FSGS) [37], hence becoming a logical part of the treatment strategy of recurrent FSGS in renal allograft [38]. Reference [39] in a systemic literature review, reported a 71% remission rate (partial and complete) in post-transplant recurrent FSGS patients treated with plasma exchange. 9.09% (N=3) patients in our study group received 30 sessions for renal transplant-related indications (Post-transplant FSGS=2, AMR=1). There were no treatment complications.

### *E. Replacement Solutions for Plasma Exchange*

In plasma exchange, plasma is exchanged with a colloid replacement solution. Albumin is the preferred replacement solution mostly; allergic and febrile reactions are unlikely as it is pasteurized to inactivated viruses and easy to administer and store; still, Albumin solution may lead to a mild transient deficiency of serum proteins. Another suitable option is Plasma (Single donor), it must be type-specific, so prior blood group knowledge is needed; also, plasma is usually thawed before use. It replaces all plasma constituents, so it is generally preferred over Albumin in thrombotic thrombocytopenic purpura and existing coagulopathy [40]. In our study group, Albumin and Thawed fresh frozen plasma was used in 48.4%% and 51.6%, respectively. Allergic reactions and fluid overload side effects were associated with albumin treatments. Also, hospital stay was more (20 vs. 10.5, p= 0.138). The overall difference between the two replacement solutions was not statistically significant. However, Shemin and colleagues found that the complication rate was higher with FFP as compared to albumin solution [41].

## VI. Conclusion

Our registry data confirm the safety of therapeutic plasma exchange in a professional, well-equipped nephrology setting when used for proper evidence-based indications with a lower rate of overall complications (1.4%) and mortality rate of 3%, which was mainly related to non-procedure consequences and associated with the severity of the underlying disease. Our limitations were a small number of procedures in different indications. Further registries, large-scale data, and controlled randomized trials are needed to provide substantial evidence for the impact of therapeutic plasma exchange on the outcome of different disease conditions.

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## Conflict of Interest

Authors declare that they do not have any conflict of interest.

## Ethical Approval

The study was approved by the scientific research committee of the Dubai Health Authority.

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