Practical Aspects of Therapeutic Plasma Exchange (PLEX / TPE) for Neurologists

David M. Ward, MD, FRCP
Professor, Division of Nephrology, University of California San Diego
Medical Director, Therapeutic Apheresis Program
Associate Medical Director, Kidney/Pancreas Transplantation

DISCLOSURES:
The speaker has the following potential conflicts
- TerumoBCT, Inc. – Honoraria, Consulting
- Therakos, Inc. – Honoraria
- Alexion Pharmaceuticals – Advisory Board
- Aethlon Medical Inc. – Consulting

WARNING: OFF-LABEL USES
Therapeutic plasma exchange (plasmapheresis) is widely acknowledged as standard treatment for many diseases.
In the USA, the FDA has approved numerous devices for the performance of plasma exchange, but not for specific indications.
Thus all specific indications are regarded as “off-label” uses.
OUTLINE:

- Types of therapeutic apheresis
- Expanding utilization of apheresis therapies
- Methods and technologies of plasma exchange (TPE / PLEX):
  - centrifugal
  - membrane
- TPE / PLEX treatment options and prescription
- Kinetics of removal of autoantibodies
- Intensity and adequacy of plasma exchange therapy
- Adverse events
- Applications in neurology

Practical Aspects of Plasma Exchange for Neurologists

- Plasma Exchange ("PLEX")
  = Therapeutic Plasma Exchange ("TPE")
  ≈ Plasmapheresis ("PE")

- "Apheresis" derives from
  - Ancient Greek "αφαίρειν" = “to remove forcibly”
  - different root than “phoresis”, as in “electrophoresis”.

- PLEX / TPE / PE is one type of Therapeutic Apheresis
PLASMA REMOVAL WITH RETURN OF CORPUSCLES
(PLASMAPHAERESIS)

FIRST PAPER

JOHN J. ABEL, L. G. ROWNTREE AND B. B. TURNER
From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, July 16, 1914

I. In connection with our experiments on vividiffusion with
a view to the ultimate use of the method for the relief of toxae-
mia the idea suggested itself to try the effects of the repeated
removal of considerable quantities of blood, replacing the plasma
by Locke’s solution and reinjecting this together with the sedi-
mented corpuscles.

J Pharmacol Exp Ther, 5:625, 1914
UC San Diego Therapeutic Apheresis Program

Status as of May 2014:

- Now at 32 years of the program (inception January 1982).
- Approximately 28,000 apheresis procedures performed.
- Of those, about 20,000 were plasma exchange procedures.
- 15 apheresis RN's
- 19 faculty attending physicians with apheresis privileges

http://health.ucsd.edu/specialties/apheresis

Less-Conventional Apheresis Modalities (require additional equipment)

- Immuno-adsorption
- Filtration selective removal
- LDL apheresis
- Online plasma purification
- Online WBC processing
- WBC's (for ex-vivo immune modulation)
- Blood stem cells (for ex-vivo genetic modification)

Conventional Therapeutic Apheresis Modalities

- Plasmapheresis = plasma removal or exchange (requires centrifugal machine or plasmafiltration system)
  - Replace with FFP (for TTP)
  - Replace with albumin (for all other uses)

- Cytapheresis = cell removal or exchange (requires centrifugal machine)
  - Erythrocytcapheresis = red cell exchange (sickle cell, etc.)
  - Thrombocytapheresis = platelet reduction (thrombocytosis)
  - Leukapheresis = white cell apheresis
  - WBC reduction (leukemia)

- LDL apheresis
- Online plasma purification
- Online WBC processing

Blood stem cells (for BM transplant)

Less-Conventional Apheresis Modalities (require additional equipment)
- Plasmapheresis = plasma removal or exchange (requires centrifugal machine or plasmafiltration system)
  - Replace with FFP (for TTP)
  - Erythrocyt-apheresis = red cell exchange (sickle cell, etc.)
- Cytapheresis = cell removal or exchange (requires centrifugal machine)
  - Thrombocyt-apheresis = platelet reduction (thrombocytosis)
- Leukapheresis = white cell apheresis
  - WBC reduction (leukemia)
- Blood stem cells (for BM transplant)

Conventional Therapeutic Apheresis Modalities
- Plasmapheresis
- Cytapheresis
- Erythrocyt-apheresis
- Leukapheresis
- Thrombocyt-apheresis
- Blood stem cells

Online plasma purification
- Immuno-adsorption
- Filtration selective removal
- LDL apheresis

Online WBC processing
- Photopheresis (= ECP)
- Other

WBC's (for ex-vivo immune modulation)

UC San Diego Therapeutic Apheresis Program

Number of procedures per year by modality

Plasmapheresis (TPE) - outpatient
Plasmapheresis (TPE) - inpatient*
Stem cell harvest (HPC-A)
Photopheresis (ECP)
Cytapheresis (WBC, Plt, RBCX)
LDL-apheresis (since March 2012)
Research

(Opposite to the modality)

(Academic years run from July 1st to June 30th)


dmward@ucsd.edu
### UC San Diego Therapeutic Apheresis Program

**Status by modality as of May 2014:**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage of Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma exchange (TPE/PLEX)</td>
<td>61%</td>
</tr>
<tr>
<td>(Removes antibodies that cause autoimmune diseases, etc.)</td>
<td></td>
</tr>
<tr>
<td>Photopheresis (ECP)</td>
<td>30%</td>
</tr>
<tr>
<td>(Modulates cellular immunity towards tolerance: heart/lung rejection, GVHD)</td>
<td></td>
</tr>
<tr>
<td>Stem cell harvest (HPC-A)</td>
<td>5.2%</td>
</tr>
<tr>
<td>(Harvests hematopoietic stem cells for subsequent Blood-Marrow Transplant)</td>
<td></td>
</tr>
<tr>
<td>LDL-apheresis (LDL-A)</td>
<td>2.1%</td>
</tr>
<tr>
<td>(For severe hypercholesterolemia)</td>
<td></td>
</tr>
<tr>
<td>RBC Exchange (RBCX-A)</td>
<td>0.9%</td>
</tr>
<tr>
<td>(For sickle cell, etc.)</td>
<td></td>
</tr>
<tr>
<td>WBC / platelet depletion</td>
<td>0.3%</td>
</tr>
<tr>
<td>Research (ex-vivo cell modification)</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

### Practical Aspects of Plasma Exchange for Neurologists

**OUTLINE:**

- Types of therapeutic apheresis
- Expanding utilization of apheresis therapies
- **Methods and technologies of plasma exchange (TPE / PLEX):**
  - centrifugal
  - membrane
- TPE / PLEX treatment options and prescription
- Kinetics of removal of autoantibodies
- Intensity and adequacy of plasma exchange therapy
- Adverse events
- Applications in neurology
In connection with our experiments on vivisfusion with a view to the ultimate use of the method for the relief of toxemia, the effects of the repeated removal of blood, replacing the plasma this together with the sediments.
Evolution of membrane plasmafiltration

Modern hollow-fiber membrane plasmafiltration

on a CRRT machine

on the NxStage machine

Separation by membrane filtration

Hollow-fiber plasma-filter
Pore size: ~0.3 microns
Cut-off: >1000 kDa

Membrane specifications are those of Asahi products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8, 101, Japan)

dmward@ucsd.edu
Separation by centrifugation

Whole Blood in
RBC out
WBC out
Plasma out

Cobe Spectra – disposable centrifuge insert

Separation by centrifugation

Whole Blood in
RBC out
WBC out
Plasma out

Cobe Spectra

Tubing set harness connects via “omega-1 omega-2” principle
Separation by centrifugation

Whole Blood in
RBC out
WBC out
Plasma out

Cobe Spectra

Tubing set harness connects via “omega-1 omega-2” principle

dmward@ucsd.edu

Separation by centrifugation

“Omega-1 Omega-2” principle

Clockwise

Counter-clockwise

Terumo Optia

dmward@ucsd.edu
Separation by centrifugation

Whole Blood in
RBC out
WBC out
Plasma out

Cobe Spectra

Separation by centrifugation

Specific Gravity

Plasma 1.027
Platelets 1.04
Lymphocytes 1.06
Monocytes 1.06
Blasts
PMNs 1.085
RBCs 1.095

dmward@ucsd.edu
Stoke's Law:

\[ S_v = \frac{2 \omega^2 r^2 (\rho_{\text{cell}} - \rho_{\text{plasma}})}{9\mu} \]

Stoke's law says that the cellular velocity of sedimentation \((S_v)\) is proportional to:

- Centrifugal acceleration \((\omega^2 R) \) or \(g\)
- Square of the cell radius \((r^2)\)
- Difference between the density of cell and plasma \((\rho_{\text{cell}} - \rho_{\text{plasma}})\)
- Inverse of the fluid viscosity \((\mu)\)

Centrifugal separation is a function of:

- \(S_v\)
- Dwell time (inverse of inlet blood flow rate)

To get pure cell product:

1. Interface position
2. Accurate RPM's (G's)
3. Flow rate (dwell time)

Separation by centrifugation
Separation by centrifugation

**OUTLINE:**
- Types of therapeutic apheresis
- Expanding utilization of apheresis therapies
- Methods and technologies of plasma exchange (TPE / PLEX):
  - centrifugal
  - membrane
- TPE / PLEX treatment options and prescription
  - Kinetics of removal of autoantibodies
  - Intensity and adequacy of plasma exchange therapy
- Adverse events
- Applications in neurology
Choice of machine type for TPE

1. Centrifugal plasmapheresis (cTPE)
   - Usually citrate anticoagulation

2. Membrane plasmapheresis (mTPE)
   - Usually heparin anticoagulation

Machine operating characteristics

<table>
<thead>
<tr>
<th>Therapeutic Plasma Exchange “TPE” or “PLEX”</th>
<th>cTPE = Centrifugal Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Centrifugal plasmapheresis (cTPE)</td>
<td>Replacement volume for 3-liter exchange: 0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
</tr>
<tr>
<td>2. Membrane plasmapheresis (mTPE)</td>
<td>Plasma removal rate: 35 ml/min</td>
</tr>
<tr>
<td></td>
<td>Plasma extraction ratio: 80% (75 - 85%)</td>
</tr>
<tr>
<td></td>
<td>Plasma flow rate: 42 ml/min</td>
</tr>
<tr>
<td></td>
<td>Blood flow rate (Hct 40%): 70 ml/min</td>
</tr>
<tr>
<td></td>
<td>Vascular access: Needles in arm veins or Central venous catheter</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation: Citrate (occasionally heparin)</td>
</tr>
</tbody>
</table>
### Machine operating characteristics

<table>
<thead>
<tr>
<th></th>
<th>cTPE = Centrifugal Plasmapheresis</th>
<th>mTPE = Membrane Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement volume for 3-liter exchange</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>~ 35 ml/min</td>
<td>~ 35 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>~ 80% (75 - 85%)</td>
<td>~ 35% (30 - 50%)</td>
</tr>
<tr>
<td>Plasma flow rate</td>
<td>~ 42 ml/min</td>
<td>~ 100 ml/min</td>
</tr>
<tr>
<td>Blood flow rate (Hct 40%)</td>
<td>~ 70 ml/min</td>
<td>~ 165 ml/min</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Needles in arm veins or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Citrate (occasionally heparin)</td>
<td>Heparin (occasionally citrate)</td>
</tr>
</tbody>
</table>
Citrate anticoagulation

- Citrate anions “chelate” Ca^{++} ions. The positive calcium ions are covered up by the negative carboxylic arms of the citrate.
- The number of remaining free Ca^{++} ions is diminished.
- This prevents activation of calcium-dependent clotting factors.

“Chelation” of calcium ions by citrate ions

Citrate anticoagulation for TPE

- The ionized Ca^{++} in the systemic blood is never reduced far enough to inhibit clotting.
- Citrate is an “obligatory regional” anticoagulant, i.e. only the blood outside the body is anticoagulated.
- There is zero risk of causing systemic bleeding.
- Occasionally, delay in metabolizing citrate causes modest reduction of the ionized Ca^{++} level in the systemic blood and cause symptoms of “citrate reaction”
- Infusing calcium to the return line or to the replacement fluid reduces the incidence of symptomatic citrate toxicity:

<table>
<thead>
<tr>
<th>Calcium regimen</th>
<th>Symptom rate (%)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No calcium</td>
<td>9.1%</td>
<td>Mokrzycki M, Kaplan A. Am J Kidney Dis 1994</td>
</tr>
<tr>
<td>I.V. 10% Ca^{++} gluconate</td>
<td>1 %</td>
<td></td>
</tr>
<tr>
<td>Calcium added to Albumin before infusion</td>
<td>2.7%</td>
<td>Kankirawatana et al. J Clin Apheresis 2007</td>
</tr>
</tbody>
</table>
### Comparison of anticoagulants

#### Citrate:
1. Familiar in blood-banking.
2. Used for cTPE
3. Sometimes for mTPE
4. Sometimes for hemodialysis
5. Increasingly for Continuous Renal Replacement Therapy (CRRT) in intensive care.

#### Heparin:
1. Familiar in dialysis.
2. Used for mTPE
3. Sometimes for cTPE

#### Nafamostat mesylate:
1. Available in Japan.
2. Used for dialysis and mTPE

---

**Scanning electron micrographs of the inner surface of polysulfone hollow fiber dialyzer membranes.**

Comparison of anticoagulants

- **SUMMARY**

**Citrate:**
1. Familiar in blood-banking.
2. Short-acting: prescribe ratio to blood flow
3. No systemic anticoagulant effect; risk of “citrate toxicity”
4. Suitable for low-flow circuits

**Heparin:**
1. Familiar in dialysis.
2. Long-acting: prescribe units/Kg body wt/hour
3. Systemic anticoagulant; risk of bleeding; rare HIT
4. Suitable for high-flow circuits

---

**Characteristics: machine + anticoagulant**

<table>
<thead>
<tr>
<th></th>
<th>cTPE = Centrifugal Plasmapheresis</th>
<th>mTPE = Membrane Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement volume for 3-liter exchange</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>~ 35 ml/min</td>
<td>~ 35 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>~ 85% (75 - 85%)</td>
<td>~ 35% (30 - 35%)</td>
</tr>
<tr>
<td>Plasma flow rate</td>
<td>~ 42 ml/min</td>
<td>~ 100 ml/min</td>
</tr>
<tr>
<td>Blood flow rate (Hct 40%)</td>
<td>~ 70 ml/min</td>
<td>~ 165 ml/min</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Needles in arm veins or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Citrate (ACD-A at ~1:12 ratio with whole blood)</td>
<td>Heparin (usually) or Citrate (at ~1:20)</td>
</tr>
<tr>
<td>If citrate used</td>
<td>6 ml/min (to machine), minus 85% (extraction) = 1 ml/min to patient</td>
<td>8 ml/min, minus 35% = 5 ml/min</td>
</tr>
</tbody>
</table>
Comparing characteristics

<table>
<thead>
<tr>
<th></th>
<th>cTPE = Centrifugal plasma exchange</th>
<th>mTPE = Membrane plasma exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement volume</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
<td>0.5L Sal + 2.5L 5% Alb or 12 u FFP</td>
</tr>
<tr>
<td>for 3-liter exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>~ 35 ml/min</td>
<td>~ 35 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>~ 85% (75 - 85%)</td>
<td>~ 35%</td>
</tr>
<tr>
<td>Plasma flow rate</td>
<td>~ 42 ml/min</td>
<td>~ 100 ml/min</td>
</tr>
<tr>
<td>Blood flow rate (Hct 40%)</td>
<td>~ 70 ml/min</td>
<td>~ 165 ml/min</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Needles in arm veins or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>AntiCoagulation</td>
<td>Citrate (ACD-A at ~1:12 ratio with whole blood)</td>
<td>Heparin (usually)</td>
</tr>
<tr>
<td>If citrate used</td>
<td>6 ml/min (to machine), minus 85% (extraction) = 1 ml/min to patient</td>
<td>Higher risk of citrate symptoms if citrate used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 ml/min, minus 35% = 5 ml/min</td>
</tr>
</tbody>
</table>

TPE (Plasma Exchange)

Choice of replacement solution

1. FFP (Fresh-Frozen Plasma)
   - To replace deficient or defective plasma constituents: use FFP for whole replacement volume.
     Examples: TTP (Thrombotic Thrombocytopenic Purpura), other Thrombotic Microangiopathies.
   - To prevent exacerbating active lung hemorrhage: use FFP for all or part of replacement volume.
     Examples: Goodpasture’s Syndrome, ANCA vasculitis.
<table>
<thead>
<tr>
<th>TPE (Plasma Exchange)</th>
<th>Choice of replacement solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis = plasma removal or exchange (requires centrifugal machine or plasmafiltration system)</td>
<td><strong>2. Albumin (or other colloid)</strong></td>
</tr>
<tr>
<td>1. Replace with FFP (for TTP)</td>
<td></td>
</tr>
</tbody>
</table>
| 2. Replace with albumin (for all other uses) | ▪ Use for most applications.  
▪ Either 5% albumin for whole replacement volume.  
▪ Or one-quarter saline and three-quarters 5% albumin.  
▪ Or other colloidal solution (France).  
▪ If needed for clotting-factor depletion, give 2 units FFP as last part of replacement volume (e.g. if fibrinogen at start is <110 mg/dl). |
| 3. Re-use on-line purified plasma | **3. Plasma regeneration** |
|  |
|  | ▪ The patient’s own plasma is passed through a purification system on-line to remove the pathogenic molecule, and then re-infused to the patient as the replacement volume. |
3. Plasma regeneration

- The patient’s own plasma is passed through a purification system on-line to remove the pathogenic molecule, and then re-infused to the patient as the replacement volume.

- These “selective” plasmapheresis modalities include:
  - Immunoadsorption columns
  - Double (“cascade”) filtration
  - Chemical affinity columns
  - etc.

Typical prescriptions for centrifugal plasmapheresis (cTPE) and membrane plasmapheresis (mTPE) differ markedly. The risk of hemolysis in mTPE filters requires the plasma extraction ratio to be lower; therefore more blood must be processed to extract the same amount of plasma. This requires a higher blood flow rate (and higher-flow vascular access) or may take longer than cTPE. Citrate or heparin anticoagulation can be used in either, though citrate is more suited to cTPE, and heparin to mTPE. Secondary plasma processing (plasma regeneration) is an option with either cTPE or mTPE.

Fig. 3. Circuit diagrams of (a) primary membrane plasma separation plus secondary plasma fractionation, and (b) primary centrifugal plasma separation plus secondary plasma perfusion column. In the left panel (a), the primary separation of plasma from blood (#1) is in a hollow-fiber membrane plasma filter with a pore size of 0.3 microns and a molecular weight cut-off in excess of 1,000 kDa. The secondary processing of plasma (#2) is in a hollow-fiber membrane plasma fractionator with a pore size of 0.01–0.03 microns and a molecular weight cut-off of approximately 100 kDa. Albumin (67 kDa) passes through the secondary membrane and can be used as replacement fluid for the patient. Immunoglobulins, including IgG (146 kDa), stay within the hollow-fiber lumen which drains to the effluent bag, thus removing most of the autoantibody present in the plasma. Membrane specifications are those of Asahi® products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8,101, Japan). In the right panel (b), the primary separation of plasma from blood (#1) is by a continuous-flow centrifuge, and the secondary processing of plasma (#2) is in a perfusion column that can contain an immuno-adsorbent or chemical adsorbent (see text). The pathogenic molecule binds to the column, which is replaced when exhausted. Other systems employ pairs of columns that can be regenerated by washing out the bound pathogenic molecule; one column is in active use while the other is being washed clean, and they switch periodically during the procedure. Either type of primary separation (#1) can in principal be coupled to any type of secondary plasma purification (#2). Many secondary devices in use in Europe and Japan, and some primary/secondary combination systems, are not FDA-approved in the USA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Dose of Therapeutic Plasma Exchange (TPE / PLEX)

- Prescribed volume of each plasma exchange procedure
- Number and frequency of procedures

\[ \text{PRES} \times \text{FREQ} = \text{DOSE} \]

- depends on patient’s size (plasma volume)
- depends on pathogenic molecule
- volume of distribution
- disease characteristics

Example:
"Volume to remove: 3.5 liters"

Example:
"Rx daily x3, then q.o.d. x3, then reassess"


dmward@ucsd.edu
Size of each TPE (PLEX) procedure

Volume exchanged depends on the patient’s size:

\[ y = e^{-x} \]

Adult blood volume (BV) ~ 70ml/Kg.
Plasma vol (PV) = BV x (1 - Hct/100)

Example: 70 Kg woman:
BV = 70ml/Kg x 70Kg = 4.9 liter
Hematocrit = 39%
PV = 4.9 liter x (61%) = 3 liter

1.0 PV exchange = 3 liters
1.5 PV exchange = 4.5 liters

Choose 3.6 liter TPE
\[ x = 3.6 / 3.0 = 1.2 \]
\[ y = e^{-x} = e^{-1.2} = 0.30 \]
Therefore removes 70%

Number of TPE / PLEX procedures needed

Removal of IgM
(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)

Monoclonal IgM (mg/dl)

- 5000
- 980
- 254

Plasmapheresis procedures

Waldenstrom’s macroglobulinemia
- IgM is large (~970,000 Daltons)
- 85% of IgM stays intravascular
Waldenstrom's macroglobulinemia
• IgM is large (~970,000 Daltons)
• 85% of IgM stays intravascular

Most antibody mediated diseases:
• IgG is smaller (~146,000 Daltons)
• Only 30%-40% is intravascular

Number of TPE / PLEX procedures needed

Removal of IgM
(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)

Removal of IgG
(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)

Plasmapheresis procedures

Dose of Therapeutic Plasma Exchange (TPE / PLEX)

Prescribed volume of each plasma exchange procedure

(Number and frequency of procedures)

= DOSE

depends on
- patient’s size (plasma volume)

Example:
“Volume to remove: 3.5 liters”

depends on
- pathogenic molecule
- volume of distribution
- disease characteristics

Example:
“Rx daily x3, then q.o.d. x3, then reassess”
Table 2-2. Distribution and Metabolism of Plasma Proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>Concentration (mg/mL)</th>
<th>M.W. $\times 10^{3}$</th>
<th>Percent Intravascular</th>
<th>Fractional Turnover Rate (% day)</th>
<th>Half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal physiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (subclasses 1,2,4)</td>
<td>0.7</td>
<td>150</td>
<td>64</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>IgG4</td>
<td>2.5</td>
<td>160</td>
<td>42</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IgD</td>
<td>0.02</td>
<td>175</td>
<td>75</td>
<td>37</td>
<td>2.8</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>0.1</td>
<td>100-340</td>
<td>71</td>
<td>150</td>
<td>0.6</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>0.2</td>
<td>56-58</td>
<td>45</td>
<td>55</td>
<td>2.4</td>
</tr>
<tr>
<td>Lipoprotein</td>
<td>1.3-2.0</td>
<td>1300</td>
<td>&gt;90</td>
<td>—</td>
<td>3-5</td>
</tr>
<tr>
<td>Pathologic conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroglobulins, IgM</td>
<td></td>
<td>50-130</td>
<td>89</td>
<td>25*</td>
<td>5.9</td>
</tr>
<tr>
<td>Bence Jones protein</td>
<td>4-10</td>
<td>10-25</td>
<td>&lt;50</td>
<td>—*</td>
<td>—</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>3-25 $\times 10^{-6}$</td>
<td>100-2400</td>
<td>&gt;50</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>3-5 $\times 10^{-7}$</td>
<td>50 (rimet)</td>
<td>&lt;50</td>
<td>6-20 min</td>
<td></td>
</tr>
</tbody>
</table>

Total body water (TBW) = 50% - 60% of weight, say 57% = 40 liters

Plasma ~8% = 3 liters

Interstitial fluid (third space) = 25 - 30% of TBW, say 30% = 12 liters

Intracellular fluid = 60 - 65% of TBW, say 62.5% = 25 liters

Extracellular fluid = 35 - 40% of TBW, say 37.5% = 15 liters
Total Body Water

- Intracellular: 25 liters
- Extracellular: 15 liters
  - Interstitial: 12 liters
  - Plasma: 3 liters

Liters exchanged

- Removing IgM from plasma
  \[ y = e^{-x} \]
  \[ x = \frac{3.6}{3} = 1.2 \]
  One TPE
  2 hours

- Removing IgG from extracellular fluid
  \[ y = e^{-x} \]
  \[ x = \frac{18}{15} = 1.2 \]
  7 TPE procedures
  9 days

Number of TPE / PLEX procedures needed

Dose of Therapeutic Plasma Exchange (TPE / PLEX)

Prescribed volume of each plasma exchange procedure \( x \)

- depends on
  - patient’s size (plasma volume)

Example:
- “Volume to remove: 3.5 liters”

Number and frequency of procedures

- depends on
  - pathogenic molecule
  - volume of distribution
  - disease characteristics

Example:
- “Rx daily x3, then q.o.d. x3, then reassess”

\[ x = \frac{3.6}{3} = 1.2 \]
\[ x = \frac{18}{15} = 1.2 \]
Total body water = ~40 liters

Standard 70 Kg Adult

Body water compartments

Brain total 1.7 liter
Plasma 3 liters

Intracellular 25 liters
Interstitial 12 liters

Brain water 1.2 liter
CSF 150 ml
Plasma 3 liters

Intracellular 25 liters
Interstitial 12 liters
Brain water
1.2 liters
CSF 150 ml

Body water compartments

![Diagram showing body water compartments with IgG, Urea, and IgG concentrations in different compartments.

PLEX / TPE

Intracellular
25 liters
Interstitial
12 liters
Plasma
3 liters

Hemodialysis

Intracellular
25 liters
Interstitial
12 liters
Plasma
3 liters

CSF 150 ml
Brain water
Urea
IgG
**Body water compartments**

**PLEX / TPE**

- Brain water
  - IgG is slower
  - CSF 150 ml

- Plasma
  - IgG
  - Plasma 3 liters

- Intracellular
  - 25 liters

- Interstitial
  - 12 liters

**Dose of Therapeutic Plasma Exchange (TPE / PLEX)**

\[
\text{Prescribed volume of each plasma exchange procedure} \times \text{Number and frequency of procedures} = \text{DOSE}
\]

- Depends on patient’s size (plasma volume)
- Pathogenic molecule
- Volume of distribution
- Disease characteristics

**Example:**
- "Volume to remove: 3.5 liters"
- "Rx daily x3, then q.o.d. x3, then reassess"
### A typical TPE prescription

**Diagnosis:** Neuromyelitis Optica (NMO) in exacerbation

1. **Anticoagulant:** Acid Citrate Dextrose-A at 1:14 ratio to blood or Heparin
2. **Machine type:** Centrifugal machine or Membrane system
3. **Vascular access:** Bilateral antecubital vein needles or IJ catheter or AV fistula
4. **Dose of plasmapheresis**
   - Volume of each procedure: 3.5 liter plasma removal, based on patient’s size
   - Frequency of procedures: 3 per week for 3 weeks, or more intense initially
5. **Replacement solutions:**
   - 0.5 liter saline, 3.0 liter 5% albumin (total 3.5L); fluid balance of 115%.
   - or (if start fibrinogen <110mg/dl) 0.5 liter saline, 2.5 liter albumin, 2 units FFP.
6. **Medications:**
   1. If citrate anticoagulation: Give Calcium chloride or gluconate (~8 mEq/hr)
   2. If FFP: Premed with diphenhydramine (Benadryl) 25 mg I.V., and acetaminophen (Tylenol, paracetamol) two 325mg tablets p.o.
7. **Labs:**
   - Pre-apheresis each time or weekly if less intensive: Fibrinogen
   - Pre-apheresis weekly or monthly: CBC, Chem Panel + Mg + Phos.
   - At end of first apheresis: Fibrinogen, K, Ca, Mg, Phos.

---

**Practical Aspects of Plasma Exchange for Neurologists**

**OUTLINE:**

- Types of therapeutic apheresis
- Expanding utilization of apheresis therapies
- Methods and technologies of plasma exchange (TPE / PLEX):
  - centrifugal
  - membrane
- TPE / PLEX treatment options and prescription
- Kinetics of removal of autoantibodies
- Intensity and adequacy of plasma exchange therapy
- **Adverse events**
- Applications in neurology
Therapeutic plasmapheresis (TPE): adverse effects

### Common Adverse Symptoms in Therapeutic Plasma Exchange

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia (&quot;Citrate toxicity&quot;)</td>
<td>Parasthesias, Nausea/Vomiting, Lightheadedness, Twitching</td>
<td>1.5–9.0</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Hypotension, Muscle cramps, Headaches</td>
<td>0.3–5.0</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>Urticaria, Rigors</td>
<td>0.7–12</td>
</tr>
</tbody>
</table>


### Rare Complications of Therapeutic Plasma Exchange

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Myocardial ischemia / infarction / shock / arrhythmia</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Respiratory arrest/pulmonary edema Pulmonary embolism</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombosis/bleeding</td>
</tr>
<tr>
<td>Infectious</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizure CNS ischemia</td>
</tr>
<tr>
<td>Pyrogenic</td>
<td>Hyperthermia</td>
</tr>
</tbody>
</table>

Therapeutic plasmapheresis (TPE): adverse effects

Fig. 2. Incidence of Adverse Events in Therapeutic Plasma Exchange is Low, <10% in most series.


Therapeutic plasmapheresis (TPE): adverse effects

Mortality precipitated by apheresis

<table>
<thead>
<tr>
<th>Apheresis-related deaths</th>
<th>UCSD</th>
<th>Benchmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY '10-'11</td>
<td>zero</td>
<td>1 death* in 32 yrs. (in approx. 28,000 procedures)</td>
</tr>
<tr>
<td>FY '11-'12</td>
<td>zero</td>
<td>3 to 5 deaths per 10,000 procedures (1-4)</td>
</tr>
<tr>
<td>FY '12-'13</td>
<td>zero</td>
<td></td>
</tr>
<tr>
<td>FY '13-'14 (to date)</td>
<td>zero</td>
<td></td>
</tr>
</tbody>
</table>

Benchmarks:

UCSD:
* In 2007, cardio-pulmonary arrest after aborted stem cell collection leukapheresis in known high risk patient.
Therapeutic plasmapheresis (TPE): adverse effects

**FFP transfusion-related acute lung injury (TRALI)**

<table>
<thead>
<tr>
<th>UCSD</th>
<th>Benchmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY '10-'11 - one*</td>
<td>During 4 procedures in last 12 yrs. (in approx. 20,000 procedures)</td>
</tr>
<tr>
<td>FY '11-'12 - zero</td>
<td></td>
</tr>
<tr>
<td>FY '12-'13 - zero</td>
<td></td>
</tr>
<tr>
<td>FY '13-'14 (to date) - zero</td>
<td></td>
</tr>
</tbody>
</table>

**Benchmark:**
   - Adverse reactions are substantially more common when fresh frozen plasma (FFP) is administered during apheresis, compared to procedures not using FFP (20% versus 1.4%).
   - Mechanisms include allergic reactions to transfusion products, and increased citrate load.

**UCSD:**
* In April 2011, after FFP, after completion of procedure while patient still in outpatient unit; patient hospitalized and recovered.

---

Therapeutic plasmapheresis (TPE): adverse effects

**Central line-associated blood-stream infections (CLABSI) data,**
**UCSD Apheresis Program, 2013**

<table>
<thead>
<tr>
<th>INFECTION RATES 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
</tr>
<tr>
<td># of Infections Line Days Rate</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>July</td>
</tr>
<tr>
<td># of Infections Line Days Rate</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

**Infection Rates 2013**

![Graph showing infection rates over time](image)
Therapeutic plasmapheresis (TPE): adverse effects

- **Grade I:**
  Mild (no intervention required). 1.5%

- **Grade II:**
  Moderate (intervention required but treatment completed). 2.5%

- **Grade III:**
  Severe (procedure interrupted or abandoned). 0.8%

- **Grade IV:**
  Fatal. <0.05%

---


---

TPE applications

**To remove**

- **AutoAb (+ probable autoAb):** Thrombotic Thrombocytopenic Purpura (TTP), Immune Thrombocytopenia (ITP), Autoimmune Hemolytic Anemia, Evan’s syndrome, Antiphospholipid crisis, Anti-GBM glomerulonephritis (& Goodpasture’s), ANCA nephritis, ANCA vasculitis (& Wegener’s), MPGN (C3 nephritic factor autoantibody), Acute Guillain-Barré syndrome, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Myasthenia Gravis, Lambert-Eaton syndrome, Stiff Person syndrome, Acute Disseminated Encephalitis (ADEM), Anti-NMDA-R Encephalitis, Anti-VGKC (Voltage-gated potassium channel) Limbic Encephalitis, Neuromyelitis Optica (NMO), some Multiple Sclerosis (MS), etc.

- **Antigen-Antibody complexes:** Hepatitis C vasculitis, Lupus vasculitis, etc.

- **AlloAb:** Transplant sensitization, Transplant rejection (humoral), Transfusion reactions, etc.

- **Paraproteins:** Waldenstrom’s, Hyperviscosity, Light-chain neuropathy, Light-chain glomerulopathy, Myeloma cast nephropathy, etc.

- **Non-Ig proteins:** Focal Segmental Glomerulosclerosis (FSGS).

- **Endogenous toxins:** Hypercholesterolemia, Liver failure, Sepsis (& SIRS), Phytanic acid (Refsum’s disease), etc.

- **Exogenous poisons:** *Amanita*, drugs, etc.

**To replenish plasma factors:** TTP, MPGN with inactive Factor H, etc.
Table 2. Autoimmune diseases with well-characterized autoantibodies that are treated with plasmapheresis (partial list).

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Autoantibodies react with</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP), sporadic type</td>
<td>ADAMTS13 (von Willebrand factor protease)</td>
<td>2, 12</td>
</tr>
<tr>
<td>Myasthenia gravis, classic type</td>
<td>Acetylcholine receptor</td>
<td>8</td>
</tr>
<tr>
<td>Myasthenia gravis, MuSK type</td>
<td>Muscle-specific kinase</td>
<td>8</td>
</tr>
<tr>
<td>Guillain-Barré syndrome (1) Miller–Fisher variant (2) other variants</td>
<td>Neuronal gangliosides: (1) GQ1b (2) GM1, GM1b, GD1a, GalNAcGd1a, GD1b, Gd3, etc.</td>
<td>3, 6</td>
</tr>
<tr>
<td>Neuromyelitis optica (Devic’s disease)</td>
<td>Aquaporin 4</td>
<td>4, 5</td>
</tr>
<tr>
<td>Stiff-person syndrome and related neuropathies</td>
<td>Glutamic acid decarboxylase (GAD65 antigen)</td>
<td>9</td>
</tr>
<tr>
<td>Anti-GBM glomerulonephritis (GN), including Goodpasture’s syndrome</td>
<td>Alpha-3 chain of collagen type IV</td>
<td>13</td>
</tr>
<tr>
<td>ANCA-associated GN (focal necrotizing GN, microscopic polyangitis, Wegener’s granulomatosis)</td>
<td>Myeloperoxidase (MPO), proteinase 3 (PR3), other lysosomal antigens, possibly lysosomal membrane protein 2 (LAMP2)</td>
<td>7, 11</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>Cardiac beta-1 receptors and cardiac myosin</td>
<td>10</td>
</tr>
</tbody>
</table>


Indications for therapeutic apheresis


Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

Joseph Schwartz,1 Jeffrey L. Winters,2 Anand Padmanabhan,3 Rashneet A. Balogum,4 Meghan Delany,5 Michael L. Linenberger,6 Zbigniew M. Szczepiorkowski,7 Mark E. Williams,8 Yanyun Wu,9 and Beth H. Shaz10,11

1Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York
2Division of Transfusion Medicine, Mayo Clinic, Rochester, Minnesota
3BloodCenter of Wisconsin, Milwaukee, Wisconsin
4Division of Nephrology, University of Virginia, Charlottesville, Virginia
5Puget Sound Blood Center, Seattle, Washington
6Department of Medicine, Seattle Cancer Care Alliance, Seattle, Washington
7Department of Pathology and Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
8Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts
9Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut
10New York Blood Center, New York, New York
11Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia

The American Society for Apheresis (ASFA) Apheresis guidelines are approved and published by the Writing Committee of the American Society for Apheresis. The Writing Committee is charged with reviewing, updating, and categorizing indications for therapeutic apheresis. The Sixth Special Issue of the Journal of Clinical Apheresis includes evidence-based guidelines for the use of therapeutic apheresis in clinical practice.
Example page from ASFA 2013 guidelines

<table>
<thead>
<tr>
<th>Grade</th>
<th>Name of the disease</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled trials/ Case series/ Case reports</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Description of the disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current management/treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rationale for therapeutic apheresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Technical notes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration/ discontinuation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>References</td>
<td></td>
</tr>
</tbody>
</table>

Example page from ASFA 2013 guidelines
## TPE: typical treatment courses

### Acute indications:
- **TTP**: Daily often for weeks; taper.
- **Anti GBM nephritis**: Daily or q.o.d. (minimum 14 days)
- **Hep C vasculitis**: 3 per wk for 2-6 weeks
- **FSGS in renal transplnt**: 2-4 per week for 2-3 months
- **Guillain Barré**: Daily or q.o.d. (total 5-6)
- **Myasthenia crisis**: Daily or q.o.d. (total 5-6)
- **NMO acute attack**: Average 5 (range 2-20)
- **Hyperviscosity (IgM)**: One or two procedures

### Chronic indications:
- **CIDP (polyneuropathy)**: 1-2 weekly, or q.o.week, for months
- **Myasthenia unremitting**: 1-3 per week, for weeks or months
- **NMO maintenance**: Weekly, or 3 per month
- **Hyperviscosity (IgM)**: Weekly, or q. 2-3 weeks, for years

---

## TPE / PLEX in Neurology: CNS diseases

### CNS diseases
- Stiff Person (anti-GAD65)
- PANDAS
- Sydenham’s chorea
- Acute disseminated encephalomyelitis (ADEM)
- Anti-NMDA (N-methyl D-aspartate) receptor encephalitis
- Limbic encephalitis (anti-VGKC)
- Hashimoto’s encephalitis
- Rassmussen’s encephalitis (chronic focal)
- Acute inflammatory CNS demyelination unresponsive to steroids, including Multiple Sclerosis (MS)
- Neuromyelitis Optica
TPE / PLEX in Neurology: peripheral nerve diseases

Peripheral nerve diseases
- Myasthenia Gravis (MG) (anti-AChR type)
- Myasthenia Gravis (MG) (anti-MUSK type)
- Eaton-Lampert myasthenic syndrome
- Guillain-Barré syndrome (GBS)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Monoclonal IgM with anti-MAP (myelin-associated – protein) activity
- Light chain neuropathy (in multiple myeloma)
- Other paraprotein polyneuropathies


TPE / PLEX for Myasthenia Gravis

85% are "seropositive", i.e. have antibodies to acetylcholine receptors (AChR)

6% have antibodies to Muscle Specific Kinase (MuSK)

Other targets not yet identified

Insight into pathogenesis

- Exposure to Campylobacter, other bacteria, or immunization may trigger formation of Ab’s to bacterial lipooligosaccharides (LOS).
- These Ab’s cross-react (molecular mimicry) with various neuronal gangliosides (GQ1b, GM1, GM1b, GD1a, GalNAcGD1a, GD1b, GD3, etc.)
- The pattern of autoimmune neuropathy corresponds to the abundance of these gangliosides in different regions of neural anatomy; e.g. GQ1b corresponds to predominantly facial involvement (Miller-Fisher variant).

Guillain-Barré Syndrome


---

**Guillain-Barré Syndrome**

TPE vs. IVIG vs both

**RANDOMIZED TRIAL (379 patients)**
- Comparing three treatment plans:
  1. TPE (5 exchanges)
  2. IVIg (0.4 gm/Kg/day x 5 days)
  3. Both (TPE + IVIg)

**RESULTS:**
- TPE and IVIg have equivalent efficacy
- Combination not significantly better than either treatment alone.

**DISCUSSION:**
"IVIg may be preferable to TPE... equal benefit, greater convenience, similar overall cost... provided there are no contraindications to IVIg."

But the cost of IVIG has jumped between 1997 and 2009 (and further in 2012).

*75:25 blend of liquid and lyophilized IVIG

PROPRIETORY INFORMATION, ACTUAL $ VALUES REDACTED

UCSD: P Helmons, Pharm D, 2009.
Thirst for blood leaves toddlers wanting

JULIE ROBOTHAM
February 6, 2010

IVY TREGENZA has been out of hospital for 15 whole weeks. . .

She is now . . . enjoying the results of intravenous immunoglobulin (IVIg). This is infused into her body every three weeks to compensate for her inability to produce an immune molecule that fights common infections.

But despite her poor health, Ivy's doctors had to apply three times before she was allowed IVIg. Specialists fear it will become even harder for such children to qualify . . . amid a surge in demand from adults with neurological illnesses . . .

Serious and quiet ... Ivy Tregenza has spent most of her four years among adults in hospital. Photo: Dean Osland

IVIG shortage

dmward@ucsd.edu

Neurological diseases account for a large subset of the indications for and overall usage of TPE.

TPE is effective and established therapy for acute attacks of Guillain-Barré, CIDP, myasthenia gravis, MS, NMO, other CNS inflammatory demyelinating diseases, CNS vasculitis, CNS microangiopathy, and other rare neurological diseases.

In acute situations, TPE is best performed early. The most common mistake is to perform too few procedures.

Chronic maintenance TPE has a place in the management of CIDP, paraprotein-related neuropathies, some cases of myasthenia gravis, probably NMO and other selected CNS demyelinating cases.
SUMMARY:

- Types of therapeutic apheresis
- Expanding utilization of apheresis therapies
- Methods and technologies of plasma exchange (TPE / PLEX):
  - centrifugal
  - membrane
- TPE / PLEX treatment options and prescription
- Adverse events
- Kinetics of removal of autoantibodies
- Intensity and adequacy of plasma exchange therapy
- Applications in neurology

The patient (third from left) celebrated his 1000th TPE in March 2013. He has received TPE weekly (occasionally more often) since 1994 for a painful peripheral neuropathy caused by a monoclonal IgM with anti-MAP (anti-myelin-associated-protein) activity, unresponsive to other therapies.
Thank you for your attention