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*
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 thrombocytopenia, 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 standard BMT, gene therapy, immune effector therapy, etc.
Peripheral blood mononuclear cells via apheresis
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, autoAbs, paraproteins, high triglycerides

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

• Possibly immunomodulatory
  – Adjunctive to other immunosuppressive drugs—cytokine removal?
More common Indications for TPE

• Hematologic
  – TTP (cat I)
  – Hyperviscosity in monoclonal gammopathies (cat I) – symptoms or rituximab prophylaxis
  – Myeloma cast nephropathy (cat I)
  – Severe cryoglobulinemia (cat II)
  – Catastrophic antiphospholipid Ab syndrome (cat II)

• Neurologic:
  – Primary treatment of Guillain-Barre Syndrome (AIDP) (Cat I)
  – Chronic inflammatory demyelinating polyneuropathy (CIDP) (Cat I)
  – Myasthenia gravis (Cat I)
  – Acute neuromyelitis optica spectrum disorders (cat II)

• Renal
  – Dialysis-dependent ANCA-positive rapidly progressive glomerulonephritis (Wegener’s, microscopic polyangiitis) (Cat I)
  – Dialysis-independent Goodpasture’s syndrome (Cat I)
  – Diffuse alveolar hemorrhage with either category above (Cat I)
  – Recurrent FSGS (focal segmental glomerulosclerosis) in transplanted kidney (Cat I)
  – Renal (LD), liver (LD), & cardiac transplant desensitization (Cat I-II)
  – Renal transplant Ab-mediated rejection (cat I-II)
TPE principles

Fraction remaining vs Plasma volume replaced

IgG g/l vs Day

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

*% recovery = % recovered of the amount removed

## 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>

Orlin & Berkman, Blood 1980
TPE orders

Volume and frequency
• 1-1.5 plasma volumes
• qd-qod until response/endpoints
  – 5-6 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 repletion: 25-30% PV replacement with plasma (~1 L) typically sufficient
Important considerations with TPE

• 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

• Follow PT/aPTT and fibrinogen
  – Especially with daily procedures
  – Check pre- or 24 hr post-TPE to allow recovery

• Follow platelet count
  – 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 (cat I), acute chest (cat II), multi-organ failure, fat embolism syndrome, severe hepatic complications, priapism (cat III)
  – **Chronic:** stroke prophylaxis (cat I)

• Red cell parasitemia
  – Severe babesiosis (cat II)
  – Severe malaria: ≥ 10% infected RBCs, organ compromise (cat III)
  – Always adjunctive to anti-parasitic drugs

Advantages vs simple transfusion

• Sickle cell
  – Less viscosity increase
  – Less volume overload
  – Less iron overload
  with chelation also

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 20-10%
- 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%
- **Isovolemic hemodilution:**
  - Minimum Hct
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)**
  - Symptoms (cat II)
  - Prophylaxis (cat III) if >100K WBC (AML), > 400K WBC (ALL)
  - Standard procedure (without hetastarch) removes MNC not PMN

- **Thrombocytosis**
  - Symptoms (cat II)
  - Prophylaxis (cat III) with >1M platelets & acquired vWF syndrome

- **Red cell removal**
  - Polycythemia vera Hct ≥ 45% (cat I)
  - Hereditary hemachromatosis (cat I)

**Orders**

- 1.5-2 total blood volumes (TBV) processed decreases counts by ~30-60%:
  - WBC depletion: ~2x TBV
  - Plt depletion: ~1.5x TBV

- RBC depletion: specify desired end Hct

- Replace significant volume loss (> 10-15% TBV) with saline or 5% albumin
Extracorporeal Photopheresis

• Main Indications
  – Cutaneous T-cell lymphoma (cat I)
  – Cardiac and lung allograft rejection (cat II)
  – Chronic graft versus host disease (cat II)

• 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
  – AV fistula or graft if available
  – Suitable for short-term or less frequent procedures

• **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>Procedure</th>
<th>Blood processed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma exchange</td>
<td>1-1.5 PV</td>
</tr>
<tr>
<td>Red cell exchange</td>
<td>~1 RCV</td>
</tr>
<tr>
<td>Leukodepletion</td>
<td>2 TBV</td>
</tr>
<tr>
<td>Platelet depletion</td>
<td>1.5 TBV</td>
</tr>
</tbody>
</table>

Gilcher’s Rules (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>
### 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>(\text{RCV} / 180 \text{ mL})</td>
<td>(1800 / 180 = 10 \text{ units})</td>
</tr>
<tr>
<td>% EC TBV</td>
<td>(\text{Kit volume} / \text{TBV})</td>
<td>(170 / 5000 = 0.03 = 3%)</td>
</tr>
<tr>
<td>% EC RCV</td>
<td>(\text{Kit RCV} / \text{RCV})</td>
<td>(68 / 1800 = 0.4 = 4%)</td>
</tr>
<tr>
<td>Intra-procedure Hct</td>
<td>((\text{RCV} - \text{EC RCV}) / \text{TBV})</td>
<td>((1800 - 68) / 5000 = 0.35 = 35%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Spectra kit</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>

<table>
<thead>
<tr>
<th>Optia Kit</th>
<th>TPE/RCE</th>
<th>MNC</th>
<th>CMNC</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>

Nightcap Kit
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 by liver
    • metabolism consumes H\(^+\) ions, generates HCO\(_3\)-
  – Citrate also excreted by kidney
    • 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
- IV Ca gluconate/chloride usually resolves sx
- Prevention:
  - Oral calcium carbonate, up to 2 elemental grams pre-procedure
  - Part heparin protocol
  - Adjust replacement fluid if possible

![Citrate content graph](image)
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 inhibitors inhibit bradykinin breakdown, which can be generated from pre-kallikrein in albumin
    - Hypotension, flushing, respiratory sx
  - Beta- or calcium channel blockers: may 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, esp with older devices:**
  – Usually +: plt depletion, MNC collection, TPE
  – Usually -: WBC depletion, red cell depletion
  – Can adjust fluid balance for TPE
ASFA Guidelines– Practical & User-friendly

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

Joseph Schwartz, Anand Padmanabhan, Nicole Aqui, Rasheed A. Balogun, Laura Connelly-Smith, Meghan Delaney, Nancy M. Dunbar, Volker Witt, Yanvun Wu, and Beth H. Shaz

• For each indication/disease, guidelines review:
  – Description of disease
  – Current management/treatment
  – Rationale for TA
  – Technical considerations: volume, replacement fluid, frequency
  – Duration and discontinuation/number of procedures
  – 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>

- **New Cat I-II indications in 2016 edition**
  - Hashimoto’s encephalopathy (Cat II)
  - N-methyl D-aspartate receptor Ab encephalitis (Cat I)
  - Progressive multifocal leukoencephalopathy associated with natalizumab (Cat I)
  - Hep B virus associated polyarteritis nodosa (Cat II)
## 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.