Overview of therapeutic apheresis

Patricia Shi
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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: 3-4% Hct
  - Granulocytes: 7-8% Hct

*Median measurements for separation by specific gravity*
Purpose of therapeutic apheresis

• **Removal of diseased cells**
  – Eg. sickle red cells, parasite-infected red cells, or leukoblasts

• **Removal of excess normal cells**
  – Eg. essential thrombocythemia, polycythemia vera

• **Removal of disease mediator**
  – Eg. auto- or allo- Abs, immune complexes, monoclonal proteins

• **Replacement with normal blood components**
  – Eg. AA red cells, ADAMTS13
Overview of Procedure Types & Indications

- Therapeutic Plasma Exchange (TPE) -- 80%
- Red Blood Cell Exchange (RBCX) -- 15%
- Cellular Depletions -- 5%
  - White Cells
  - Platelets
  - Red Cells
Overview of Practical Issues

• Vascular access
• Procedural considerations/calculations
• Citrate toxicity & other adverse events
• Pediatric considerations
• ASFA guidelines
• Ideal consult/order
Therapeutic Plasma Exchange (TPE)

- Plasma Out
- RBC, WBC, and Platelet Return
- Whole Blood In
- "return line"
- "waste bag"
- "access line"
Why TPE?

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

• Plasma replacement replaces absent/dysfunctional substances
  – Eg. ADAMTS13, coagulation factors

• Often adjunctive to other types of therapy, eg. immunosuppresive agents
Common Indications for TPE

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

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

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

Blood Banking & Transfusion Medicine, Hillyer Silberstein Ness eds.
## Removal of plasma constituents with 1 PV

<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>Fibrinogen</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>

<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>
TPE orders

Volume and frequency

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

Replacement fluid

- 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: requires ≤25% plasma replacement (~1 liter)
Important considerations

• **Drug removal**
  – 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
    • Ceftriaxone, ceftazidime, vancomycin, tobramycin, acyclovir
    • Diltiazem, verapamil, glipizide, warfarin
  – Monitor sedation in ICU patients

• **Coag factor removal**
  – Possible with daily procedures
  – Check pre- or 24 hr post-TPE to allow recovery

• **Platelet removal**
  – ~5-10% platelets can be removed with each TPE with older devices

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

Volume and frequency

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

Input variables

- Current Hct
- Desired ending Hct
- Desired FCR (Fraction of Cells Remaining)
- Average Hct of replacement red cells
  - Adsol: 55-60%
  - CPDA: 75%
Cellular Depletions

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

Indications

• Leukostasis
  – >100K blasts or symptoms
  – Procedure without hetastarch removes MNC not PMN

• Thrombocytosis
  – >1M platelets or symptoms

• Red cell removal
  – Polycythemia vera
  – Hereditary hemachromatosis

Orders

• 1-2 total blood volumes to decrease by ~30-50%
  – WBC depletion: 2x TBV
  – Plt depletion: 1-1.5x TBV

• RBC depletion: specify desired end Hct

• Replace volume loss with albumin or saline
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
  – Crosslinks DNA → apoptosis of treated cells → induction of regulatory T-cells/anti-inflammatory cytokines
Practical issues
Vascular Access

• Peripheral veins must be good: 60-80 mL/min
  – At least 16-17 gauge needed for access line
  – At least 17-18 gauge needed for return line
  – Suitable for short-term or less frequent procedures

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

• Permanent access
  – Two single lumen ports preferable:
    • 6-10 French
    • Vortex port, 9 French silicone best
  – Tunneled double-lumen HD catheter
Total Blood Volume calculation

- Procedure | Blood processed
- Plasma exchange | 1-1.5 PV
- Red cell exchange | 1 RCV
- Leukodepletion | 2 TBV
- Platelet depletion | 1.5 TBV

- Essential to obtain accurate wt & ht for TBV

- Nadler’s formula
  
  Gender | Total blood volume \( (H=m, W=kg) \)
  --- | ---
  female | \( 0.3561 * H^3 + 0.03308 \times Wt + 0.1833 \)
  male | \( 0.3669 * H^3 + 0.03219 \times Wt + 0.6041 \)

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

- Gilcher’s Rules (mL/kg)
  
  Gender | Normal | Obese (-10) | Thin (-5) | Muscular (+5)
  --- | --- | --- | --- | ---
  Female | 65 | 55 | 60 | 70
  Male | 70 | 60 | 65 | 75
## 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 - \text{Hct}) \times \text{TBV})</td>
<td>((1 - 0.36) \times 5000 = 3200 \text{ mL})</td>
</tr>
<tr>
<td>Red cell volume</td>
<td>(\text{Hct} \times \text{TBV})</td>
<td>((0.36) \times 5000 = 1800 \text{ mL})</td>
</tr>
<tr>
<td># red cell units</td>
<td>(\frac{\text{RCV}}{180 \text{ mL}})</td>
<td>(\frac{1800}{180} = 10 \text{ units})</td>
</tr>
<tr>
<td>% EC TBV</td>
<td>(\frac{\text{Kit volume}}{\text{TBV}})</td>
<td>(\frac{170}{5000} = 0.03 = 3%)</td>
</tr>
<tr>
<td>% EC RCV</td>
<td>(\frac{\text{Kit RCV}}{\text{RCV}})</td>
<td>(\frac{68}{1800} = 0.4 = 4%)</td>
</tr>
<tr>
<td>Intraprocedure Hct</td>
<td>(\frac{(\text{RCV} - \text{EC RCV})}{\text{TBV}})</td>
<td>(\frac{(1800 - 68)}{5000} = 0.35 = 35%)</td>
</tr>
</tbody>
</table>

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

### Kit volume (Spectra)

<table>
<thead>
<tr>
<th></th>
<th>TPE/RCE</th>
<th>WBC</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECV</td>
<td>170</td>
<td>285</td>
<td>131</td>
</tr>
<tr>
<td>RCV = 0.4 x kit volume</td>
<td>68</td>
<td>114</td>
<td>52</td>
</tr>
</tbody>
</table>
Citrate (ACD-A) anticoagulation

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

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 resolve
- Parenteral Ca gluconate/citrate usually resolves sx
- Prevention:
  - Oral calcium carbonate, up to 2 elemental grams pre-procedure
  - Part heparin protocol
  - Adjust replacement fluid if possible

![Citrate content](chart.png)
Other Potential Adverse Events

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

- **Vascular access:**
  - < 3 kg: 2 single-lumen 5 French catheters

- **Citrate toxicity**
  - Switch to part heparin protocol
  - Use blood warmer (increases citrate metabolism)

- **Need for prime**
  - Risk of hypotension/anemia if EC TBV or RCV >15%
  - RBC prime (vs albumin) prime is safest except with RCE
    - RBC unit: undiluted (Hct 55-65%) or diluted to current Hct
    - MNC removal: Hct is 3-5%
  - No rinseback typically done with prime: must consider red cell loss if use albumin prime outside of RCE

- **Pay attention to fluid balance:**
  - 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 I</th>
<th>First-line therapy, either as a primary stand-alone treatment or with other modes of treatment</th>
</tr>
</thead>
<tbody>
<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
    - 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
Strength of evidence—type and quality

<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.