Therapeutic Plasma Exchange in Renal Disorders

Review Article

Therapeutic Plasma Exchange in Renal Disorders

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Abstract

Nephrologists use hemodialysis and hemofiltration to remove low molecular weight toxic constituents, and increasingly deploy therapeutic plasma exchange (TPE)/plasmapheresis to eliminate higher molecular weight substances such as immunoglobulins or immune complexes from plasma. This review discusses different modalities of TPE, their application in renal disorders, its rationale and complications. TPE is recommended based on evidence, in alloantibody-mediated diseases such as humoral antibody mediated renal transplant rejection, autoantibody mediated glomerulonephritis (GN) disorders for example, anti-glomerular basement membrane GN, as well as in antineutrophil cytoplasmic antibody mediated GN and antibody mediated thrombotic thrombocytopenic purpura. In many other renal illnesses, the rational use of TPE is gaining currency. Double membrane filtration, immune adsorption and cryofiltration are important modifications in TPE

Keywords: *Plasmapheresis, renal, therapeutic plasma exchange*

Introduction

Therapeutic plasma exchange (TPE) interchangeably termed as plasmapheresis is a process involving extracorporeal removal of plasma from other components of blood, discarding and replacing plasma with physiological fluids.[1] TPE targets removal of a single or allied group of high molecular weight (MW) substances (>15 kD) compared to hemodialysis and hemofiltration and reduces the concentration of target molecule(s), thereby providing a therapeutic window for drugs to act.[2] TPE is an appropriate choice if the pathogenic substance(s) that cannot be removed by conventional therapy, requires rapid removal and/or has a relatively long half-life, slow re-synthesis rate and has intravascular distribution.[3] Since its introduction in 1952, TPE has been used in many disorders either alone or in combination with other therapies, with improved safety and efficacy.[4,5] This review focus on the role of TPE in renal disorders. Cytapheresis, the selective removal of cellular elements, and hemoperfusion is not discussed.

Procedure

TPE is performed either using centrifugation (cTPE) devices that separate the plasma from cellular components based on density or membrane apheresis, based on molecular size (mTPE).[6] Both technologies are comparable in safety and efficacy.[7] The former removes target substances at a higher plasma extraction ratio but at a lower blood flow rate, while the latter, though with a lower plasma extraction ratio, compensates with a higher blood pump speed.[7] Nephrologists largely favor mTPE, an adaptation of technology on the dialysis machine, while others use cTPE when feasible. Details on prescription for plasmapheresis are outlined in Table 1.

Centrifugal Separation

Modern-day centrifugal separation devices operating on continuous flow technology utilize gravitational forces to separate plasma and cellular components of blood. Blood is collected from the patient; anticoagulant, usually citrate, is added before centrifugation, pumped through centrifuge bowl (spinning container) through the inlet port, and spun at 2000–2500 rpm, separating components [Figure 1a]. During this process, red blood cells move to the outer rim of the bowl, plasma near the axis of rotation far from the bowl, and white blood cells and platelets between the red cell and plasma layers. These fractionated components are collected in separate collection bags and reinfused.

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Table 1: Therapeutic plasma exchange procedure

Procedure	Centrifugal TPE				Membrane TPE
Plasma exchange volume	To be individualized, plasma exchange volume is 1-1.5 times patient's plasma volume (depending on condition and severity) Estimated plasma volume (L)=0.07 (set) × weight (kg) × (1−hematocrit) E.g., for a 70 kg patient with a hematocrit of 35% the calculation would be as follows (0.07 kg × 70 kg × 1 - 0.35)				
Apparatus	COM.TEC (Fresenius Kabi)/or Spectra Optia Apheresis system				Fresenius 4008/5008
Kit	Plastic disposable Kit PL1/Spectra Optia Exchange set				Plasma flux P2S/bloodlines
Investigations	Complete blood count, renal function tests, calcium, coagulation parameters, and fibrinogen				
Premedication	Hydrocortisone 100 mg IV (draw up with 10 ml of 0.9% saline) Phenergan 12.5 mg IV (draw up with 5 ml of 0.9% saline) Paracetamol 1 g orally				
Anticoagulation	AC; ensure maximum infusion rate does not exceed 0.9 ml/min/L TBV. The inlet: AC ratio defaults to 13:1 for all TPE procedures				Heparin: Bolus: 1000 units and maintenance: 500 units/h
Priming the circuit	Prime lines with 0.9% saline; draw and return lines of central venous catheter are connected to the tubing. Draw and return tubing is primed with packed red blood cells if the patient is weighing <20 kg				
Prophylaxis for citrate toxicity	10 ml of 10% calcium gluconate for every liter of plasma volume filtered				If citrate is used as an anticoagulant - for example, CRRT machines
Replacement fluid	Option 1		Option 2		Option 3
	HUS/TTP/following renal biopsy/renal transplant		For patients requiring frequent TPE or with depleting coagulation factors		Patients requiring infrequent exchanges and satisfactory coagulation parameters
Proportion of total volume	FFP 75%	HSA - 25%	FFP - 20%	HSA - 80%	HSA - 100%
E.g., 2 L	1.5 L	0.5 L	0.4 L	1.6 L	2 L
Disconnection	Disconnect after required plasma removal. Instill heparin into central venous catheter lumen. Check post-TPE fibrinogen if HSA is used as the replacement fluid				

TPE: Therapeutic plasma exchange, IV: Intravenous, AC: Acid citrate, CRRT: Continuous renal replacement therapy, HSA: Human serum albumin, FFP: Fresh frozen plasma, TTP: Thrombotic thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, TBV: Total Blood Volume

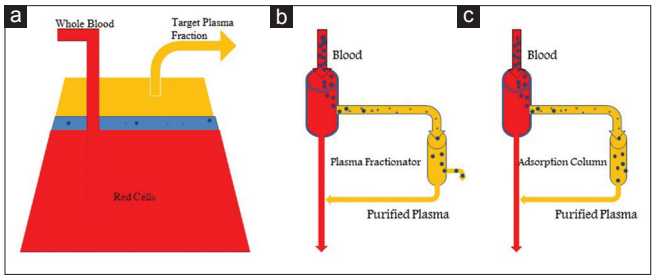

Figure 1: Therapeutic plasma exchange – Modalities. (a) Centrifugal TPE. (b) Double Membrane -Filtration. (c) Immunoadsorption

Membrane Separation

In this system, plasma is filtered from cellular components of the blood by filtration through a highly permeable membrane filter.[7] Blood passes through the filter having large pores that allow plasma only to pass through but retain the large cellular constituents. Membrane filtration is nonselective in removing plasma with dissolved "toxins" and useful components. The concept is similar to hemofiltration where microporous membrane sieves a number of solutes. The membranes used in this system have larger pores compared to hemofilters but <0.6 μ, thereby rejecting the cellular components. This procedure can be performed using a hemodialysis machine in isolated ultrafiltration-dialysis bypass mode or with continuous renal replacement therapy machines.[2] Efficiency depends on filter characteristics, filtration rates, formed element deposition, clotting of fibers, and protein adsorption. This technology is simple, cost-effective, and reliable with no loss of cellular constituents of blood compared to centrifugation technique.

Mechanisms of Action of Therapeutic Plasma Exchange

The principal factors influencing the removal of the target substance in plasma are the relative distribution of the substance in intravascular and extravascular compartments, transfer rates of the substance across compartments, plasma half-life, regeneration of the substance, and ratio of plasma volume removed.[6] These features are applicable to the removal of immunoglobulins (Ig) IgM, IgG and immune complexes. Antibodies with a prolonged half-life will remain for longer duration even when endogenous production has stopped.[8] IgG molecules have MW of 150 kD, prolonge half-life for 21 days, 60% extravascular distribution, and a slow redistribution across vascular compartments.[9] A number of autoimmune disorders are mediated by IgG requiring several TPE sessions. IgM, MW 970 kD, has a plasma half-life of 5 days and 80% intravascular distribution that allows for early clearance once production ceases, necessitating fewer exchanges.[10] The removal of immune complexes resulted in better monocyte/macrophage functions in an *in vitro* study.[11] Certain autoimmune disorders treated with

TPE show increasing T-suppressor cell function and the Th1/Th2 ratio shifting to a predominance of Th1 subsets.[12] Cytokines and soluble adhesion molecules in the plasma are removed by TPE but counteracted by their persistent production on contact of blood with the membrane.[13]

Replacement Fluids

Human serum albumin (HSA) is the common replacement fluid though, in certain clinical conditions, plasma is preferred for replacing missing plasma components. In thrombotic thrombocytopenic purpura (TTP), there is a deficiency in activity of A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). TPE improves the survival of patients suffering from TTP with the removal of autoantibodies against ADAMTS13 and replacement of ADAMTS13 with plasma infusion.[14] Concomitant immunosuppressive therapy reduces rebound autoantibody production.[15]

The replacement fluid often is 5% HSA. Some centers prefer replacement of initial one-third the volume with saline followed by albumin substitution.[16] This is economical as significant proportion of infused albumin is lost during TPE. There are complications associated with the use of HSA and also with fresh frozen plasma (FFP) that is occasionally used as a replacement fluid during TPE [Table 2].[2,17-19] FFP is a sole replacement fluid in patients with TTP as this provides a therapeutic replacement of missing ADAMTS13.

Vascular Access

Central venous catheters either temporary or tunneled are preferred to antecubital veins when multiple exchanges are planned. Permanent arteriovenous fistula or a graft is ideal if multiple TPE sessions are required as in postrenal transplant recurrence of focal segmental glomerulosclerosis. Antecubital veins can be used for low flow treatment and for short duration.

Renal Indications for Therapeutic Plasma Exchange

The recent American Society for Apheresis recommendations classifies the considered disorders into four categories and grades recommendations [Table 3].[5] The KDIGO guidelines discuss the status of TPE for various glomerulonephritis (GN).[20]

Antiglomerular Basement Membrane Disease

Antiglomerular basement membrane (anti-GBM) disease is an autoimmune disorder mediated by anti-GBM antibody binding to the "good pasture autoantigen" – the noncollagenous domain of α3 chain of type 4 collagen of GBM in isolation or frequently with alveolar basement membrane binding.[21] This results in rapidly progressive GN (RPGN) and diffuse alveolar hemorrhage (DAH). Majority present with renal disease, about a half will have simultaneous DAH, and a minority present with isolated DAH.[21] Pathogenic antibodies are present in almost in all patients, usually of IgG (IgG1, IgG3), though IgA and IgG4 can occur.[21]

Nonrandomized case–control studies and a single small randomized control study (RCT) have shown that adjunct TPE in addition to steroids and cyclophosphamide provides rapid clearance of anti-GBM antibodies, resulting in quicker resolution of DAH, improved patient, and renal survival.[22,23] A prospective study from North India found that most patients presented with dialysis-dependent renal failure with poor prognosis.[24] A Chinese center found that serum level of anti-GBM antibodies was an independent factor associated with mortality.[25] Early implementation of TPE targeting undetectable levels of anti-GBM antibodies is the goal of the therapy. A follow-up study involving 71 patients from Hammersmith Hospital has shown renal dysfunction at presentation and crescent score correlating with renal and patient survival. Patients who were dialysis dependent and having 100% crescents did not recover renal function despite therapy.[24] However, even in patients presenting with renal failure requiring dialysis, it is appropriate to initiate adjunct TPE. Renal biopsy done at the earliest opportunity showing 100% crescents (regardless of cellularity – personal opinion) indicates that renal recovery is unlikely and disease-modifying treatment including TPE can be withdrawn.[20] Patients presenting with both anti-GBM antibodies and antineutrophil cytoplasmic antibodies (ANCAs) will require aggressive early treatment as for anti-GBM disease including TPE and in addition long-term maintenance immunosuppression for ANCA-associated GN.[26]

Anti-neutrophil Cytoplasmic Antibody-associated Glomerulonephritis

Granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) presents as pauci-immune complex GN and has elevated cytoplasmic ANCA/proteinase 3 in GPA and perinuclear ANCA/myeloperoxidase in MPA. Approximately 70% of the patients presenting with RPGN in India have pauci-immune complex GN.[27] ANCAs being IgG can be rapidly reduced with TPE, improving outcome. A randomized trial of TPE or methyl prednisolone in severe renal vasculitis (MEPEX trial; n = 137) demonstrated that TPE increased the rate of renal recovery.[28] A substudy of MEPEX showed that TPE improved renal survival despite disquieting renal histological findings.[29] A meta-analysis of nine RCTs, including the MEPEX trial comprising 387 patients with ANCA-associated vasculitis or idiopathic RPGN, showed that with TPE there was a 20% relative risk reduction in the composite outcome of end-stage renal disease or death.[30] At 3.95 years, however, the MEPEX study participants did not sustain the earlier renal benefits of TPE.[31] There was a nonsignificant increase

Table 2: Complications

Complications	Reasons	Management
Vascular access related		
Hemothorax, pneumothorax, retroperitoneal bleed, local or systemic infection	Central venous line related	
Procedure related		
Hypotension	Externalization of blood in extracorporeal circuit; decreased intravascular oncotic pressure due to delayed, insufficient, and/or hypo-oncotic fluid replacement; anaphylaxis	Adequate and timely fluid replacement
Anaphylactic reactions (hypotension, fever, rigors, urticaria, wheezing, laryngeal edema)	Common with FFP; rare with albumin; increased risk with patients on ACE inhibitors	Stop ACE inhibitors 24-48 h before treatment; pretreatment with intravenous/antihistamine is advisable
	Membrane bio-incompatibility (complement mediated) or sterilizing agent (ethylene oxide) related	Use biocompatible membranes and adequate priming of the filter to clear ethylene oxide
Loss of cellular elements	Common with centrifugal TPE	Use membrane TPE
Anticoagulation related		
Citrate toxicity	Occurs with citrate anticoagulation and administration of FFP as replacement fluid; FFP contains (14%) citrate, and therefore citrate-related complications (hypocalcemia and metabolic alkalosis) may occur. Not reported with albumin	Check serum electrolytes and calcium; administer 10% IV calcium gluconate 10 ml for every liter exchange
		Perform TPE first followed by dialysis to correct citrate induced alkalemia if HD and TPE are required on the same day
Bleeding	Related to heparin administration or depletion coagulopathy due replacement with albumin	
Replacement fluids related: Albumin		
Depletion coagulopathy	Depletion of coagulation factors XIII and fibrinogen; international normalized ratio increases by 30% and activated partial thromboplastin time doubles after a single therapy; reversing in 24 h	With multiple consecutive treatments and albumin replacement, FFP administration is advisable
Immunoglobulin depletion	Single TPE serum immunoglobulin will reduce by 60%	A single dose of intravenous Igs is advisable as multiple TPE can decrease Igs for several weeks
FFP		
Viral transmission	FFP is obtained from multiple donors; increased risk of viral transmission	Use albumin as replacement fluid

FFP: Fresh frozen plasma, ACE: Angiotensin-converting enzyme, TPE: Therapeutic plasma exchange, IV: Intravenous, HD: Haemodialysis, Igs: Immunoglobulins

in infection-related deaths in patients randomized to the TPE arm raising concerns that TPE could cause harm. This could be a major detriment in the tropics. The role of TPE in DAH in these patients is based on observational data from a case series. Mortality in patients with DAH is mainly due to infection and TPE may further increase the risk of infection as Igs are removed. The ongoing PEXIVAS study with an open-label randomization of TPE is designed to address these questions.[32] Replacement with plasma is indicated in patients with DAH to avoid dilutional coagulopathy.[5] In patients with DAH and severe pulmonary compromise, the risk of an allergic reaction may be reduced with solvent detergent-treated plasma.[33]

Catastrophic Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS), an acquired hypercoagulable condition, is characterized by arterial or venous thrombosis with the presence of persistent antiphospholipid antibodies (APLAs), lupus anticoagulant, anticardiolipin, and or anti-β2-glycoprotein 1. Catastrophic APS is a life-threatening presentation with the presence of APL and acute thrombosis of at least three organs over a period of days to a few weeks. Kidneys, lungs, brain, skin, and other sites may be involved. TPE removes APLA, cytokines, and complement components. TPE in conjunction with steroids, anticoagulants, and intravenous Ig (IVIG) improve survival. Case series have shown that TPE is useful in managing these patients though the mechanism is unclear[34] and APLA titers may be monitored to assess response to treatment.

Cryoglobulinemic Renal Disorders

Cryoglobulinemic disorders are mediated by circulating cryoglobulins. TPE can remove these molecules but has

Table 3: Therapeutic plasma exchange in renal disorders

Condition	Number of exchanges/replacement solution	ASFA grade/category
ANCA-associated GN-serum creatinine >500 umol/L or dialysis dependent	7 exchanges (1-1.5 plasma volume) in 14 days	I/IA
	5% albumin unless DAH or need to prevent coagulopathy	I/IC
ANCA-associated GN with DAH/cerebral vasculitis		III/2C
ANCA-associated GN-dialysis independence		
ANCA-negative rapidly progressive GN; no DAH	7 exchanges in 14 days; 5% albumin	III/2C
Anti-GBM disease with DAH	14 daily exchanges	I/IC
Anti-GBM disease	5% albumin and likely to require plasma as 50% replacement fluid by 2nd plasma exchange; 100% plasma replacement fluid in the presence of DAH	I/IB
No DAH, renal failure, not requiring dialysis (potential for renal recovery)		
Anti-GBM disease	Exchanges until the time of renal biopsy	III/2B
No DAH; renal failure requiring dialysis	5% albumin unless DAH or need to prevent coagulopathy	
Anti-GBM disease partially responding with elevated ant-GBM titers	14 daily exchanges, then cease if renal function stabilized for final 72 h; Consider a further 7 exchanges over 14 days if renal function continues to progressively improve after initial 14 daily exchanges	I/IB
	Consider changing immunosuppressive agents	
Catastrophic antiphospholipid antibody syndrome	Daily; 1-3 weeks then re-evaluate	II/2C
	Albumin unless plasma is required to prevent coagulopathy	
Cryoglobulinemia	Consider daily for 7 exchanges; may require weekly-monthly maintenance	II/2A
	Albumin unless plasma is required to prevent coagulopathy	
FSGS - steroid resistant in native kidney	LDL apheresis	III/2C
IgA nephropathy-crescentic GN IgA vasculitis - severe extrarenal involvement		III/2C
		III/2C
Multiple myeloma		II/2B
TMA		
Acquired TTP	Daily; plasma or cryoplasma	I/1A
STEC-associated HUS	No standard approach; depend on patient's condition and response	IV/IC
Complement-mediated TMA (atypical HUS)	Consider TPE; plasma or cryoplasma	I/2C
Factor H autoantibodies		III/2C
Gene mutation		
Secondary TMA autoimmune related, e.g., SLE	Consider TPE (7 sessions)	II/2C
	Albumin unless plasma is required to prevent coagulopathy	
Secondary TMA - drug related	Consider TPE (7 sessions)	I/2B (ticlopidine)
	Albumin unless plasma is required to prevent coagulopathy	Other drugs: III/2B/C
Antibody-mediated rejection (TPE is used in combination with Intravenous immunoglobulin)	Alternate days for 10 days; 5% albumin unless plasma is required to prevent coagulopathy; IVIG 100 mg/kg post-TPX	I/1B
Recurrent posttransplantation FSGS	3 daily exchanges followed by ≥6 more exchanges in subsequent 2 weeks. May require ongoing therapy; albumin unless plasma is required to prevent coagulopathy	IB

Category 1: TPE as first-line stand-alone or in conjunction with other therapies, Category II: TPE as second-line therapy, Category III: TPE is not established, decision should be individualized, Category IV: No evidence for TPE efficacy. ASFA graded recommendations range from 1A to 2C, based on evidence. ASFA: American Society for Apheresis, ANCA: Antineutrophil Cytoplasmic Antibodies, GN: Glomerulonephritis, DAH: Diffuse alveolar hemorrhage, GBM: Glomerular basement membrane, LDL: Low-density lipoprotein, TMA: Thrombotic microangiopathy, TTP: Thrombotic thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, TPE: Therapeutic plasma exchange, SLE: Systemic lupus erythematosus, IVIG: Intravenous immunoglobulin, FSGS: Focal segmental glomerulosclerosis, STEC: Shiga toxin-producing *Escherichia coli*

no effect on their production or on the underlying primary disease. There are case series to support the use of TPE in cryoglobulinemic vasculitis in conjunction with antiviral and immunosuppressive therapy.[35] TPE is indicated in catastrophic hepatitis C virus cryoglobulinemic vasculitis presenting with RPGN, gastrointestinal (GI) system, central nervous system, and/or pulmonary involvement.[36]

Idiopathic Immune-Complex Rapidly Progressive Glomerulonephritis

RPGN with crescent formation can occur occasionally in IgA nephropathy, membranoproliferative GN, postinfectious GN, and GN associated with infective endocarditis. TPE has no evidence of benefit.[37]

IgA Vasculitis and IgA Nephropathy

IgA nephropathy and IgA vasculitis (Henoch-Schonlein purpura) are mediated by IgA containing immune complexes which TPE can remove. TPE can be used in IgA vasculitis with RPGN, severe GI or cerebral manifestations based on anecdotal reports and a case series.[38,39]

Multiple Myeloma

Renal involvement in multiple myeloma can be myeloma cast nephropathy or renal amyloidosis. Cast nephropathy occurs when there are high circulating levels of free kappa or lambda light chains. TPE effectively removes culprit-free light chains, but the results are conflicting. The Mayo Clinic study (n = 40) showed that TPE improved renal survival in biopsy-proven cast nephropathy.[40] The Canadian RCT did not find a significant benefit from TPE, but only a few renal biopsies were performed.[41] TPE is likely beneficial if in conjunction with chemotherapy in patients with biopsy-proven recent-onset acute kidney injury due to cast nephropathy. Case reports suggest enhanced free light chain removal with "high cutoff" membranes compared to TPE;[42] however, this has not shown survival benefits.

Thrombotic Microangiopathies

There is deficiency in TTP, of ADAMTS13, an enzyme that normally cleaves von Willebrand factor multimers leading to prevention of microthrombosis, whereas most hemolytic-uremic syndrome (HUS) patients have normal activity of this enzyme.[43] The clinical features and rationale for the use of TPE in a spectrum of thrombotic microangiopathy are presented in Table 4.

Renal Transplantation in Human Leukocyte Antigen-sensitized Patients

Pretransplantation desensitization protocols increasingly use TPE for recipients with living donors who have an

Table 4: Indications for therapeutic plasma exchange in thrombotic microangiopathy

Condition	Features	Rationale to use TPE
Primary TMA		
Acquired TTP	Thrombocytopenia, unexplained MAHA, severe ADAMTS13 deficiency, normal clotting factors	Randomized controlled trial has shown that TPE reduces mortality; initiate TPE within 24 h of presentation and continue until platelet, hemoglobin, and LDH normalize
Congenital TTP	Severe ADAMTS13 (<10%); no ADAMTS13 autoantibody inhibitor	TPE is indicated at the time of the first presentation
HUS		
Shiga toxin-mediated TMA (STEC HUS)	Thrombocytopenia, MAHA, severe renal impairment secondary to Shiga toxin-producing bacteria - *Escherichia coli*; ADAMTS13 activity preserved	Case reports; no supportive evidence
Complement-mediated TMA (atypical HUS)	Thrombocytopenia, MAHA, severe renal impairment, Shiga toxin negative, ADAMTS13 activity preserved; have mutations in complement factor 3, H, H receptor, membrane cofactor	Eculizumab® - first-line therapy; TPE add "good" complement proteins and remove inflammatory products causing endothelial dysfunction. Case reports show TPE reduce mortality though long-term prognosis is poor. TPE is used as initial therapy for patients with unexplained thrombocytopenia and anemia with normal ADAMTS13 (>10%) and no obvious secondary cause or with a secondary cause that has received appropriate therapy
Secondary TMA	Variable ADAMTS13 activity; no strong evidence to support treatment of TMA associated with other drugs including cyclosporine, tacrolimus	Case studies
Drug mediated		Good response seen in ticlopidine-associated TMA; no strong evidence to support treatment of TMA associated with other drugs including cyclosporine, tacrolimus
Autoimmune disease, e.g., SLE[44]		Case reports; in SLE besides TMA, TPE is indicated in cerebritis and or patients presenting with DAH

TTP: Thrombotic thrombocytopenic purpura, MAHA: Microangiopathic hemolytic anemia, ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin Type 1 motif, member 13, TPE: Therapeutic plasma exchange, LDH: Lactate dehydrogenase, HUS: Hemolytic uremic syndrome, STEC: Shiga toxin-producing *Escherichia coli*, TMA: Thrombotic microangiopathy, DAH: Diffuse alveolar hemorrhage, SLE: Systemic lupus erythematosus

incompatible crossmatch from donor-specific human leukocyte antigen (HLA) antibodies. There is a demonstrable survival advantage with transplantation in these individuals when compared to remaining on dialysis.[45] The number of TPE sessions is influenced by the degree of sensitization and HLA mismatch. The sessions are planned daily or on alternate days till crossmatch becomes negative leaving a week's window to transplantation before antibodies rebound.

ABO-incompatible Transplantation

ABO-incompatible renal transplantation requires TPE to remove significant levels of blood group isoagglutinins and a protocol of anti-CD20 antibodies and IVIG to restrict its production.[46] The 5-year and 10-year survival rates are comparable with ABO-compatible transplantation,[47] with an increased infective risk, in some reports. Double membrane filtration (DMF) TPE is economical compared with the specific Glycosorb® columns.

Antibody-mediated Rejection

Antibody-mediated rejection of kidney allografts occurs not only in up to 60% of high-risk recipients (HLA-sensitized or ABO-incompatible) but also in about 23% of unselected low-risk recipients.[48] TPE, daily or alternate days using 5% HSA, and IVIG (a high dose 2 g/kg or a low dose of 100 mg/kg) are commonly used to clear donor-specific antibodies and suppress antibody production, respectively. Recent years has seen anti-CD20 antibody used alongside though the evidence toward safety and efficacy is weak.[49]

Focal and Segmental Glomerulosclerosis with Recurrence Post-transplantation

Among those kidney transplant recipients with primary focal segmental sclerosis, severe proteinuria recurs in 30%–55% of patients, often within hours or days of surgery due to a permeability factor of 30–50 kD.[50] DMF is unsuitable for removal of this small MW factor. A meta-analysis of uncontrolled data shows full or partial remission with early TPE.[51] There are recommendations for initial daily and later alternate day TPE to keep patients in remission. In practice, some patients require weekly to monthly TPEs long term, to sustain remission.

Other Blood Purification Techniques[4,52]

Double membrane filtration or cascade filtration

In a single pass filtration, the separated plasma is discarded. In DMF, the filtered plasma is re-filtered through a plasma fractionator filter with smaller pore size [Figure 1b]. Smaller proteins and albumin (<100 kD) will pass through these pores, to be returned to the patient, while the larger target molecules are removed. DMF is used for ABO-incompatible renal transplantation, acute antibody-mediated rejection, anti-GBM disease, and ANCA-GN.[53] The requirement of replacement fluid is limited, reducing complications.

Cryofiltration

This technique is a modification of DMF and involves cooling of the initially separated plasma increasing the size of the cryoproteins to be removed, enhancing the second filtration. This is useful in cryoglobulinemic disorders.[54]

Adsorption techniques

The immunoadsorption technique is used for a known antigen or antibody that is extractable and removable in an adsorption column [Figure 1c]. Examples: antigen binding; anti-low-density lipoprotein (LDL) antibody for LDL; complement binding, e.g., for C1q nephropathy, Fc binding; staphylococcal protein A columns for immune complexes, IgG.

Another option is to use hydrostatic or hydrophobic beads in these adsorbers, for example, tryptophan and phenylalanine for immune complexes, rheumatoid factor, anti-acetylcholine receptor antibodies, and anti-DNA antibodies, and to remove toxins from plasma. Single or double column adsorber with regenerable and reusable columns is available. No substitution fluid is required.

Drugs and Therapeutic Plasma Exchange

Drug removal during TPE depends on TPE profile and pharmacokinetics of the drugs. Less likely, the drug will be removed if the drug plasma concentration at the time of initiation of TPE is lower; lower the drug's protein binding and higher the volume of distribution. Drug removal also depends on the time between the administration of the drug and TPE initiation, duration of TPE, volume of plasma removed, and sessions in succession.[55] Intravenous cyclophosphamide, Rituximab®, or IVIG must be administered post-TPE only.

Conclusion

TPE is a valuable tool in the treatment of renal disorders when evidence-based recommendations are weighed with risk stratification of patients. The results are not always predictable solely based on successful removal of a target substance. One must consider the likely benefits against the risks and economic impact in each instance.

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Conflicts of interest

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