Disclosures

• None
Apheresis

- Greek for “to take away” or “subtract”

- Apheresis is a medical technology in which the blood of a person is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation
Humorism

• Ancient and medieval medicine believed that poisonous substance in the blood cause diseases

• Therapeutic bleeding or bloodletting was performed in all ancient cultures to treat nearly every illness
Humorism

Ayurveda

movement  ether  cold

air  vata  earth

light  kapha  cohesion

fire  pitha  water

transformation

Hippocrates

HOT  Yellow bile

DRY  Fire

WET  Blood

COLD  Air

Black Bile

Phlegm

Water
Modern Apheresis

• In 1950 Dr. Cohn, envisioned a device that would separate donor plasma for purification of albumin to be used for resuscitation of wounded soldiers in World War II

• Latham improved the design resulting in “Latham bowl”, which was used in the first apheresis instruments

Edwin Cohn
Developed cold ethanol fractionation to produce albumin

Alan (Jack) Latham, Jr.

![Apheresis Device Diagram]
Modern Apheresis

• Originally performed discontinuously
• Now performed with continuous removal and separation of blood components
• Method of separation
  • Centrifugation
  • Membrane filtration
Centrifugation
Membrane Filtration

- Only for Plasma exchange
- High flow rates to achieve transmembrane pressure
- Access via a larger vein
- Lower extraction efficiency of 27%–53%
  - 86% in centrifugation
- Less effective for higher-molecular weight proteins such as IgM, fibrinogen, and immune complexes
- Preferred by nephrologists
Apheresis Procedures

- Apheresis
  - Therapeutic
    - Exchange
      - Plasma Exchange, RBC Exchange
    - Depletion
      - Leukocytapheresis, Thrombocytapheresis, Erythrocytapheresis
    - Other
      - LDL Apheresis, Photopheresis
  - Donor
    - Removal
      - RBC, Plasma, Platelets, Granulocytes, Hematopoietic cells
Logistics

• Clinical Issues
  • Consult for therapeutic apheresis (TA)
  • Confirm indication, procedure & rationale for TA
  • Treatment plan- number & frequency
  • Clinical & laboratory end points

• Technical Issues
  • Anticoagulant
  • Replacement Fluid
  • Volume Processed
  • Vascular Access
Logistics

• Clinical Issues
  • Consult for therapeutic apheresis (TA)
  • Confirm indication, procedure & rationale for TA
  • Treatment plan- number & frequency
  • Clinical & laboratory end points

• Technical Issues
  • Anticoagulant
  • Replacement Fluid
  • Volume Processed
  • Vascular Access
TABLE II. Category Definitions for Therapeutic Apheresis

<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>
## Common Indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THERAPEUTIC PLASMA EXCHANGE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Cryoglobulinemia, symptomatic/severe</td>
<td>II</td>
<td>2A</td>
</tr>
<tr>
<td>Hyperviscosity in monoclonal gammopathies, symptomatic</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Myasthenia gravis, moderate-severe</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy (GBS)</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Neuromyelitis optica spectrum disorders, acute</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>Renal transplantation, antibody mediated rejection</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Liver transplantation, antibody mediated rejection</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Cardiac transplantation, antibody mediated rejection</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease, Dialysis independent or DAH</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis, dialysis dependence or DAH</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis, recurrent in transplanted kidney</td>
<td>I</td>
<td>1B</td>
</tr>
</tbody>
</table>
## Common Indications

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL APHERESIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hypercholesterolemia, Homozygotes</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Lipoprotein (a) hyperlipoproteinemia</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td><strong>RBC EXCHANGE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease, Acute stroke</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Sickle cell disease, Stroke prophylaxis/iron overload prevention</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td><strong>LEUKOCYTAPHHERESIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperleukocytosis, Symptomatic</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td><strong>THROMBOCYTAPHHERESIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis, symptomatic</td>
<td>II</td>
<td>2C</td>
</tr>
</tbody>
</table>
Logistics

• Clinical Issues
  • Consult for therapeutic apheresis (TA)
  • Confirm indication, procedure & rationale for TA
  • Treatment plan- number & frequency
  • Clinical & laboratory end points

• Technical Issues
  • Anticoagulant
  • Replacement Fluid
  • Volume Processed
  • Vascular Access
Plasma Exchange Circuit

- Anticoagulant
- Replacement Fluid
- Volume Processed
- Vascular Access
Anticoagulants

• Extracorporeal circuit will clot without anticoagulants

• ACD-A (most common)
  • Binds to ionized calcium
  • Metabolized rapidly (kidney & Liver)

• Unfractioned Heparin or Combination (some centers)
  • HIT
  • Bleeding
Replacement Fluids

• Crystalloid (normal saline)
  • Cheap
  • Hypo-oncotic
  • No coagulation factors or immunoglobulins

• Colloid (albumin)
  • Expensive
  • Slightly hyper-oncotic, can result in volume expansion
  • Very low risk of infectious disease transmission
  • No coagulation factors or immunoglobulins

• Plasma
  • Cheaper than albumin
  • Iso-oncotic
  • Associated risks of all blood product transfusions (infectious disease, allergic reactions, TRALI)
Volume Processed

- **Dose** = Plasma volume (PV)
- PV = BV x (1-Hct)
  = (70ml/kg x Wt) x (1-Hct)
- 1 PV = ~60% removal
- No benefit in exchanging > 2 PV

**Figure 15-2.** Theoretical depletion of soluble substances from the plasma by plasma exchange according to the one-compartment model. A fixed proportion of the remaining intravascular mass of the soluble substance is removed with each increment of plasma volume removed. (Adapted with permission from Chopel and McCullough.)
Vascular Access

• Inlet and outlet for blood flow
Options

- Peripheral Veins
- Arteriovenous Fistulas & Grafts
- Central Venous Catheters
- Venous Access Ports
Vascular Access

• Why is vascular access so important?
Adverse Reactions

• Overall well tolerated by most patients
• Rate 4-5% of TA procedures
• Common adverse reactions
  • Citrate toxicity
  • Hypotension/vasovagal
  • Transfusion reactions
Adverse Reactions

• Citrate toxicity
  • Temporary decrease in $\text{Ca}_i^{2+}$
  • Tingling, numbness, nausea
  • Calcium supplementation: calcium carbonate, calcium gluconate, calcium chloride
Adverse Reactions

• Vaso-vagal reactions
  • Pallor
  • Hypotension
  • Diaphoresis
  • Bradycardia
  • Nausea/vomiting

• More common with plasmapheresis than with cytapheresis

• ACE inhibitors exacerbate
Adverse Reactions

• Coagulation alterations
  • Daily TPE without plasma replacement can deplete coagulation factors and increase bleeding
  • Consider Plasma replacement with daily exchange and in patients with coagulation abnormalities
  • Monitor fibrinogen
Adverse Reactions

- Vascular Access
  - Hematoma
  - Clotting of line
  - Insufficient for pressures required

- Infections/sepsis
  - More problematic with central lines than with peripheral access
Vascular Access

• Associated with serious TA adverse reactions

• Can be a logistic bottle neck

• Without adequate vascular access cell separation for TA is not possible
Options

- Peripheral Veins
- Arteriovenous Fistulas & Grafts
- Central Venous Catheters
- Venous Access Ports
Determinants

- Indication for TA
- Type of TA system used
- Number and frequency of treatments needed
- Anticipated duration of treatment
Pt. already has a line, Pick One!

(A) Peripheral intravenous

(B) Midline catheter

(C) Peripherally inserted central catheter

(D) Nontunneled centrally inserted central catheter

(E) Tunneled centrally inserted central catheter
Things to Consider

• Catheter Size
  • Minimum for adequate flow rate
  • Prevent mechanical hemolysis

• Flow Rate (depends on size and length)
  • The Apheresis System’s software/ Automatic Interface Management (AIM) system controls pump flow rates and centrifuge speed to establish and maintain the required RBC/plasma interface
  • 50 mL/min (5 to 150 mL/min)
  • Determines time needed to establish interface
  • Determines time needed to complete procedure
Size x Length = Flow Rate

<table>
<thead>
<tr>
<th>Use</th>
<th>Size x length</th>
<th>~Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>20 G x 30 mm</td>
<td>50 mL/min</td>
</tr>
<tr>
<td>Blood</td>
<td>18 G x 30 mm</td>
<td>50-100 mL/min</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>16 G x 30 mm</td>
<td>200 mL/min</td>
</tr>
<tr>
<td>CV Access</td>
<td>16-18 G x 125-500 mm</td>
<td>100-500 mL/min</td>
</tr>
<tr>
<td>CV Access</td>
<td>18-20 G X 550-600 mm</td>
<td>6-30 mL/min</td>
</tr>
<tr>
<td>Midline Access</td>
<td>22-18 G X 80-100 mm</td>
<td>120-420 mL/min</td>
</tr>
<tr>
<td>CV Access</td>
<td>14-16 G x 450 mm</td>
<td>50-300 mL/min</td>
</tr>
</tbody>
</table>

Gauge Scale

<table>
<thead>
<tr>
<th>24</th>
<th>23</th>
<th>22</th>
<th>21</th>
<th>20</th>
<th>19</th>
<th>18</th>
<th>17</th>
<th>16</th>
<th>15</th>
</tr>
</thead>
</table>

French Scale

| 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 |
Vein Measurements

<table>
<thead>
<tr>
<th>Vein Type</th>
<th>Length</th>
<th>Diameter</th>
<th>Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalic</td>
<td>38cm</td>
<td>6mm</td>
<td>40-90ml/min</td>
</tr>
<tr>
<td>Basilic</td>
<td>24cm</td>
<td>8mm</td>
<td>90-150 ml/min</td>
</tr>
<tr>
<td>Axillary</td>
<td>13cm</td>
<td>16mm</td>
<td>150-350ml/min</td>
</tr>
<tr>
<td>Subclavian</td>
<td>6cm</td>
<td>19mm</td>
<td>350-800ml/min</td>
</tr>
<tr>
<td>Innominate</td>
<td>2.5cm</td>
<td>19mm</td>
<td>800-1500ml/min</td>
</tr>
<tr>
<td>SVC</td>
<td>7cm</td>
<td>20mm</td>
<td>2000ml/min</td>
</tr>
</tbody>
</table>
General Rule of Thumb

• A large bore cannula is preferable to a narrow
• A shorter cannula is preferable to a longer
• A larger proximal vein is preferable to smaller distal vein
• Upper limbs are preferable to lower limbs
• Maintain integrity of vein
• Adequate flow rate
• Avoid hemolysis due to excessive pressure
• Avoid clotting due to sluggish flow
Peripheral Veins

- Antecubital and forearm veins evaluated for adequate vascular access
- Patient preparation, hydration, warming extremity, distractions, relaxation, etc.
- Skill of RN is paramount (vein choice, access skills, warming extremity)
- Access (16-17 G, antecubital vein)
- Return (18-20 G, non-antecubital vein)
Peripheral Veins

- Centrifugation based TA
- Acute or intermittent TA
- Short-term, less frequent & shorter treatments (1-3 treatments, over 1-2 weeks)
- Outpatient treatments
- Patient’s vascular anatomy, mobility, and hygiene
- Experience/comfort level of providers
- Low rate of infections and adverse reactions, less invasive
Central Venous Catheters

Non-Tunneled CVC
- Short term (< 2 weeks) treatments
- Risk of infection/sepsis if kept for longer time
- Patient cannot bathe or swim
- Invasive
- Acute or intermittent TA

Tunneled CVC
- Long term (weeks to months) treatments
- Comparatively lower infection rates
- Patient cannot bathe or swim
- Invasive
Placement of Apheresis CVCs

• Anatomic locations:
  • Most common choices: great vessels (chest); femoral veins
  • Right IJ >> Right SC >> Left SC > Left IJ
  • Catheter tip: junction of SVC and right atrium; proximal right atrium
  • Preparation (NPO for ≥8 hours)
  • Placement verification (fluoroscopy; CXR; ultrasound; TEE)

• Who places apheresis CVCs:
  • Interventional radiologists (IR suite: scheduled; weekend: emerg only)
  • Surgeons (OR suite; scheduled: often delayed due to other surgeries)
  • Intensivists (ICU; ultrasound guidance; may be faster than IR or OR
  • Other (residents; nephrologists)
  • Tunneled CVCs (currently interventional radiologists or surgeons only)
Care of Apheresis CVCs

• Inpatient care (for nurses):
  • Intra-luminal catheter-locking agents (port patency):
    • Heparin: usually 1000-5000 U/ml (total of 5-6 ml)
    • Studies using 100U/ml; 10,000 U/ml
    • Citrate (4%)(5, 30, 47%): similar efficacy; ↓ bleeding risk & cost; no risk of HIT
    • rt-PA (recombinant tissue plasminogen activator)
    • Tego caps (non-heparin)
  • Dressing changes:
    • usually after each treatment
    • antiseptic technique (mask, etc)
    • protection of line

• Outpatient care (for patients):
  • Temporary lines (keep dressing dry/no showers; care with dislodging line)
  • Tunneled lines (first 2-3 weeks: keep dressing dry/no showers)
  • Monitoring for site infection
  • Compliance with catheter flush schedule
Tissue plasminogen activator vs heparin for locking central venous catheters between apheresis procedures

Gagan Mathur¹, Sarah L. Mott², Laura Collins³, Annette J. Schlueter³
### TABLE 1  Cost associated with performing locks

<table>
<thead>
<tr>
<th>Lock</th>
<th>Packaging</th>
<th>Costs</th>
<th>Dose per port</th>
<th>Cost per lock (two ports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant tissue plasminogen activator</td>
<td>2 mg vial</td>
<td>$38 per vial</td>
<td>2 mg</td>
<td>$76</td>
</tr>
<tr>
<td>Heparin</td>
<td>10 000 units/10 mL vial</td>
<td>$1 per vial</td>
<td>2 mL</td>
<td>$0.50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intervening line locking procedure</td>
<td>-</td>
<td>$90 per lock</td>
<td>-</td>
<td>$90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Approximately two locks per vial (8 mL for locks plus wastage).

<sup>b</sup>Approximately 60% of $151 charge per lock.

### TABLE 3  Cost of locks based on interval between extracorporeal photopheresis (ECP) procedures

<table>
<thead>
<tr>
<th>Interval between procedures (days)</th>
<th>Recombinant tissue plasminogen activator (rt-PA)</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost of rt-PA</td>
<td>IF&lt;sup&gt;a&lt;/sup&gt; needed</td>
</tr>
<tr>
<td>1-7</td>
<td>$76</td>
<td>0</td>
</tr>
<tr>
<td>8-14</td>
<td>$76</td>
<td>0</td>
</tr>
<tr>
<td>15-21</td>
<td>$76</td>
<td>0</td>
</tr>
<tr>
<td>22-28</td>
<td>$76</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>IF = intervening flush/lock (between procedures).

<sup>b</sup>Charge for the initial flush is included in the ECP procedure performed.
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant issues</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Some issues</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>No issues</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td><strong>rt-PA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant issues</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Some issues</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>No issues</td>
<td>16</td>
<td>70</td>
</tr>
</tbody>
</table>

**TABLE 2** Extracorporeal photopheresis procedure flow rate issues with heparin vs recombinant tissue plasminogen activator (rt-PA) line locks
FIGURE 1  Lack of association between central venous catheter lock interval and flow rate issues for (A) heparin locks and (B) recombinant tissue plasminogen activator locks. The numbers in parentheses below each interval (on the x axes) represent the total number of procedures within that interval.
Arteriovenous Fistulas & Grafts

- Long-term (years) treatments
- Requires trained staff for cannulation
- Requires surgery & adequate patient vascular anatomy
- 2-3 months “to mature”
- Issues with maturity & maintenance
- Lowest complications, cost & mortality rates
Venous Access Ports

• Long-term (weeks to months) treatments
• Lower infection & dysfunction rates
• Requires trained staff for cannulation
• Requires surgical placement, 2-3 weeks to heal
• Patients are free to bathe, swim, or exercise
• Can get infected & thrombosed
• Typically used for red cell exchanges & extracorporeal photopheresis
## TABLE II. Option of Vascular Access for TA

<table>
<thead>
<tr>
<th>Access Type</th>
<th>Use</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Vein</td>
<td>Short-term, less frequent and shorter treatments, large veins</td>
<td>Lower side effects, less invasive</td>
<td>Thrombophlebitis, not suitable for cases with high platelet or WBC counts, not suitable for filter-based systems</td>
</tr>
<tr>
<td>Nontunneled CVC</td>
<td>Short-term treatments, filter-based and centrifugation-based systems</td>
<td>Better BFR compared to peripheral veins</td>
<td>Risk of infection, not suitable for prolonged TA, patients cannot bathe or swim</td>
</tr>
<tr>
<td>Tunneled CVC</td>
<td>Long-term (weeks to months) treatments, filter-based and centrifugation-based systems</td>
<td>Lower infection rates compared to nontunneled CVC</td>
<td>Higher infection, malfunction and mortality rates compared to AVF, patients cannot bathe or swim</td>
</tr>
<tr>
<td>Totally implantable ports</td>
<td>Long-term (weeks to months) treatments, filter-based and centrifugation-based systems</td>
<td>Lower infection rates compared to tunneled CVC, patients can bathe, swim and exercise</td>
<td>Infection and thrombosis</td>
</tr>
<tr>
<td>AVF</td>
<td>Long-term (years) treatments</td>
<td>Lowest complication, cost and mortality rates</td>
<td>Issues with maturity and maintenance</td>
</tr>
</tbody>
</table>

*Journal of Clinical Apheresis* DOI 10.1002/jca

### Summary

A Comparison of the Advantages and Disadvantages Associated With Vascular Access Types Used in Therapeutic Apheresis (TA) Procedures

<table>
<thead>
<tr>
<th>Vascular access type</th>
<th>Indications for use</th>
<th>Advantage</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Veins</td>
<td>Centrifugal based TA Acute or intermittent TA Short term use only (&lt;2 weeks)</td>
<td>Low rate of infections Immediate use Easy to place at bedside</td>
<td>Patient discomfort Infiltration and sclerosis of veins Risks inherent to catheter insertion</td>
</tr>
<tr>
<td>Non-tunneled central venous catheters</td>
<td>Acute or intermittent TA Centrifugal or filter based TA</td>
<td>Blood flow rate high</td>
<td>Dysfunction Infection, including sepsis, and metastatic infections Central vein stenosis Risks inherent to catheter insertion</td>
</tr>
<tr>
<td>Tunneled central venous catheters</td>
<td>Short or long term use Centrifugal or filter based TA</td>
<td>Reduced infection rate when compared to non-tunneled catheters Blood flow rate high</td>
<td>Dysfunction Infection, including sepsis, and metastatic infections Central vein stenosis</td>
</tr>
<tr>
<td>Arteriovenous Fistula (AVF)</td>
<td>Chronic TA (&gt;3 months) Centrifugal or filter based TA</td>
<td>Lowest infection and dysfunction rates compared to other vascular access types</td>
<td>Requires surgery and adequate patient vascular anatomy Requires a maturation period before use (~6–8 weeks) May be associated with primary maturation failure and subsequent need for additional procedures</td>
</tr>
<tr>
<td>Arteriovenous grafts (AVG)</td>
<td>Chronic TA (&gt;3 months) Centrifugal or filter based TA</td>
<td>Lower infection and dysfunction rates compared to catheters Most AVGs may be used within 2 weeks of placement</td>
<td>Requires trained staff for cannulation Requires surgery Higher infection/thrombosis rates compared to AVFs</td>
</tr>
</tbody>
</table>
Conclusions

• Therapeutic apheresis is frequently used for management of various disease processes

• Vascular access is an important logistic & clinical issue to consider when evaluating a new patient for TA

• Main determinants of vascular access for TA depend on type of procedure; acuity; number, frequency, and anticipated duration of treatment; patient’s vascular anatomy; and providers’ comfort level

• Proper maintenance of peripheral & central access is needed to maintain adequate access and minimized adverse reactions
Questions
Thank You....