Overview of therapeutic apheresis

Patricia Shi
Medical Director, Clinical Services
Apheresis principle

- Greek apairesos: “to take away by force”

- Very different from hemodialysis, where goal is water/electrolyte balance
Separation by density centrifugation

- **RBC contamination**
  - Mononuclear cells: 3-5% Hct
  - Granulocytes: 7-8% Hct

*Median measurements for separation by specific gravity*
Continuous circuit

Collect/waste
Replace

Access
Return

Plasma
Buffy Coat
Packed Red Cells
Platelet
Lymphocyte
Granulocyte
Purpose of apheresis

**Therapeutic Apheresis (TA)**
- Removal of disease mediator in plasma
  - Eg. auto- or allo- Abs, immune complexes, monoclonal proteins
- Removal of diseased cells
  - Eg. sickle or parasite-infected red cells
- Removal of excess cells
  - Eg. essential thrombocythemia, polycythemia vera, acute leukemia
- Replacement with normal blood components
  - Eg. AA red cells, ADAMTS13

**Donor apheresis**
- Blood donor apheresis
  - 2 unit red cells
  - 2 unit plasma
  - Single donor platelet (equivalent to ~ 6 units)
  - Granulocytes
- Mononuclear cells for cellular therapy collections
  - For BMT programs, gene therapy, etc.
Overview of TA Procedure Types & Indications

• Therapeutic Plasma Exchange (TPE) -- 80% procedures
• Red Blood Cell Exchange (RBCX) -- 15% procedures
• Cellular Depletions -- 5% procedures
  – White Cells
  – Platelets
  – Red Cells
Therapeutic Plasma Exchange (TPE)

Also returned: replacement volume for plasma removed.

“return line”

“access line”

“waste bag”
Why TPE?

• Removal of pathogenic substances in plasma
  – Eg. immune complexes, auto-Abs, paraproteins, high triglycerides

• Plasma replacement replaces dysfunctional or low levels of plasma proteins
  – Eg. ADAMTS13, coagulation factors

• Possibly immunomodulatory
  – Often adjunctive to other types of therapy, eg. immunosuppressive drugs—cytokine removal?
Common Indications for TPE

• Hematologic
  – TTP
  – Paraproteinemias: myeloma, Waldenstrom, cryoglobulinemia

• Neurologic:
  – Guillain-Barre (AIDP)
  – CIDP (Chronic inflammatory demyelinating polyneuropathy)
  – Myasthenia gravis

• Renal
  – Renal transplant rejection
  – Goodpasture’s syndrome
  – Wegener’s granulomatosis
  – Recurrent FSGS (focal segmental glomerulosclerosis)
TPE principles

![Graphs showing fraction remaining and plasma volume replaced over days with IgG levels.]
## Removal of plasma constituents with 1 PV

<table>
<thead>
<tr>
<th>Plasma constituent</th>
<th>% decrease from baseline</th>
<th>Mean % recovery 48 hrs post TPE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulins</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>C3</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Platelets</td>
<td>25-30</td>
<td>90</td>
</tr>
<tr>
<td>Clotting factors</td>
<td>25-50</td>
<td>90</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>30-60</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*% recovery = % recovered of the amount removed

<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)&lt;sub&gt;n&lt;/sub&gt;</td>
<td>190</td>
<td>66</td>
</tr>
</tbody>
</table>

Orlin & Berkman, Blood 1980
TPE orders

Volume and frequency
- 1-1.5 plasma volumes
- qd-qod until response/endpoints
  - 4-6 procedures for autoantibodies
  - 1-2 procedures if IgM (Waldenstrom’s)

Replacement fluid
- To prevent hypovolemic collapse
- 5% albumin is standard to maintain oncotic pressure
  - >30% normal saline risks hypotension
- Plasma only for specific indications
  - TTP, alveolar hemorrhage, bleeding risk, coagulopathy
  - Fibrinogen depletion: 25-30% PV (~1 liter) replacement with plasma typically sufficient
Important considerations

• False negative or abnormally low tests
  – Eg. ID markers, Abs, enzyme levels

• Drug removal
  – Monitor sedation in ICU patients
  – Dose drugs post-procedure, especially if:
    • Low volume of distribution (< 0.3 L/kg)
    • Highly protein-bound (> 80%)
    • Long half-life
  – Examples:
    • rituximab, IVIG, basiliximab, cisplatin, vincristine
    • Ceftriaxone, ceftazidime, vancomycin, tobramycin, acyclovir
    • Diltiazem, verapamil, glipizide, warfarin

• Coag factor removal, especially fibrinogen
  – Especially with daily procedures
  – Check pre- or 24 hr post-TPE to allow recovery

• Platelet removal
  – Usually no more than ~5-10% decrease

• Fluid balance
  – “100% fluid balance” actually is ~195 mL positive with Cobe Spectra
Red cell exchange (RCE)

Also red cell replacement
Plasma Return
RBC removal
Whole Blood In
Red cell exchange

Main indications

• Sickle cell disease
  – Acute: Stroke, acute chest, multi-organ failure, fat embolism syndrome, severe hepatic crisis, retinal infarction
  – Chronic: stroke prophylaxis

• Red cell parasitemia
  – Severe babesiosis
  – Severe malaria: ≥ 10% infected RBCs, organ compromise

Advantages

• Sickle cell
  – Less viscosity increase
  – Less volume overload
  – Less iron overload

• Parasitemia
  – In conjunction with anti-parasitic drugs

Fasano RM et al, Transfusion 2016
RCE orders

Volume and frequency

• Sickle: ~1 red cell volume exchange for FCR ~30%
• Parasite: 1.5-2.0 red cell volume exchange for FCR 10-20%
• One procedure should be adequate

Device input variables

• Current Hct
• Desired ending Hct
• Desired FCR (Fraction of Cells Remaining) or volume of red cells available for procedure
• Average Hct of replacement red cells
  – Adsol: 55-65%
  – CPDA: 75%
**Cellular Depletions**

- Removal of increased WBC, RBC, or platelets
- Benefits
  - Decreases stroke, respiratory, hemorrhage/thrombosis risk
  - Restores normal blood viscosity
  - Restores normal tissue oxygen delivery
  - Improves metabolic derangement
  - More efficient than phlebotomy for hemachromatosis
Cellular depletions

Indications

• Leukostasis (except APL)
  – >100K blasts or symptoms
  – Standard procedure (without hetastarch) removes MNC not PMN

• Thrombocytosis
  – >1M platelets or symptoms

• Red cell removal
  – Polycythemia vera Hct > 45%
  – Hereditary hemachromatosis

Orders

• 1-2 total blood volumes (TBV) processed decreases counts by ~30-50%
  – WBC depletion: ~2x TBV
  – Plt depletion: ~1.5x TBV

• RBC depletion: specify desired end Hct

• WBC/RBC depletion:
  – Replace sig volume loss (> 10% TBV) with saline or 5% albumin
Extracorporeal Photopheresis

• **Main Indications**
  – Cutaneous T-cell lymphoma
  – Cardiac and lung allograft rejection
  – Chronic graft versus host disease

• **Procedure**
  – MNC separated
  – Treated extracorporeally with photoactive psoralen and UVA light
  – Reinfused to the patient during the same procedure

• **Mechanism of action:**
  – CTCL: Enhanced tumor Ag immunogenicity
  – Rejection/cGVHD: Crosslinks DNA → apoptosis of treated cells → induction of regulatory T-cells/anti-inflammatory cytokines
Practical issues
Overview of Practical Issues

- Vascular access
- Procedural considerations/calculations
- Citrate toxicity & other adverse events
- Pediatric considerations
- ASFA guidelines
- Ideal consult/order
Vascular Access

• Use peripheral veins if possible: 60-80 mL/min
  – Usually 16-20 gauge needed for access line
  – Usually 18-22 gauge needed for return line
  – Suitable for short-term or less frequent procedures
  – AV fistula or graft if available

• Temporary central access: 60-100 mL/min
  – Double-lumen dialysis catheter, 10-14 French
    • IJ preferred over SC location: ↓ thrombosis risk
    • Minimum: DL 7 French or 2 single-lumen 5 French

• Permanent central access
  – Tunneled double-lumen HD catheter, 8-11.4 French
  – Specialized ports (Vortex, Sportport, Norport, Bardport)
    • Double-lumen, 11.4 French
    • Single-lumen, 7.5-9.6 French
Total Blood Volume calculation

- Essential to obtain accurate wt & ht for TBV

- Nadler’s formula

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total blood volume ((H=m, W=kg))</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td>(0.3561 \times H^3 + 0.03308 \times Wt + 0.1833)</td>
</tr>
<tr>
<td>male</td>
<td>(0.3669 \times H^3 + 0.03219 \times Wt + 0.6041)</td>
</tr>
</tbody>
</table>

- Neonate- age 2: 80-100 mL/kg

<table>
<thead>
<tr>
<th>Gender</th>
<th>Normal</th>
<th>Obese (-10)</th>
<th>Thin (-5)</th>
<th>Muscular (+5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>65</td>
<td>55</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>60</td>
<td>65</td>
<td>75</td>
</tr>
</tbody>
</table>

- Gilcher’s Rules (mL/kg)
## Calculation of other variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Formula</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume</td>
<td>(1-Hct) * TBV</td>
<td>(1- 0.36) * 5000 = 3200 mL</td>
</tr>
<tr>
<td>Red cell volume</td>
<td>Hct * TBV</td>
<td>( 0.36) * 5000 = 1800 mL</td>
</tr>
<tr>
<td># red cell units</td>
<td>RCV/180 mL</td>
<td>1800/180 = 10 units</td>
</tr>
<tr>
<td>% EC TBV</td>
<td>Kit volume / TBV</td>
<td>170 / 5000 = 0.03 = 3%</td>
</tr>
<tr>
<td>% EC RCV</td>
<td>Kit RCV / RCV</td>
<td>68 / 1800 = 0.4 = 4%</td>
</tr>
<tr>
<td>Intra-procedure Hct</td>
<td>(RCV – EC RCV) / TBV</td>
<td>(1800 – 68) / 5000 = 0.35 = 35%</td>
</tr>
</tbody>
</table>

EC=extracorporeal, TBV=total blood volume, RCV= red cell volume

### Spectra kit

<table>
<thead>
<tr>
<th></th>
<th>TPE/RCE</th>
<th>WBC</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC TBV</td>
<td>170</td>
<td>285</td>
<td>131</td>
</tr>
<tr>
<td>EC RCV = 0.4 x kit volume</td>
<td>68</td>
<td>114</td>
<td>52</td>
</tr>
</tbody>
</table>

### Optia Kit

<table>
<thead>
<tr>
<th></th>
<th>TPE/RCE</th>
<th>Collection</th>
<th>IDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC TBV</td>
<td>185</td>
<td>191</td>
<td>253</td>
</tr>
<tr>
<td>EC RCV</td>
<td>58</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>
Citrate (ACD-A) anticoagulation

- Added at access to prevent blood clotting in machine
  - Chelates ionized Ca required for clotting
  - No bleeding risk due to hemodilution & liver metabolism
- TBV determines citrate infusion rate
- Risk of hypoCa symptoms with increasing procedure duration
  - **Mild:**
    - Paresthesias, tremors, muscle cramps
    - Lightheadedness, agitation, sweating
    - Altered taste, nausea
  - **Severe:**
    - Increased QT interval, cardiac arrhythmia, hypotension
    - Confusion, seizures
    - Carpopedal spasm, tetany, laryngospasm
Potential citrate toxicity

Other effects

- **HypoMg**
  - Citrate also chelates free Mg$^{2+}$

- **Metabolic alkalosis/ hypoK+**
  - Citrate metabolized/excreted by liver/kidney
  - Citrate metabolism consumes H+ ions, generates HCO$_3$-
  - With renal disease, decreased HCO$_3$- excretion causes metabolic alkalosis with intracellular influx of K+

Symptoms

- **HypoMg**
  - Neuromuscular excitation, cardiac, GI, CNS
  - Also muscle weakness: SOB, dysphagia

- **Metabolic alkalosis**
  - Neuromuscular excitation, GI, cardiac, CNS

- **HypoK**
  - Neuromuscular, cardiac
Management of citrate toxicity

- Operator should pause procedure to stop citrate infusion
  - Citrate $t^{1/2}$ 30-60 minutes: baseline reached in ~ 4 hrs
  - Should not resume until sx$s$ resolve
- IV Ca gluconate/chloride usually resolves sx$s$
- Prevention:
  - Oral calcium carbonate, up to 2 elemental grams pre-procedure
  - Part heparin protocol
  - Adjust replacement fluid if possible
Other Potential Adverse Events

• Vascular access issues
  – Hematoma
  – Local infection
  – Line thrombosis
• Hypotension due to ECV
• Vasovagal
  – Hypotension, pallor, sweating, N/V, syncope, convulsions
  – Differentiate from hypotension by slow pulse
• Fluid balance
  – Older devices: net positive/negative depending on procedure type
• Transfusion reactions
  – Allergic reactions to plasma common
• Drug interactions - hold if possible:
  – ACE inhibitor: inhibits bradykinin breakdown
    • Possibly generated from pre-kallikrein in albumin
    • Hypotension, flushing, respiratory sx's
  – Beta/Ca channel-blockers: increase risk of hypotension with volume shifts
Pediatric considerations

• Vascular access:
  – smallest: 2 single-lumen 5 French catheters
  – Can use standard Port-a-Cath if willing to have inlet flow rates of < 20 mL/min

• Citrate toxicity
  – Switch to part heparin protocol
  – Use blood warmer (increases citrate metabolism)

• Need for red cell prime
  – Risk of hypotension/anemia if EC TBV or RCV >15%
  – RBC prime
    • RBC unit: undiluted (Hct 55-65%) or diluted to lower Hct
    • Leukodepletion: Hct is 3-5% in waste product

• Pay attention to fluid balance with older devices:
  – Usually +: plt depletion, MNC collection, TPE
  – Usually −: WBC depletion
  – Can adjust fluid balance for TPE
For each indication/disease, guidelines review:

- Description of disease
- Current management/treatment
- Rationale for TA
- Technical considerations
- Duration and discontinuation
- References
### ASFA Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I</td>
<td>First-line therapy, either as a primary stand-alone treatment or with other modes of treatment</td>
</tr>
<tr>
<td>Category II</td>
<td>Second-line therapy, either as a stand-alone treatment or with other modes of treatment.</td>
</tr>
<tr>
<td>Category III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>Category IV</td>
<td>Published evidence indicates apheresis is ineffective or harmful. Obtain IRB approval</td>
</tr>
</tbody>
</table>

**Examples of notable changes in 2013 edition**

- **Heparin-induced thrombocytopenia (Cat III)**
  - Pts who need heparin anticoagulation for emergent CPB
  - Continued thrombotic complications despite D/C heparin and anticoagulation

- Hereditary Hemachromatosis and Polycythemia Vera moved from Cat III to Cat I indications
### TABLE II. Grading Recommendations adopted from Guyatt and coworkers [8].

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</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>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</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>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</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>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Weak recommendation, high quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Weak 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>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
## Ideal consult/order

<table>
<thead>
<tr>
<th>Factor to consider</th>
<th>Order affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate rationale</td>
<td>Diagnosis, ASFA category</td>
</tr>
<tr>
<td>Appropriate procedure</td>
<td>Type of apheresis</td>
</tr>
<tr>
<td>Dz pathophysiology, clinical status</td>
<td>Replacement solution and volume to be processed</td>
</tr>
<tr>
<td>Treatment plan/regimen</td>
<td>Frequency &amp; total number of procedures</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Peripheral versus central access, femoral vs. internal jugular</td>
</tr>
<tr>
<td>Clinical or laboratory endpoint</td>
<td>Laboratory monitoring: eg. Hb fractionation, CBC</td>
</tr>
<tr>
<td>Timing and location</td>
<td>Urgency; need for monitoring (ICU vs regular floor)</td>
</tr>
<tr>
<td>Volume status</td>
<td>Fluid balance</td>
</tr>
<tr>
<td>Need for RBC prime</td>
<td>Small size, pediatric, anemia</td>
</tr>
<tr>
<td>Citrate toxicity risk</td>
<td>Calcium gtt or heparin protocol: small size, pediatric, plasma use</td>
</tr>
<tr>
<td>Impact of TA on interventions</td>
<td>Timing of apheresis in relation to meds, dialysis, blood transfusion, blood tests</td>
</tr>
<tr>
<td>Impact of meds on TA</td>
<td>ACE inhibitors, β or Ca channel blockers</td>
</tr>
<tr>
<td>Daily suitability</td>
<td>CBC, lab criteria to proceed</td>
</tr>
</tbody>
</table>
Thank you!

Questions?
**Fluid balance issues with Spectra**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Typical Fluid Balance (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma exchange</td>
<td>+195 mL</td>
</tr>
<tr>
<td>Red cell exchange</td>
<td>-100 mL (no rinseback)</td>
</tr>
<tr>
<td>Leukodepletion</td>
<td>Rinseback (263 cc) + AC– product volume (negative)</td>
</tr>
<tr>
<td>Platelet depletion</td>
<td>Rinseback (190 cc)+ AC – product volume (positive)</td>
</tr>
<tr>
<td>HPC collection</td>
<td>Rinseback (185 or 263cc) + AC – product volume (positive)</td>
</tr>
</tbody>
</table>

Rinseback is not performed with a RBC exchange or when using a red cell prime with other types of procedures.