CORE CURRICULUM IN NEPHROLOGY

Therapeutic Plasma Exchange: Core Curriculum 2008

Andre A. Kaplan, MD

Given their expertise in vascular access, anticoagulation, volume management, and solute clearance, nephrologists are well suited to manage all methods of blood purification, including therapeutic plasma exchange (TPE). This core curriculum is an annotated primer and bibliography for understanding the indications, technique, and complications associated with TPE.

INTRODUCTION AND RATIONALE

TPE is an extracorporeal blood purification technique designed for the removal of large-molecular-weight substances. Examples of these substances include pathogenic autoantibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxin, and cholesterol-containing lipoproteins.

For TPE to be a rational choice as a blood purification technique, at least 1 of the following conditions should be met: (1) the substance to be removed is sufficiently large (≥15,000 d) to make other less expensive purification techniques unacceptably inefficient (ie, hemofiltration or high-flux dialysis), (2) the substance to be removed has a comparatively prolonged half-life so that extracorporeal removal provides a therapeutically useful period of diminished serum concentration, and (3) the substance to be removed is acutely toxic and resistant to conventional therapy so that the rapidity of extracorporeal removal is clinically indicated.

The removal of pathogenic autoantibodies offers an example. If one considers that the natural half-life of immunoglobulin G (IgG) is approximately 21 days and assuming that an immunosuppressive agent could immediately halt production (unlikely), serum levels would still be 50% of the initial values for at least 21 days after initiating therapy. Such a delay might be unacceptable in the presence of a very aggressive autoantibody, such as that involved with Goodpasture syndrome.

From the University of Connecticut Health Center, John Dempsey Hospital, and the UConn Dialysis Center, Farmington, CT.

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Address correspondence to Andre A. Kaplan, MD, University of Conneciticut Health Center, Division of Nephrology, MC 1405, Farmington, CT 06030. E-mail: kaplan@nso.uchc.edu

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INTRODUCTION AND RATIONALE: SUGGESTED READINGS

Cohen S, Freeman T: Metabolic heterogeneity of human gamma globulin. Biochem J 76:475-487, 1960

INDICATIONS

In 1985, the American Medical Association (AMA) Council on Scientific Affairs convened a panel of 10 experts to review the available data for the efficacy of plasma exchange. Their assessment assigned each potential indication into 1 of 4 categories:

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

Since this AMA review, there have been several well-designed randomized controlled trials that added significant new insight into the proper application of TPE. In consideration of these new studies, 2 subsequent reviews have attempted to update the original AMA recommendations. Added to these updated reviews is an assessment by the American Academy of Neurology. Most recently, in June 2007, the American Society for Apheresis published their exhaustive review of the indications for plasma exchange and the most current assessment of the available supportive evidence. The rating system of this most-up-to-date review uses categories (I to IV) similar to the previous reviews.

The original AMA indications, updated and modified by the 4 subsequent reviews, are listed in Table 1.

Another means of assessing the standard of care currently acceptable in the United States is to refer to the current indications for which Medicare is willing to reimburse. This list of

Table 1. Indications for TPE

Reference	1	2	3	4	5
Year	1986	1993	1994	1996	2007
	Rating	Rating	Rating	Rating	Rating
Neurological diseases					
Guillain-Barre syndrome	I	I	I	est	I
Myasthenia gravis	I	I	I	est	I
Chronic inflammatory demyelinating polyneuropathy	III	I	I	est	I
Paraprotein-associated polyneuropathy	nl	II	nl	est	I-III
Multiple sclerosis	II	III	III	pos	II-III
Eaton Lambert syndrome	nl	I	nl	pos	II
Stiff man syndrome	nl	nl	nl	invest	III
Amyotrophic lateral sclerosis	IV	IV	IV	nl	nl
Neuromyotonia	nl	nl	nl	invest	nl
Acute disseminated encephalomyelitis	nl	nl	nl	invest	III
Refsum's disease	nl	I	nl	invest	II
Sensorineural hearing loss	nl	nl	nl	nl	nl
Hematologic disorders					
Hyperviscosity syndrome	I	I	I		I
Cryoglobulinemia	II	I	I		I
Thrombotic thrombocytopenic purpura	I	I	I		I
Hemolytic uremic syndrome	nl	II	II		III-IV
Idiopathic thrombocytopenic purpura	III	III	III		II-IV
Posttransfusion purpura	II	I	I		III
Autoimmune hemolytic anemia	III	III	III		III
Maternal-fetal incompatibility-Rh disease	II	III	nl		II
Removal of factor VIII inhibitors	II	II	III		III
Metabolic disorders					
Hypercholesterolemia	II	I-II	I		I-II
Hypertriglyceridemia	nl	nl	nl		III
Pruritis associated with cholestasis	II	nl	nl		nl
Hepatic failure	III	III	nl		III
Graves' disease and thyroid storm	I	III	III		III
Insulin receptor antibodies	nl	nl	nl		nl
Dermatological disorders					
Pemphigus vulgaris	III	II	nl		III
Bullous pemphigus	nl	II	nl		nl
Toxic epidermal necrolysis (Lyell syndrome)	nl	nl	nl		nl
Porphyria cutanea tarda	nl	nl	nl		nl
Psoriasis	III	IV	IV		nl
Rheumatological disorders					
Systemic lupus erythematosus	II	II	nl		III-IV
Antiphospholipid syndrome/(lupus anticoagulant)	nl	nl	nl		III
Scleroderma	III	III	III		III
Rheumatoid arthritis/rheumatoid vasculitis	II	III	IV&II		II
Vasculitis	II	II	II		nl
Polymyositis/dermatomyositis	III	III/IV	IV		nl
Renal disease					
Goodpasture syndrome	I	I	I		I
Rapidly progressive glomerulonephritis	I	II	II		III
Multiple myeloma, cast nephropathy	II	II	nl		III
Henoch-Schönlein purpura/IgA nephropathy	II	nl	nl		nl
Focal segmental glomerulosclerosis					
Recurrence posttransplantation	nl	nl	nl		III
Renal allograft rejection	II	IV	IV		II
Removal of cytotoxic antibodies in the transplant candidate	nl	nl	nl		II

(*Continued*)

Table 1 (Cont'd). Indications for TPE

Reference	1	2	3	5
Year	1986	1993	1994	2007
	Rating	Rating	Rating	Rating
Indications for TPE in the ICU				
Fulminant systemic meningococcemia	nl	nl	nl	nl
Endotoxemia	nl	nl	nl	III
Burn shock	III	nl	nl	nl
Human immunodeficiency virus	III	nl	nl	nl
Immune thrombocytopenic purpura	nl	II	nl	nl
Thrombotic thrombocytopenic purpura	nl	I	nl	nl
Peripheral neuropathy	nl	I	nl	nl
Intoxications	I	II	II	II-III
Arsine				
Carbamazepine				
Cisplatin				
Digitoxin				
Digoxin				
Diltiazem				
Mushroom poisoning		II		II
Paraquat		II		
Parathion		II		
Phenylbutazone				
Phenytoin				
Quinine				
Sodium chlorate		II		
Theophylline				
Thyroxine				
Tricyclic antidepressant				
Vincristine				

Note: Ratings: I, standard therapy, acceptable but not mandatory; II, available evidence tends to favor efficacy: conventional therapy usually tried first; III, inadequately tested at this time; IV, no demonstrated value in controlled trials; est, established therapy; invest, investigational; pos, possibly useful; nl, not listed.

Abbreviations: IgA, immunoglobulin A; TPE, therapeutic plasma exchange; ICU, intensive care unit.

Table 1 adapted with permission from Kaplan AA: A Practical Guide to Therapeutic Plasma Exchange. Blackwell Science, Malden, MA, 1999, copyright Andre Kaplan.

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indications is available on the Medicare website and is reproduced in Table 2.

Therapeutic Apheresis for Renal Disorders

Many primary renal diseases are associated with autoantibodies, rendering them appealing indications for TPE. Some indications are well established by randomized controlled studies and are considered standard of care (Goodpasture and thrombotic thrombocytopenic purpura [TTP]). Others have less compelling or only anecdotal supporting evidence.

Table 2. Medicare Reimburseable Indications for Plasma Exchange*

Apheresis is covered for the following indications:
Plasma exchange for acquired myasthenia gravis
Leukapheresis in the treatment of leukemia (cytapheresis)
Plasmapheresis in the treatment of primary macroglobulinemia (Waldenstrom)
Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia, and hyperviscosity syndromes
Plasmapheresis or plasma exchange as a last resort treatment of thromobotic thrombocytopenic purpura
Plasmapheresis or plasma exchange in the last resort treatment of life-threatening rheumatoid vasculitis
Plasma perfusion of charcoal filters for treatment of pruritis of cholestatic liver disease
Plasma exchange in the treatment of Goodpasture syndrome
Plasma exchange in the treatment of glomerulonephritis associated with anti–glomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage
Treatment of chronic relapsing polyneuropathy for patients with severe or life-threatening symptoms who have failed to respond to conventional therapy
Treatment of life-threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy
Treatment of Guillain-Barre syndrome
Treatment of last resort for life-threatening systemic lupus erythematosus when conventional therapy has failed to prevent clinical deterioration

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

*Centers for Medicare and Medicaid Services: NCD for Apheresis (therapeutic Pheresis). Available at: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=110.14&ncd_version=1&basket=ncd%3A110%2E14%3A1%3AApheresis+%28Therapeutic+Pheresis%29. Accessed May 21, 2008.

I. Anti–Glomerular Basement Membrane (anti-GBM) Antibody–Mediated Disease (Goodpasture syndrome)

A randomized controlled trial found TPE to provide a more rapid decrease in anti-GBM antibodies, lower posttreatment serum creatinine level, and decreased incidence of end-stage renal disease (ESRD). Given these results and the integral role of the anti-GBM antibody, TPE as a means of rapidly decreasing anti-GBM titers has become the standard of care.

A. Treatment strategy:
   1. Early initiation of TPE is essential to avoid ESRD
   2. Initial prescription is 14 daily 4-L exchanges
   3. Continued apheresis may be required if antibody titers remain increased
   4. Steroids, cyclophosphamide, or azathioprine are added to decrease production of anti-GBM antibody and minimize the inflammatory response

II. Crescentic Rapidly Progressive Glomerulonephritis (RPGN; not associated with anti-GBM antibody)

Several controlled studies have failed to show a generalized benefit of TPE for all patients with RPGN; however, subset analysis of all these studies showed TPE to be beneficial for patients presenting with severe disease or dialysis dependency. A more recent study (Jayne et al) limited to patients presenting with creatinine levels greater than 5.8 mg/dL (to convert creatinine in mg/dL to μmol/L, multiply by 88.4) appears to support this conclusion (Table 3).

Patients with Wegener granulomatosis and microscopic polyarteritis who present with pulmonary hemorrhage appear to be more likely to present with IgM antineutrophil cytoplasmic antibodies (ANCAs). These patients may also respond to TPE.

III. Renal Failure in Multiple Myeloma

After exclusion of other forms of renal failure associated with multiple myeloma (eg, hypercalcemia, volume depletion, hyperuricemia, infection, and amyloidosis), patients considered to have light-chain–related "cast nephropathy" may benefit from TPE. TPE can decrease serum levels of light chains more rapidly than chemotherapy alone. A randomized controlled study found TPE to provide a more likely

Table 3. Controlled Trials of TPE for Patients With Severe or Dialysis-Dependent Rapidly Progressive Glomerulonephritis

Reference	Index of severity	TPE	no TPE
Mauri et al,[1] 1985	Creatinine > 9 mg/dL		
Initial creatinine, mg/dL (no. of patients)		13.5 (6)	13.1 (5)
Creatinine after 3 y (mg/dL)		8.7*	13.4
Glockner et al,[2] 1988	Dialysis dependent		
Initial creatinine, mg/dL (no. of patients)		7.4 (8)	9.2 (4)
Creatinine after 6 mo		1.7*	5.5
Pusey et al,[3] 1991	Dialysis dependent		
Initial no. of patients on dialysis		11	8
Patients off dialysis at 12 mo		10†	3
Cole et al,[4] 1992	Dialysis dependent		
Initial no. of patients on dialysis		4	7
Patients off dialysis at 12 mo		3	2
Jayne et al,[5] 2007	Creatinine > 5.8 mg/dL		
Initial no. of patients		70	67
Patients off dialysis at 12 mo		57	40

Note: Subset analysis. All studies used concomitant treatment with steroids and immunosuppressive agents. To convert serum creatinine mg/dL to μmol/L, multiply by 88.4.

Abbreviation: TPE, therapeutic plasma exchange.

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*$P < 0.05$ with day 0.

†$P < 0.05$, TPE versus no TPE.

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return of renal function and better overall survival (Zucchelli et al). However, despite a 50% decrease in need for dialysis, a recently reported study did not find a statistically significant benefit for TPE (Clark et al).

A. Treatment considerations:
   1. Demonstration of free light chains in serum is essential if TPE is to be considered a rational treatment option (by standard immunofixation or the new free light chain assay)
   2. Successful TPE prescription is 3 to 4 L of plasma exchanged on 5 consecutive days
   3. Well-established (chronic) renal failure considered to be caused by cast nephropathy may respond less dramatically
   4. Newly available highly permeable hemofilter membranes may allow for light chain removal without significant albumin loss (Hutchison et al)

IV. IgA Nephropathy and Henoch-Schönlein Purpura

Case reports and small clinical series suggest a possible beneficial effect of TPE in the treatment of IgA-associated RPGN.

V. Cryoglobulinemia

Despite a lack of randomized controlled studies, most experts agree TPE can be a useful adjunct for severe active disease manifested by progressive renal failure, coalescing purpura, or advanced neurop-

athy. TPE can rapidly decrease cryoglobulin levels without the use of immunosuppressive agents, which might be problematic in hepatitis C–associated disease.

A. Treatment strategy:
   1. A reasonable TPE prescription is to exchange 1 plasma volume 3 times weekly for 2 to 3 weeks
   2. An average of 13 treatments may be required to induce clinical improvement (range, 4 to 39)
   3. The replacement fluid can be 5% albumin, which must be warmed to prevent precipitation of circulating cryoglobulins

VI. TTP and Hemolytic Uremic Syndrome (HUS)

A. TTP

A large randomized controlled study found 78% survival with TPE and fresh frozen plasma (FFP) replacement compared with 50% survival with FFP infusions alone (Rock et al). TPE with FFP replacement is the treatment of choice for TTP and is considered standard of care.

1. Treatment considerations:
   i. FFP is required as replacement fluid to replace missing metalloprotease (ADAMTS13 [A Disintigrin-like And Metalloprotease with ThromboSpondin type 1 repeats])
   ii. Plasma removal with TPE removes antibody to ADAMTS13
   iii. Treatments are performed daily until the platelet count is normalized and hemolysis has largely ceased (normalization of lactate dehydrogenase)
   iv. Exchanged volumes should be at least 1 plasma volume. Some experts recommend 1.5 plasma volume exchanges for the first week
   v. Previous recommendations suggest switching to cryoprecipitate-poor plasma in resistant cases because it may contain lower levels of von Willebrand factor. However, a recent review suggests that cryoprecipitate-poor plasma contains less ADAMTS13 and may be less effective than FFP (Raife et al)

B. HUS in adults

Although renal failure tends to dominate the clinical presentation, unless a specific cause can be identified, HUS is often difficult to distinguish from TTP

1. Causes:
   i. Verotoxin induced by *Escherichia coli* 0157-H7: prodrome of bloody diarrhea
   ii. Drugs: cyclosporine, tacrolimus, mitomycin, cisplatinum, quinine, oral contraceptives, antiplatelet agents, and so on
   iii. Lupus
   iv. Cancer
   v. Bone marrow transplant
   vii. Posttransplantation recurrence
2. Prognosis in adults is poor:
   i. Mortality between 25% and 50%
   ii. ESRD in 40%

Although treatment success depends on the cause, HUS in adults is often treated with TPE as with TTP.

C. HUS in children

Prognosis is usually good in verotoxin-induced disease, with only a small percentage of patients experiencing strokes or sustained renal failure. Controlled trials with plasma infusion have shown only minimal benefit.

TPE may be beneficial in children:

1. Without a diarrheal prodrome
2. Older than 5 years
3. With significant central nervous system involvement

VII. Systemic Lupus Erythematosus

Randomized controlled trials could not document systematic benefit of TPE when added to standard immunosuppressive therapy.

TPE may still be useful in certain special situations:

A. Pregnancy, when cytotoxic agents are undesirable
B. Lupus-associated TTP

C. Lupus anticoagulant (LA)/antiphospholipid antibody syndrome

VIII. LA, Anticardiolipin Antibodies, and Antiphospholipid Antibody Syndrome

LA and anticardiolipin antibody are antiphospholid antibodies associated with thromboses, recurrent fetal loss, and renal disease. TPE has been successful in removing antiphospholipid antibodies to avoid spontaneous abortion, treatment of LA-associated renal failure, and in the management of catastrophic antiphospholipid syndrome (CAPS).

IX. Scleroderma

TPE may be useful in rare coexistence of scleroderma and ANCA-positive or antinuclear antibody (ANA)-positive renal disease.

X. Focal Segmental Glomerulosclerosis (FSGS): Recurrence Posttransplantation

Fifteen percent to 55% of patients with ESRD secondary to FSGS have rapid recurrence of proteinuria after renal transplantation. Some patients with early recurrence of proteinuria have a circulating 30- to 50,000-d protein capable of increasing glomerular permeability to albumin. Standard TPE and immunoadsorption have been successful in decreasing the level of proteinuria. The addition of cyclophosphamide to TPE may lead to more prolonged remission. TPE may be effective in the treatment of recurrent FSGS if treatment is initiated promptly after the initiation of proteinuria.

XII. Transplant Candidates With Cytotoxic Antibodies

TPE and immunoadsorption have been successful in decreasing high levels of preformed cytotoxic antibodies (panel reactive antibody [PRA]), allowing for successful transplants for up to 34 months.

Often used with concomitant cyclophosphamide and prednisolone.

XIII. Renal Allograft Rejection

TPE can provide a rapid decrease in anti-human leukocyte antigen (HLA) antibodies. However, 2 controlled trials of TPE for acute vascular rejection did not find this treatment to be useful.

TPE together with cyclophosphamide and methylprednisolone has been reported to result in greater improvement in renal function and improved graft survival.

XIV. Renal Transplantation Across Blood Group Type ABO Groups

TPE can be used to remove anti-A or anti-B antibodies before transplantation. Five-year graft survival has been as high as 78% when kidneys from donors in blood A2 or B subgroups are transplanted into group O recipients. Donor-specific skin grafting can be used to predict outcome.

PLASMAPHERESIS AND RENAL DISEASE: SUGGESTED READINGS

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GENERAL GUIDELINES FOR PRESCRIBING TPE

The amount of plasma to be exchanged during TPE must be determined in relation to the patient's estimated plasma volume (EPV). A simple means of estimating plasma volume can be calculated from the patient's weight and hematocrit using the following formula:

$$\text{EPV} = (0.065 \times \text{weight [kg]}) \times (1 - \text{hematocrit}) \quad (1)$$

In general, large-molecular-weight substances (immunoglobulins, cholesterol-containing lipoproteins, and cryoglobulins) are only slowly equilibrated between their extravascular and intravascular distribution. Thus, removal during a single treatment essentially is limited to that in the intravascular compartment and the amount of plasma to be exchanged to provide a given decrease in pretreatment levels can be determined by application of first-order kinetics using the formula:

$$X_1 = X_o e^{-Ve/EPV} \quad (2)$$

where X_1 equals the final plasma concentration, X_o equals the initial concentration, and Ve equals the volume exchanged. (Of interest to nephrologists, the relation shown on this graph and the posttreatment percentage of reduction is exactly analogous to the Kt/V calculations associated with urea reduction ratios during dialysis in which Ve is Kt and EPV is V). The relation is plotted in Fig 1.

Extravascular to intravascular reequilibration of a large-molecular-weight substance will be relatively slow (~1% to 3% per hour). Thus, several consecutive treatments separated by 24 to 48 hours each will have to be performed to remove a substantial percentage of the total-body burden. An example of the progressive reduction in serum levels of an immunoglobulin is shown in Fig 2, with a net 70% decrease in total-body IgG level 1 day after 3 consecutive TPE treatments equaling 1 plasma volume each. In general, if production rates (resynthesis) are modest (ie, slowly forming antibody), at least 5 separate treatments during a 7- to 10-day period will be required to remove 90% of the patient's initial total-body burden. If production rates are high (ie, rapidly forming antibody, complement components), additional treatments may be required.

The results shown in Fig 2 describe a best-case scenario concerning immunoglobulin removal. In some autoimmune diseases, the rate of autoantibody production may greatly exceed that of the total immunoglobulin class. Such has been documented for certain cases of Goodpasture syndrome in which anti-GBM activity will be predictably decreased by a given plasma exchange treatment, but for which the intertreatment increases in serum levels are too rapid to be compatible with a simple reequilibration of extravascular stores. Thus, a 70% absolute decrease in a pathogenic autoantibody requires at least 3 plasma exchange treatments and may require a far more intensive treatment schedule if production rates cannot be adequately controlled by the concomitant immunosuppressive medications.

Production rates (half-lives), molecular weights, and percentages of intravascular distribution of several serum proteins are listed in Table 4.

GENERAL GUIDELINES FOR TPE PRESCRIPTION: SUGGESTED READING

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TECHNIQUE

Traditionally, plasma exchange was performed with centrifugation devices used in blood-banking procedures. These devices offer the advantage of allowing for selective cell removal (cytapheresis). Plasma exchange also can be performed using a highly permeable filter and standard dialysis equipment.

I. Centrifugation

Centrifugation separates the plasma by density gradients.Whole-blood constitu-

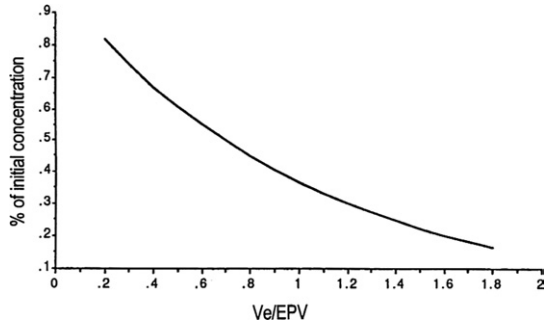

Figure 1. Relation of volume exchanged, estimated plasma volume (EPV), and percentage of decrease in initial concentration for large-molecular-weight substances removed during therapeutic plasma exchange (TPE). For example, if the volume exchanged (Ve) is equal to the patient's EPV, Ve/EPV will equal 1 and pretreatment values will be decreased by 63%. If the plasma exchanged is equal to 1.4 times the EPV, pretreatment levels will be decreased by 75%. As shown in the figure, increasingly voluminous exchanges during a single treatment yield a progressively smaller decrease in pretreatment levels. For most indications, each treatment should provide an exchange volume equal to 1 to 1.4 times the EPV. (Reproduced from Kaplan AA: A Practical Guide to Therapeutic Plasma Exchange, copyright Andre Kaplan)

ents are layered into plasma (specific gravity [SG], 1.025 to 1.109), platelets (SG, 1.040), lymph (SG, 1.070), granulocytes (SG, 1.087 to 1.092), and red blood cells (SG, 1.093 to 1.096).

II. Filtration (membrane plasma separation [MPS])

Separation of plasma from the blood's cellular components can also be accomplished by filtration though a highly permeable membrane. Blood is separated into its cellular and noncellular components by subjecting it to sieving through a membrane with pores that allow plasma proteins to pass, but that retain the larger cellular elements within the blood path.

III. TPE With Dialysis Equipment

TPE can be performed with a highly permeable filter connected to the blood pump and pressure monitoring system of the dialysis machine. The machine is used in its "isolated" ultrafiltration mode, bypassing the dialysate proportioning system.

IV. Anticoagulation

For centrifugal techniques, anticoaglation is often provided by citrate. For MPS with dialysis equipment, heparin can be used as during standard dialysis.

VII. Replacement Fluids:

A. Albumin

Pros: no viral transmission, allergies are rare

Cons: depletion coagulopathy, immunoglobulin depletion

1. Electrolyte composition

Sodium, 145 ± 15 mEq/L; potassium, less than 2 mEq/L (sodium and potassium in mEq/L is equivalent to sodium and potassium in mmol/L)

2. Anaphylactic reactions

Rare, antibodies to polymerized albumin?

3. "Depletion coagulopathy"

Replacement with albumin will lead to depletion of coagulation factors.

i. After a single plasma exchange, prothrombin time (PT) increases 30%, partial thromboplastin time (PTT) doubles: these increases often reverse 1 day after treatment

ii. Multiple consecutive treatments result in prolonged increases in PT/PTT

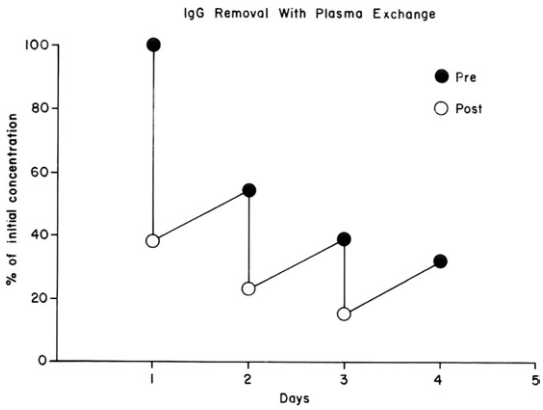

Figure 2. Progressive decrease in immunoglobulin G (IgG) levels after 3 consecutive therapeutic plasma exchange (TPE) treatments equaling 1 plasma volume each. Intertreatment increases between treatments represent a combination of extravascular to intravascular reequilibration and a variable amount of new IgG synthesis. (Reproduced from Kaplan AA: A Practical Guide to Therapeutic Plasma Exchange, copyright Andre Kaplan)

Table 4. Distribution and Metabolism of Plasma Proteins

Protein	Concentration (mg/mL)	MW × 103 d	Intravascular (%)	Fractional Turnover Rate (%/d)	Half-life (d)
Normal physiology					
IgG (except IgG3 subclass)	12	150	45	7	22
IgG3	0.7	150	64	17	7
IgMa	0.9	950	78	19	5
IgA	2.5	160	42	25	6
IgD	0.02	175	75	37	2.8
IgE	0.0001	190	45	94	2.5
Albumin	45	66	44	11	17
C3	1.4	240	67	41	2
C4	0.5	200	66	43	2
Fibrinogen	3-4	340	81	24	4.2
Factor VIII	0.1	100-340	71	150	0.6
Antithrombin III	0.2	56-58	45	55	2.4
Lipoprotein cholesterol	1.5-2.0	1,300	>90		3-5
Pathological conditions					
Macroglobulinemia, IgM	50-130	950	89	25*	5.9
Bence-Jones protein	4-10	10-25	<50	†	†
Endotoxin	3-25 × 10-7	100-2,400*	>50	‡	‡
Immune complexes	*	>300*	>50	‡	‡
Tumor necrosis factor	3-5 × 10-7	50 (trimer)	<50		6-20 min

Note: Values listed are averaged from those reported in the literature. Removal of a substance during a single TPE treatment will be limited to that which is intravascular. Substances with substantial extravascular distribution will require several consecutive TPE treatments to decrease total body burden. Substances with short half-lives (high turnover rate) will have a rapid return to pre-TPE levels unless production rates can be slowed by concomitant therapy.

Abbreviations: MW, molecular weight; TPE, therapeutic plasma exchange; IgG, immunoglobulin G.

*Highly variable or poorly defined.

†Highly dependent on degree of renal function, half-life greatly increased with renal failure.

‡Half life will be variable and dependent on the clearing capabilities of the reticuloendothelial system.

iii. FFP administered toward the end of the procedure can minimize hemorrhagic risks

4. Immunoglobulin depletion
   i. A single 1-plasma volume exchange reduces serum immunoglobulin levels by 60%
   ii. Multiple treatments can decrease immunoglobulin levels for several weeks
   iii. A single infusion of immunoglobulin (IVIG) administered after a series of TPE treatments can reconstitute normal immunoglobulin levels
5. Risk of viral transmission

   Albumin is heat treated and considered to be devoid of transmissible virus.

B. FFP

Pros: Does not lead to postpheresis coagulopathy or immunoglobulin depletion. FFP is essential for the treatment of TTP.

Cons: Anaphylactoid reactions, citrate toxicity, small risk of viral transmission.

1. Anaphylactoid reactions
   i. Fever, rigors, urticaria, wheezing, hypotension, and laryngeal edema
   ii. Angiotensin-converting enzyme (ACE) inhibitors should be avoided given their ability to inhibit kinin metabolism
   iii. Consider pretreatment with diphenhydramine intravenously (IV): 0.3 to 0.5 mL of epinephrine (1:1,000 solution) should be available for subcutaneous

administration for severe reactions

2. Citrate toxicity

FFP contains 14% citrate by volume; can lead to hypocalcemia and metabolic alkalosis

3. Risk of viral transmission

1/63,000 units for hepatitis B, 1/100,000 units for hepatitis C, 1/680,000 units for human immunodeficiency virus (HIV), and 1/641,000 units for human T-lymphotrophic virus

3 L of FFP is obtained from 10 to 15 donors (15 separate units).

C. Starch replacement for TPE

Similar attributes with albumin, may be less expensive.

VIII. Vascular Access

A. Antecubital veins:
1. Ideal for low-flow treatments
2. Increasingly difficult to use after multiple punctures

B. Temporary vascular catheters:

Catheter removal may be hazardous after an intensive run of TPE treatments, which can result in depletion coagulopathy and increased PT/PTT.

1. Femoral vein cannulation
2. Subclavian and internal jugular catheters
3. Tunneled jugular venous catheters

C. Permanent arteriovenous access:

Preferred if treatments are to be repeated regularly (hyperlipidemia).

1. Primary arteriovenous fistula
2. Arteriovenous graft

IX. Selective Plasmapheresis Techniques

A. Designed to remove a particular pathogenic substance
B. Decreases need for replacement fluid
C. Minimizes risks of depletion coagulopathy and hypogammaglobulinemia
D. Many systems available in Japan and Europe, few in United States
1. Cascade filtration ("double filtration")
i. Separated plasma is refiltered through a secondary filter with smaller pore size
ii. Larger, unwanted molecules removed by secondary filter
iii. Indications: Waldenstrom macroglobulinemia, cryoglobulinemia, familial hypercholesterolemia, and immune complex–mediated disease
2. Cryofiltration
i. Removed plasma is cooled, causing certain substances to aggregate
ii. Increasing size allows for efficient secondary filtration
iii. Indications: cyroglobulins and immune complexes
3. Immunoadsorbant techniques
i. Systems for selective immunoadsorption
ii. Indications: nonselective immunoglobulin removal, low- density lipoprotein (LDL) cholesterol.
a. Protein A columns

Protein A: 42,000-d protein released from *Staphylococcus aureus.* Used for the ex vivo adsorption of 3 of the 4 classes of IgG (1, 2, and 4).

aa. Prosorba column (Cypress Biosciences Inc, San Diego, CA)

Single-use nonregenerating system placed in series with a standard plasma exchange circuit. When the plasma is separated from the blood, it is slowly perfused over the column (at 20 mL/min). This column saturates rapidly with very limited IgG removal. Postulated mode of action is by "immunomodulation" of perfused plasma.

Food and Drug Administration approved for idiopathic thrombocytopenic purpura (ITP) and rheumatoid arthritis. Secondary effects are

common: fever, chills, musculoskeletal pains, hypotension. Contraindicated in patients using ACE inhibitors.

bb. Excorim (Lund, Sweden)

Alternating columns repeatedly regenerated to allow for more efficient IgG removal

Renal indications: removal of anti-HLA antibodies in highly sensitized recipients, RPGN

4. Selective LDL cholesterol removal
   i. Limits the loss of plasma proteins and high-density lipoprotein (HDL) cholesterol
   ii. Indicated in patients with familial hypercholesterolemia who cannot tolerate or whose condition is unresponsive to pharmacological treatment and who have either known cardiovascular disease and a plasma LDL cholesterol level greater than 200 mg/dL or no known cardiovascular disease and a plasma LDL cholesterol level greater than 300 mg/dL
   iii. Four systems:
      a. Imunoadsorbant
      b. Dextran sulfate binding to apoprotein B

      Contraindication for patients on ACE-inhibitor therapy
      c. Heparin-mediated extracorporal LDL precipitation (HELP)
      d. Direct adsorption of LDL (DALI). Does not require plasma separation, removes LDL directly from whole blood
5. Endotoxin adsorption
   i. Fibers impregnated with polymyxin B. Can bind endotoxin fragments
   ii. Japanese experience documents improvement in systemic hemodynamics of sepsis
   iii. Not currently available in the United States

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COMPLICATIONS

Most common: citrate-induced parethesias, muscle cramps, urticaria (Table 5).

Most serious: anaphylactoid reactions to FFP

Incidence of death is 0.05%, but many patients have severe preexisting conditions

I. Citrate-Induced Hypocalcemia
   A. Citrate as anticoagulant or in FFP
   B. Perioral or distal extremity tingling or paresthesias
   C. Prophylactic replacement of IV calcium can reduce citrate-induced paresthesias
II. Coagulation Abnormalities
   A. Depletion coagulopathy
      1. After a single plasma exchange with albumin, clotting factors decrease by 60%
      2. When multiple treatments are performed, depletion more pronounced
   D. Thrombocytopenia
   E. Anemia: hemorrhage associated with vascular access, treatment-related hemolysis
   F. Thrombosis: hypercoaguable state from depletion of anticoagulant factors
III. Infection
   A. Resulting from posttreatment depletion of immunoglobulins

      Management: IVIG (100 to 400 mg/kg IV)

Table 5. Complications of Plasmapheresis

Symptom	Percentage
Urticaria	0.7-12
Paresthesias	1.5-9
Muscle cramps	0.4-2.5
Dizziness	<2.5
Headaches	0.3-5
Nausea	0.1-1
Hypotension	0.4-4.2
Chest pain	0.03-1.3
Arrhythmia	0.1-0.7
Anaphylactoid reactions	0.03-0.7
Rigors	1.1-8.8
Hyperthermia	0.7-1.0
Bronchospasm	0.1-0.4
Seizure	0.03-0.4
Respiratory arrest/pulmonary edema	0.2-0.3
Myocardial ischemia	0.1
Shock/myocardial infarction	0.1-1.5
Metabolic alkalosis	0.03
Disseminated intravascular coagulation	0.03
Central nervous system ischemia	0.03-0.1
Hepatitis	0.7
Hemorrhage	0.2
Hypoxemia	0.1
Pulmonary embolism	0.1
Access related	
Thrombosis/hemorrhage	0.02-0.7
Infection	0.3
Pneumothorax	0.1
Mechanical	0.08-4

Adapted from Mokrzycki and Kaplan, Am J Kidney Dis 23:817, 1994. Reproduced from: Kaplan AA: A Practical Guide to Therapeutic Plasma Exchange. Blackwell Science, Malden, MA, 1999, copyright Andre Kaplan

B. Viral transmission from replacement fluid (FFP)

IV. Reactions to Protein Containing Replacement Fluids (FFP, purified protein fraction, albumin)

Reactions to FFP are anaphylactoid in nature and characterized by fever, rigors, urticaria, wheezing, and hypotension and may eventually progress to laryngospasm.

V. Atypical Reactions Associated With ACE Inhibitors

Flushing, hypotension, abdominal cramping, and severe anaplylactoid reactions have been reported with the dextran sulfate systems for selective lipid removal and in patients treated with the Prosorba column. Concurrent treatment with ACE inhibitors is considered contraindicated in patients treated with these selective removal techniques. ACE-inhibitor–induced inhibition of kinin metabolism may be unifying factor. Discontinuation of ACE inhibition should be accomplished well before initiation of these treatments. Timing of this discontinuation will depend on individual ACE-inhibitor half-life and pharmacodynamics.

VI. Electrolyte Abnormalities
- A. Hypokalemia: albumin has potassium levels less than 2 mEq/L
- B. Alkalosis: from citrate used for anticoagulation or in FFP
- C. Aluminum: albumin solutions have 4 to 24 mmol/L of aluminum

  Risk of aluminum toxicity greatest with renal insufficiency

VII. Vitamin Removal
- A. Vitamins B_{12}, B_6, A, C, and E and β-carotene decrease of 24% to 48%, but there is a rebound to pretreatment levels within 24 hours
- B. Water-soluble vitamins, folate, thiamin, nicotinate, biotin, riboflavin, and pantothenate are not significantly altered by a single plasma exchange
- C. Long-term effects of repetitive treatments are not known

VIII. Miscellaneous Complications
- A. Apneic events in those anesthetized with succinylcholine due to low posttreatment levels of plasma cholinesterase
- B. Hypotension, dyspnea, and chest pain secondary to complement-mediated membrane bioincompatibility
- C. Anaphylactoid symptoms due to ethylene oxide sensitivity used as a sterilizing agent
- D. Severe hemolysis as a result of hypotonic priming solutions or aggressive transmembrane pressure during MPS
- E. Chills and hypothermia due to inadequately warmed replacement fluid

IX. Hypotension During TPE
- A. Incidence of hypotension is 1.7%
- B. Causes: see Table 6

X. Deaths
- A. Incidence of 0.05%
- B. Causes: cardiovascular, respiratory, and anaphylactic
  - i. Nonhemodynamic pulmonary edema (FFP replacement resulting in

Table 6. Potential Causes for Hypotension During TPE

Delayed or inadequate volume replacement
Vasovagal episodes
Hypo-oncotic fluid replacement: 3.5% albumin solutions
Anaphylaxis:
Reactions to plasma components in replacement fluids
Anti-IgA antibodies (IgA-deficient patient)
Endotoxin-contaminated replacement fluid
Reactions to bioincompatible membranes
Sensitivity to ethylene oxide
Device-related: Prosorba protein A column
Cardiac arrhythmia
Citrate-induced hypocalcemia
Hypokalemic related (especially in patients on digitalis therapy)
Bradykinnin reactions (cf reactions to ACE inhibitors)
Hemorrhage
Associated with primary disease (ITP, factor VIII inhibitors)
Associated with heparin anticoagulation
Associated with vascular access
External
Internal
"Depletion" coagulopathy
Cardiovascular collapse
Pulmonary embolus
Disease-related hypotension
Guillain-Barre syndrome (autonomic dysfunction)
Waldenstrom macroglobulinemia (rapid decrease in plasma volume)

Abbreviations: IgA, immunoglobulin A; ACE, angiotensin-converting enzyme; ITP, idiopathic thrombocytopenic purpura; TPE, therapeutic plasma exchange.

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transfusion-related lung injury [TRALI])

ii. Cardiac arrhythmia

iii. Hemodynamic pulmonary edema

iv. Pulmonary embolism

XI. Drug Removal

When possible, all daily drug dosing should be administered after the TPE treatment.

Drug removal is most dependent on percentage of protein binding and volume of distribution. Drugs with a high percentage of protein binding and a relatively modest volume of distribution (<0.3 L/kg) will have the greatest likelihood of being removed by TPE (Table 7). The replacement volume of a given TPE treatment would have to equal 0.7 times the volume of distribution of a drug to decrease pretreatment levels by 50%.

A. Specific drugs:

1. Not significantly removed by TPE:
   i. Prednisone
   ii. Prednisolone
2. Minimal removal:
   i. Cyclophosphamide
   ii. Azathioprine
   iii. Aminoglycosides
   iv. Tobramycin
   v. Digoxin (removal of digibind-bound drug may be enhanced in patients with renal failure)
   vi. Digitoxin
   vii. Vancomycin
3. Posttreatment supplement may be necessary:
   i. Phenytoin
   ii. Acetylsalicylic acid
   iii. Propranolol
   iv. Thyroxine: 25% in the intravascular compartment 99%

Table 7. Drugs With a High Percentage of Protein Binding and Modest Volume of Distribution

	Protein Binding (%)	Volume of Distribution (L/kg)
Acetylsalicylic acid	50-90	0.1-0.2
Cefazolin	80	0.13-0.22
Cefotetan	85	0.15
Ceftriaxone	90	0.12-0.18
Chlorpropamide	72-96	0.09-0.27
Diclofenac	>99	0.12-0.17
Dicloxacillin	95	0.16
Glyburide	99	0.16-0.3
Heparin	>90	0.06-0.1
Ibuprofen	99	0.15-0.17
Indomethacin	99	0.12
Ketorolac	>99	0.13-0.25
Naproxen	99	0.10
Probenecid	85-95	0.15
Sodium valproate	90	0.19-0.23
Streptokinase	?	0.02-0.08
Tolbutamide	95-97	0.10-0.15
Warfarin	97-99	0.11-0.15

Note: In general, drugs with a high percentage of protein binding and a modest volume of distribution are likely to be removed by plasma exchange.

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protein bound: TPE can treat thyroid storm

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