Therapeutic Apheresis
An Overview

Shan Yuan
June, 2011
What is Therapeutic Apheresis?

- **Apheresis**
  - Greek: To take away
  - Modern: Separation and selective removal, exchange or modification of a blood component
  - Usually performed with automated instruments

- **Donor Apheresis**
  - Single component collection (RBCs, plasma, platelets, or WBCs) from healthy donors
  - Multi-component: a combination of components, e.g. plasma + platelets

- **Therapeutic Apheresis**
  - A component in the blood is thought to contribute to a disease state, for example
  - Component is removed, exchanged or modified in order to achieve therapeutic purposes
What Does Therapeutic Apheresis Accomplish?

- Removal of:
  - WBCs:
    - Leukocytapheresis: in the setting of high WBC count in leukemia
    - Peripheral stem cell collection
  - Platelets:
    - Thrombocytapheresis for thrombocytosis of myeloproliferative disorders

- Exchange of:
  - RBC: Erythrocytapheresis (sickle cell disease, malaria)
  - Plasma: therapeutic plasma exchange (TPE):
    - “Prototype” of therapeutic exchange procedures
    - Removal of antibodies, paraproteins, cholesterol,

- Modification of:
  - WBC (with UV light): Photopheresis
Apheresis Instrument Types

- Centrifugation
  - Baxter/Fenwal CS 3000
  - Gambro/BCT (Caridian) Cobe Spectra
  - Haemonentics MCS+
- Membrane
  - Asahi PlasmaFlo
  - Gambro BCT (Caridian) Prisma TPE
- Adsorption Column (Selective removal)
Centrifugation Based

- Blood components can be separated by centrifugation based on density
- This can be done in a centrifugation bowl, “belt” in an apheresis instrument

![Centrifugation Diagram]

- Plasma (55%)
- White blood cells and platelets (<1%)
- Red blood cells (45%)
Process Overview

- Blood is drawn from patient
- Blood is immediately mixed with an anticoagulant (typically at 1:10 to 1:14 anticoagulant to whole blood ratio)
- Anticoagulated blood pumped into a bowl/belt chamber
- Blood components separated by centrifugation according to their specific gravities
- Plasma/RBC interface maintained at steady state
- Desired component harvested /removed through outgoing tubes
- Replacement fluid added to the remaining components if plasma is removed
- Other components returned to the patient
Centrifugation Bowl or Belt

Whole blood in → Component to be removed out

Plasma
Platelet rich plasma
Leukocytes
Erythrocytes

<- Aspiration/Outflow ports
Intermittent vs. Continuous Flow

- Intermittent flow: procedure performed in cycles (withdrawal, separate, re-infuse).
  - Pro: one needle access for peripheral access
  - Con: extracorporeal volume (ECV) can be high (bad in kids and the elderly with low total blood volume or TBV), fluctuations in hemodynamics
  - E.g: Haemonetic V50

- Continuous flow: blood withdrawn, processed and reinfused simultaneously
  - Pro: smaller ECV, hemodynamic stability, faster
  - Con: 2 venipuncture sites for peripheral access
  - Examples: COBE Spectra, Fenwal C3000 Plus, Fresenius AS 104
Membrane Filtration

- Conceptually similar to hemodialysis
- Use limited to plasma exchange
- Blood is pumped to the filter membrane
- Membranes with pore sizes that can trap high MW proteins, exclude cellular elements
- Cellular components combined with replacement fluid, returned to patient
Membrane Filtration (MF) vs. Centrifugation

- Similar efficiency and safety
- Membrane filtration (MF) is faster: because time is required to set up a centrifugal interface
- Different anticoagulants:
  - Membrane filtration: heparin
  - Centrifugation: usually citrate
- MF cannot remove cellular elements, therefore use is limited to plasma exchange
- MF widely used in other areas of the world: Japan, Europe. Uncommon in the US
Adsorption Column/Selective Removal

- Plasma separated from cellular elements by centrifugation
- Perfuse plasma through a selective removal column/filter
  - Dextran sulfate column: removes LDL
  - Staphylococcal protein A: removes IgG by binding to the Fc portion
- Return to the patient
Liposorber (Kaneka)
ABOUT THE LIPOSORBER SYSTEM

The LIPOSORBER LDL-Adsorption Column

Selectively binds ApoB-containing lipoproteins (LDL, Lp(a) and VLDL). There is minimal effect on HDL or other plasma proteins.

- Dextran sulfate - cellulose bead
- LDL
- Lp(a)
- VLDL (Triglycerides)
- HDL
Prosorba

- Staphylococcal protein A bound to silica beads in the column
- Removes free IgG as well as immune complexes by binding to the Fc portion of IgG
- May have immune modulatory effects
- FDA approved for treatment of refractory ITP and rheumatoid arthritis
- Limited efficacy in ITP and RF
- No longer manufactured.
Anticoagulant: Citrate and Citrate Toxicity

- Acid Citrate Dextrose (ACD)
  - Most commonly used anticoagulant for apheresis
  - Citrate ion chelates free Ca++ ions and blocks calcium-dependent coagulation cascade
  - Ensures that extracorporeal blood remains in a fluid state
- Pros:
  - Ubiquitous compound found in all human cells, not “foreign”
  - Metabolized by liver quickly to bicarbonate, little systemic effect
- Cons:
  - Can cause transient systemic hypocalcemia (citrate toxicity), presenting with numbness, peri-oral tingling, tetany, cramping, EKG changes
Anticoagulant: Citrate and Citrate Toxicity

- Citrate toxicity exacerbated by:
  - Patient receiving additional citrate load due to infusion of FFP
  - Patient also receiving albumin as replacement fluid, which binds Ca++
  - Fast rate of infusion/return
  - Longer duration of the procedure
  - Pre-existing hypocalcemia

- Treat/Prevent By
  - Oral/IV calcium supplementation before or during the procedure
  - Increase whole blood to citrate ratio
  - Slower infusion rate
  - Stop the procedure
Anticoagulant: Heparin

- Prevents clotting by potentiating antithrombin’s activity by 1000x
- Used alone or in combination with citrate
- Required/preferred by some instruments (Liposorber LDL, photopheresis instruments, membrane filtration)
- Degree of anticoagulation similar to DVT prophylaxis (plasma concentration 0.5 to 2.0 IU/ml)
- Pro: reduce citrate dose, avoid hypocalcemia
- Con:
  - Short term systemic anticoagulation
  - Risk of inducing HIT
- Reverse overdose with protamine
Fluid Shifts

- Fluid shifts can occur when
  - When blood is removed in the beginning of a procedure
  - A blood component is selectively removed
  - Other components/replacement fluid infused

- Associated with risks of hypovolemic and vasovagral reactions

- Newer instruments (continuous flow) attempts to achieve gentler fluctuations in fluid
Fluid Shifts

- To minimize the risk of hypovolemia, limit the patient's extracorporeal (ECV) to <15% of patients' TBV at all times:
  - ECV: the “dead spaces” (tubing, chambers) of an instrument. (Range 150-500ml) that need to be filled to complete the apheresis circuit
  - TBV: 70ml/kg x body wt (kg)
- Priming the instrument with colloid solution or RBCs may be necessary for a pediatric/small pt
- Alternative: bolus saline/colloid
Replacement Fluid for Therapeutic Plasma Exchange (TPE)

- Several liters of plasma can be removed
- Volume deficit needs to be replaced by fluid infusion.
- Options:
  - Crystalloid (normal saline)
  - Colloid (albumin)
  - Plasma
Replacement Fluid for TPE

- Crystalloid (normal saline)
  - Pros:
    - Cheap,
    - No infectious/allergic risks
    - Readily available
  - Cons:
    - Hypo-oncotic, only ~1/3 stays intravascular, this may lead to intravascular fluid deficit, hypotension.
    - Therefore usually used in combination with albumin: start procedure with NS replacement, then finish with albumin replacement
    - Lacks coagulation factors/ immunoglobulins
Replacement Fluid for TPE

- Albumin (5%) (Used for most indications of TPE)
  - Pros:
    - Colloid, iso-oncotic stays intravascular,
    - No to very, very low allergic/ infectious risks
  - Cons:
    - Does not replace other protein fractions, such as coagulation factor
    - Expensive
    - Not always available, periodic national shortages of albumin can occur
Replacement Fluid for TPE

- **Plasma**
  - **Pros**
    - Iso-oncotic
    - Replaces coag factors, immunoglobulins and other plasma proteins
  - **Cons**
    - Infectious and allergic risks
    - Additional citrate load, increases risk of hypocalcemia
    - TRALI risks
    - Needs to be ABO compatible
    - Expensive
  - **Indications:**
    - Thrombotic thrombocytopenic purpura (TTP) to replace ADAMTS-13
    - Replacing coag factors in liver failure, or in patient undergoing repeated daily TPE procedures with albumin as replacement fluid
Replacement Fluid for TPE

- Cryo-poor plasma:
  - Byproduct of cryoprecipitate production
  - Made from plasma thawed at 4-6°C, after cryoprecipitate is removed, the plasma becomes “cryoprecipitate reduced”
  - Similar to plasma, except only has about ½ of the vWF, fibrinogen of FFP, normal levels of most other plasma proteins
- Pros
  - Same as plasma
  - Theoretical: better for TTP due to less high MW-vWF? (Not been confirmed by studies)
- Cons
  - Same as plasma
  - Regular plasma is still firstline therapy for TTP.
  - Cryo-poor plasma is indicated for TTP refractory to TPE with plasma
Fluid Balance

- Frequent request: “Can you take 500 cc off?”
- Possible to leave a negative fluid balance:
  Anticoagulant+Replacement Fluid < Plasma Removed
- Unlike in hemodialysis: volume removed is all intravascular, hemodynamic effects more pronounced than what’s seen with fluid removal during hemodialysis
- Must be cautious about removing larger volumes. Severe hypotension can occur
Vascular Access: Peripheral vs. Central

- **Peripheral access**
  - Use peripheral veins for access (antecubital, femoral)
  - Need large needle for both the draw (16g) and return lines (19g), to allow flow rate between 60-120ml/min for adults
  - Patient needs to have reasonable muscular tone to maintain blood flow (i.e. Squeeze/pump when asked)
  - Less invasive and faster to place
  - Good for:
    - Infrequent procedures
    - Pt with good veins and reasonable muscular tone and who are able to cooperate
Vascular Access: Peripheral vs. Central

Central Access
- For repeated procedures, critically ill patients with decreased muscle tone
- Place in subclavian, femoral, internal jugular vein commonly
- Ideal: double lumen, rigid, high flow rate, staggered ports to minimize re-circulation
- Examples: Quinton Muhurkar, Hickman,
- Requirements similar to dialysis line. Also can use AV fistula.
- Won’t work: PICC, port-a-cath, triple lumen
- Drawbacks:
  - Invasive
  - Complications: sepsis, pneumothroax, hematoma, AV fistula, arterial puncture.
  - Central line placement is an important risk factor for adverse events associated with apheresis
Effects of Plasma Exchange

- Exchange of 1 plasma volume -> net plasma exchange of 60-70%.
- Not very efficient to exchange >1.5X plasma volumes.
- Mathematical model assumes:
  - Pathogenic substance resides only intravascularly
  - No movement from the extravascular space
  - No synthesis or metabolism occurs

Plasma volume = TBV x (1-hct)
Calculating Plasma Volume

Total blood volume (TBV) x (1-Hct) = Plasma volume
6000 x 0.60 = 3600 mL

TBV 6000 mL

Plasma volume 3600 mL

RBC Volume 2400 mL
Plasma Volume Exchanged vs. % of Disease Mediators Removed

Plasma Volumes Exchanged =
% of Disease Mediator Removed =
Therapeutic Effectiveness of TPE

% Disease mediator removed

0.5 | 1 | 1.5 | 2 | 2.5 | 3
---|---|---|---|---|---
39 | 63 | 78 | 86 | 92 | 95

Plasma volumes exchanged

CaridianBCT
Removal Efficiency of TPE

- Depends on
  - Volume removed relative to the patient total plasma volume
  - Proportion of the pathogenic substance that stays intravascular
  - Rate of replenishment of the pathogenic substance by synthesis or re-equilibration with the extravascular/intracellular space

  - For example: IgG only 50% intravascular, re-equilibrates readily, therefore reduction is transient after a single exchange. Frequent daily or every other day plasma exchange usually required.
  - IgM largely intravascular, re-equilibrates and is synthesized slowly, therefore removed much more efficiently.
Effects of Plasma Exchange

- Electrolytes and small molecules like glucose: small and very transient decrease because of rapid equilibration
- Drugs: depends on volume of distribution, dosing schedule
- Proteins: recovery depends on synthesis and redistribution
  - Complement, coag factors: return to baseline 24-72 hours
  - Antibodies:
    - Variably removed. Increased infection rarely observed
    - Rebound phenomenon: TPE may actually stimulate a transient increase in synthesis
<table>
<thead>
<tr>
<th>Constituent</th>
<th>% Removed</th>
<th>% Recovered at 48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factors</td>
<td>25 – 50</td>
<td>80 – 100</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Immune globulins</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>20 – 30</td>
<td>Variable</td>
</tr>
<tr>
<td>Liver Enzymes</td>
<td>55 – 60</td>
<td>100</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45</td>
<td>100</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>
</tbody>
</table>
Coagulation Status

- Due to removal of coag proteins, immediately post exchange with albumin, will see prolonged PT, aPTT↑, and low fibrinogen
- However, bleeding complications are rare in patients without pre-existing coagulopathy
- With redistribution/synthesis, most coag factors normalizes to hemostatic levels within hours
- Avoid coag testing immediately following TPE, more informative if wait until next morning, or before the next procedure
Coagulation Status: FFP Needed?

- Routine supplementation with FFP not necessary for most patients.
- Fibrinogen replaced most slowly (but this is variable depending on patient – Fg is an acute phase reactant, elevated in many patients.
- If consecutive TPE’s with albumin replacement are performed, check fibrinogen. If falls <100mg/dL, consider increasing interval between exchanges, or supplement with FFP/cryoprecipitate.
Effects of Plasma Exchange - Cells

- Cells:

- Platelets can drop up to 33% after one single plasma volume exchange, up to 75% with multiple daily procedures.
- Returns to baseline within 2-3 days
- Sequestered platelets can be released from spleen post exchange and help count recovery
- Platelet count should be monitored in patient undergoing multiple procedures
- Transfusions rarely necessary
Adverse Reactions

- Overall rate 4-5%, higher with the first procedure
- Types of adverse reactions
  - Transfusion reactions
  - Citrate toxicity
  - Hypotension/Vasovagal
  - Access related complications
    - Infection
    - Hematoma
    - Pneumothorax
    - etc
Adverse Reactions

- Rate Varies depending on the type of procedure
  - RBC exchange 10.3%
  - TPE with FFP: 7.8%
  - TPE with albumin 3.4%
  - Leukopheresis: 7.8%
  - Autologous stem cell collection: 1.7%

- Death is rare usually due to underlying disease
  - Reported to be 1-2 per 10,000 in the French Registry.
  - 0 cases reported in >20,000 cases reported to the Swedish registry.
Citrate Toxicity

- Citrate toxicity: symptoms are due to hypocalcemia.
- Mild: numbness and tingling
- Severe: spasms (Chevostek’s and Trousseau’s signs), tetany, seizure, EKG changes
- Prevent and treat by:
  - Reduce flow/return rate
  - Increase WB to anticoagulation ratio
  - Stop procedure
  - Ca supplementation (oral, or IV 10% Ca gluconate) before or during
Other Adverse Effects

- Allergic reactions: with FFP replacement primarily
- Vasovagal/hypovolemic reactions: Associated with fluid shifts. Treat with positioning, fluid supplementation, halting the procedure
- Anaphylactoid associated with ACE inhibitors
  - ACE inhibitors prevent metabolism of bradykinin generated during procedure -> anaphylactoid reactions
  - Delay apheresis till 24-48h after last dose of ACE inhibitor
- Drug removal: Hold drugs >1 hour prior to and during apheresis
Aphresis Indication Categories (ASFA/AABB)

- **Category I**: First line therapy – proven to be effective
- **Category II**: Adjunct therapy – proven to be beneficial in some instances
- **Category III**: May be – evidence is conflicting but there is some suggestion of benefit, can be considered if conventional therapy is failing
- **Category IV**: Lack of evidence that therapeutic apheresis is beneficial, anecdotal experiences have been discouraging
- **Category P**: Pending
Category I Indications for TPE

- Guillain Barre Syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Myasthenia gravis
- Goodpasture’s
- Post-transfusion purpura
- Refsum’s disease (faulty enzymes during the alpha-oxidation of phytanic acid resulting in buildup of phytanic acid)
- TTP
Other Indications of TPE

- Rheumatoid arthritis
- Major ABO incompatible marrow transplant
- Presensitization to solid organ graft
- Cryoglobulinemia
- ITP
- Aplastic anemia
- Autoimmune hemolytic anemia
- Hemolytic uremic syndrome
- Hyperviscosity/multiple myeloma
Indications Cell Depletion Procedures

- **Category I**
  - Hyperleukocytosis
  - Thrombocytosis

- **Others**
  - Progressive MS
  - Polymyositis
  - Dermatomyositis
Indications for RBC Exchanges

- **Category I:**
  - Sickle cell disease (certain complications:
    - Acute chest syndrome
    - Stroke: prevention and treatment
    - Persistent priapism
    - Intractable pain crisis

- **Others:**
  - Protozoa infections: malaria, babesia
  - Pre-op exchange for sickle cell patients
  - Rh negative young female who received Rh+ RBCs
Photopheresis: Procedure Overview

The UVAR® XTS™ instrument draws blood from the patient. Blood is separated by centrifugation and red blood cells are returned. White blood cells are treated with methoxsalen and exposed to UVA light. The photoactivated white blood cells are returned to the patient.

Photoactivation with UVA light

Methoxsalen
Photopheresis

- Photoactivation results in crosslinking of DNA strands in treated white cells and some protein changes

- Mechanisms of action are hypothetical:
  - Apoptosis of malignant lymphocytes
  - Enhanced host immune response to malignant cells
  - General immune modulatory effects (in GVHD)
Photopheresis Indications

- **Category I**
  - Cutaneous T cell lymphoma

- **Others**
  - Acute/Chronic GVHD following stem cell transplant
  - Heart transplant rejection
The End