Therapeutic plasma exchange: What, When, Why

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Outline

- Definition – What is TPE
- When do we do it – Rationale
- Why we do it – Reasoning and indications
Apheresis

• From Greek “to carry away”

• Blood taken extracorporeally to separate and collect/discard components – cells or plasma

• Desired portion (e.g., plasma) removed and the cells returned – therapeutic plasma exchange or TPE
Donor apheresis

- Donor
  - Research
    - Mononuclear cells, granulocytes, other
  - Treatment
    - Platelet concentrates
    - Packed red blood cells
    - Hematopoietic progenitor cells for transplant
    - Plasma for fractionation – IVIg, albumin, factor VIII, etc
Therapeutic apheresis

- Therapeutic plasma exchange (TPE)
- Red blood cell exchange (RCE)
- Leukocyte depletion (WBC)
- Platelet depletion (PLT)
- Lipid apheresis
- Rheopheresis
- Extracorporeal photopheresis (ECP)

Did you know? The UAB Apheresis service is 36 years old and we perform close to 2500 procedures per year?
Fluid dynamics in TPE

INTRACELLULAR

EXTRACELLULAR

INTERSTITIAL

INTRAVASCULAR

42 L

28 L

14 L

10 L

4 L
Figure 1. Compartment model of substances removed by therapeutic plasma exchange. Adapted from Weinstein.⁶
### Blood volume and plasma volume

#### Table 2-3. Calculation of Total Blood Volume*

**Gilcher’s Rule of Fives**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Fat</th>
<th>Thin</th>
<th>Normal</th>
<th>Muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>60</td>
<td>65</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
</tbody>
</table>

**Nadler’s Formula**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total Blood Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>(0.006012xH^3)/(14.6 x W) + 604</td>
</tr>
<tr>
<td>Female</td>
<td>(0.005835xH^3)/(15 x W) + 183</td>
</tr>
</tbody>
</table>

Predicted clearance curve of a substance removed by TPE

Fig. 2. Fraction removed by plasma volume replaced (modified with permission from Brecher ME, editor. AABB Technical Manual, 14th edition. Bethesda, MD: AABB, 2002; p 136) [4].
Fig. 3. Theoretical reduction of IgG following plasma exchange of 1, 1.25, and 1.5 plasma volumes and following re-equilibration of total body IgG. The solid line indicates a 85% reduction and the dashed line a 70% reduction. The absolute reduction in IgG is reduced with each subsequent exchange. Calculations assume no degradation or synthesis of IgG, and re-equilibration of IgG at 2 days.

### What we expect

<table>
<thead>
<tr>
<th>Plasma constituent</th>
<th>% decrease from baseline</th>
<th>% recovery 48 hrs post TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulins</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>C3</td>
<td>63</td>
<td>60-100</td>
</tr>
<tr>
<td>Platelets</td>
<td>25-30</td>
<td>75-100</td>
</tr>
<tr>
<td>Clotting factors</td>
<td>25-50</td>
<td>80-100</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>30-60</td>
<td>Variable</td>
</tr>
</tbody>
</table>

### Protein

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fibrinogen</th>
<th>IgM</th>
<th>IgD</th>
<th>IgG</th>
<th>IgA</th>
<th>IgE</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>% intravascular</td>
<td>80</td>
<td>76</td>
<td>75</td>
<td>45</td>
<td>42</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>MW (kDaltons)</td>
<td>340</td>
<td>950</td>
<td>175</td>
<td>150</td>
<td>(160)_n</td>
<td>190</td>
<td>66</td>
</tr>
</tbody>
</table>
Considerations

- Venous access
  - Peripheral vs central (mostly)
- Anticoagulation
- Replacement fluid
- Patient/donor history and medications
- Plasma constituents removed
- Frequency and number of procedures
- Complications
Anticoagulation

Acid citrate dextrose (ACD) Formula A

- Chelates Ca and Mg
- Infused as the blood is being collected
Replacement fluids

- Most patients receive
  - 5% albumin
    - Isosmotic; sterile; no coagulation factors

- Specific indications such as thrombotic thrombocytopenic purpura (TTP) or bleeding (ongoing or imminent)
  - Plasma
    - Large amount of Na citrate: 14% by volume
    - Risk of transfusion reaction and disease transmission
Why do it?

- Plausible Pathogenesis
- Better Blood
- Perkier Patients

Secure understanding of the disease process suggests clear rationale for TPE

- Diseases known to be “caused” by a circulating autoantibody, high triglycerides, abnormal immunoglobulin
Clear evidence that abnormality that makes apheresis plausible is meaningfully corrected.

Candidate molecules large enough to be at least partially confined to intravascular space.

- Molecules distributed evenly through the total body water can’t be meaningfully depleted by TPE (i.e., creatinine)

Only substances consistently depleted are large macromolecules relatively long-lived and, hence, slowly resynthesized, like IgG or LDL.

Strong evidence that TPE confers clinically worthwhile benefit; not just statistically significant.

Consider:

- Effectiveness
- Risk/benefit
- Cost/benefit
- Inconvenience/benefit

Compared to other available therapies

- Unexplained severe thrombocytopenia and microangiopathic hemolytic anemia
  - Platelet count usually <30,000/µL
  - Schistocytes in peripheral blood
- Deficiency of ADAMTS13 (von Willebrand-cleaving protease) due to autoantibody (acquired form)
  - Plasma accumulation of ultra-large von Willebrand factor multimers induce widespread platelet clumps
1924
Eli Moschcowitz describes first TTP patient

1977
Byrnes and Khurana prove that TTP relapses respond to plasma
Bukowski et al report success with plasma exchange

1982
Moake et al show that UL-VWF accumulate in patients with chronic relapsing TTP

1991
Rock et al show that TPE is more efficient than plasma alone

1997 - 1998
Furlan et al link TTP to deficient VWF-cleaving protease
Furlan, Tsai, & Lian discover autoantibody against VWF-cleaving protease

2001
Zheng et al purify protease and identify it as ADAMTS13
<table>
<thead>
<tr>
<th>Disorder</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td>• Microvascular thrombosis</td>
</tr>
<tr>
<td></td>
<td>○ VWF platelet aggregates</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular defects</td>
<td>• Severe ADAMTS13 deficiency</td>
</tr>
<tr>
<td></td>
<td>○ Autoimmune inhibitors</td>
</tr>
<tr>
<td></td>
<td>○ Genetic mutations</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>• Microvascular thrombosis →</td>
</tr>
<tr>
<td></td>
<td>ischemic tissue injury</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>• Focal neurologic deficits</td>
</tr>
<tr>
<td></td>
<td>• Mental status change, seizures</td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain, pancreatitis</td>
</tr>
<tr>
<td></td>
<td>• Myocardial infarction</td>
</tr>
</tbody>
</table>
Application of McLeod’s criteria to specific diseases

- Surprisingly few conditions unequivocally meet all 3 criteria:
  - Goodpasture’s disease
  - Cryoglobulinemia
  - Guillain-Barre syndrome
  - Hyperviscosity syndrome
  - Leukostasis syndrome
General Issues to be Considered When Evaluating a New Patient for Initiation of TPE

- **Rationale**
  - Proposed mechanism for the procedure
  - Brief account of the results of published studies
  - Patient-specific risks from the procedure

- **Impact**
  - Effect of therapeutic apheresis on comorbidities and medications (and vice-versa)

General Issues to be Considered When Evaluating a New Patient for Initiation of TPE

- Therapeutic plan
  - Total number and/or frequency of procedure
- Technical issues
  - Vascular access
  - Type of anticoagulant
  - Replacement fluid
  - Volume of whole blood processed (e.g., number of plasma volumes exchanged)
General Issues to be Considered When Evaluating a New Patient for Initiation of TPE

- Timing and location
  - Based on clinical considerations (e.g., medical emergency, urgent, or routine)
  - Location of procedure (e.g., intensive care unit, medical unit, operating room, outpatient setting)
  - If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient
Clinical and/or laboratory end-points

- Parameters should be established to monitor effectiveness of the treatment
- Criteria for discontinuation of TPE should be discussed where appropriate
  - Specially for indications not clearly established
- Citrate effects:
  - Tingling, N/V, tetany or seizure, arrhythmia

- Vasovagal effects:
  - Pallor or diaphoresis, N/V, syncope and/or seizure

- Venipuncture:
  - Severe pain, nerve damage, palpable hematoma

- Central venous access:
  - Infection, thrombosis, pneumothorax or hemothorax, other hemorrhage, arterial puncture
Other serious events:

- Chills/rigors, arrhythmia (non-citrate-related), transfusion reaction, anaphylaxis

Severe cardiorespiratory events:

- Respiratory distress, circulatory collapse, cardiac arrest, death

Machine malfunctions:

- Hemolysis, air embolus, clot/leak, unable to return blood (acute blood loss)
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV</td>
<td>Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>
TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological quality of supporting evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Strong recommendation, moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>Grade 1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
</tr>
</tbody>
</table>
Category I indications based on Grade 1A recommendations

- Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre Syndrome – primary treatment
- ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis and microscopic polyangiitis) – dialysis-dependence
- Thrombotic thrombocytopenic purpura (TTP)
Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study

<table>
<thead>
<tr>
<th></th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;30 × 10^9 per L</td>
<td>1</td>
</tr>
<tr>
<td>Haemolysis variable†</td>
<td>1</td>
</tr>
<tr>
<td>No active cancer</td>
<td>1</td>
</tr>
<tr>
<td>No history of solid-organ or stem-cell transplant</td>
<td>1</td>
</tr>
<tr>
<td>MCV &lt;90 fL‡</td>
<td>1</td>
</tr>
<tr>
<td>INR &lt;1·5</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine &lt;2·0 mg/dL</td>
<td>1</td>
</tr>
</tbody>
</table>

INR=international normalised ratio. MCV=mean corpuscular volume. *Score of 0–4 denotes low risk for severe ADAMTS13 deficiency; score of 5 denotes intermediate risk; score of 6 or 7 denotes high risk. †Reticulocyte count >2·5%, or haptoglobin undetectable, or indirect bilirubin >2·0 mg/dL. ‡<9·0 × 10⁻¹⁴ L.

Table 3: The PLASMIC score for prediction of thrombotic microangiopathy associated with severe ADAMTS13 deficiency
Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study

<table>
<thead>
<tr>
<th>Score</th>
<th>Derivation cohort (n=200)</th>
<th>Internal validation cohort (n=150)</th>
<th>External validation cohort (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0/84 (0%)</td>
<td>0/89 (0%)</td>
<td>2/47 (4%)</td>
</tr>
<tr>
<td>5</td>
<td>2/44 (5%)</td>
<td>3/32 (9%)</td>
<td>6/25 (24%)</td>
</tr>
<tr>
<td>6 or 7</td>
<td>58/72 (81%)</td>
<td>18/29 (62%)</td>
<td>61/74 (82%)</td>
</tr>
</tbody>
</table>

Data are number of individuals with ADAMTS13 activity of 10% or less/total number of individuals with that score (%).

*Table 4: Validation of the PLASMIC score*
Highlights from Current management/treatment from ASFA’s Fact Sheet

- TPE decreases overall mortality of TTP from nearly 100% to <10%
- TPE to be initiated emergently once TTP recognized
- If TPE not immediately available, plasma infusion may be given until TPE can be initiated
- Corticosteroids often used; no definitive trials proving efficacy
- Rituximab often used to treat refractory or relapsing TTP; recent studies mention rituximab as adjunctive agent with initial TPE
- Since rituximab immediately binds to CD20-bearing lymphocytes, a 18–24 h interval between its infusion and TPE is used in practice.
- Other adjunts: cyclosporine, azathioprine, vincristine, other immunosuppressive agents; splenectomy used in the past
Technical notes from ASFA’s Fact Sheet

- Allergic and citrate reactions frequent due to the large volume of plasma
  - Higher AC ratio to be considered
- Fibrinogen may decrease if cryoprecipitate poor plasma (CPP) used
  - More frequent acute exacerbations?
- 5% albumin may be used for initial 50%
  - Similar efficacy to 100% plasma in one study
- Solvent-detergent treated plasma may be used for patients with severe allergic reactions
- **Volume treated:** 1–1.5 TPV  **Frequency:** Daily
- Until platelet count >150\(\times 10^9\)/L, and LDH is near normal for 2–3 days
- Role of tapering TPE over longer duration not studied prospectively
- Persistence of schistocytes alone on PB without clinical features of TTP, does not preclude discontinuation of TPE
Hemolyzed plasma in TTP patient with AIDS
Category I indications for TPE based on Grade 1B recommendations

- Antiglomerular basement membrane disease (Goodpasture’s syndrome) – dialysis independence
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Focal segmental glomerulosclerosis (FSGS) recurrent in transplanted kidney
- IgG/IgA paraproteinemic demyelinating neuropathy
- Myasthenia gravis – moderate/severe
Category I indications for TPE based on Grade 1B recommendations

- HLA desensitization prior to living-donor renal transplantation
- ABO desensitization prior to living-donor renal transplantation
- Antibody-mediated rejection of living-donor renal transplant
Category I indications for TPE based on Grade 1C recommendations

- ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis and microscopic polyangiitis) – diffuse alveolar hemorrhage
- ABOi living donor liver, desensitization prior transplant
- Myasthenia gravis – pre-thymectomy
- N-acetyl D-aspartate receptor antibody encephalitis
- IgM paraproteinemic demyelinating neuropathy
- Progressive multifocal leukoencephalopathy associated with natalizumab
- Wilson’s disease, fulminant
Categories II and III indications for TPE

- Category II
  - 20 conditions
    - Examples: Severe cold agglutinin disease, cryoglobulinemia, acute neuromyelitis optica, etc

- Category III
  - 58 conditions
    - Examples: Antibody-mediated cardiac transplant rejection, HELLP syndrome (post-partum), heparin-induced thrombocytopenia, etc
MUITO OBRIGADA

GRACIAS

THANK YOU