Apheresis Therapies:
Overview and Prescription

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Disclosures

Consulting/Lecturing Honorarium
- Terumo BCT
- Fresenius Kabi
- Angiodynamics

Principles of Apheresis

- Derives from Greek: “to carry away”
- Whole blood is taken and separated in an extracorporeal circuit (either membrane or centrifuge)
- Desired portion can be removed or treated, and remainder returned to patient
The first published description of plasmapheresis, in J. Pharmacol Exp Ther. 5:625, 1914.

>100 Years of Plasmapheresis

Principles of Apheresis

- Apheresis in the USA:
  - Blood Bank/Pathology
  - Nephrology
  - Hematology
- Use:
  - Collections
    - Donated plasma, red cells, & platelets
    - Stem cell collection
  - Therapy
    - Removing undesired substance from plasma:
      - Antibodies, lipids, etc
    - Reducing excess platelets/WBC
    - RBC exchange
    - Photopheresis

Terminology

- Apheresis (no longer “Pheresis”)
- Plasmapheresis
  - Therapeutic Plasmapheresis
  - Therapeutic Plasma Exchange or Total Plasma Exchange (TPE)
  - Plasma Exchange (PLEX, PEX, PE)
- Cytopheresis
  - Thrombocytapheresis
  - Leukocytapheresis or leukapheresis
  - Erythrocytapheresis (RBC exchange, RBCx, RCE)
- Photopheresis
  - Extracorporeal photopheresis or extracorporeal photopheresis (ECP)
Indications – American Society for Apheresis (ASFA)

ASFA “Special Issue” or ASFA Guidelines
Published every three years

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, Anward Abdalnasser, Kristy Agui, Robert A. Heffernan, Laura Carty, Mark J. Stuss, George M. Brown, Ronald P. Herman, Yelena P. M., and Beth A. Stricker

ASFA Indications

- Category I: apheresis 1st line therapy
  - Guillain-Barre & TTP
  - Myasthenia Gravis + immunosuppression
- Category II: apheresis 2nd line therapy
  - Acute disseminated encephalomyelitis (ADEM) after high dose steroid failure
  - ECP for refractory GVHD
- Category III: role of apheresis unclear
  - ECP for NSF, TPE for sepsis
- Category IV: apheresis ineffective or harmful
  - Acute rheumatoid arthritis, schizophrenia

87 diseases / 179 indications (from 78 in 2013 & 68 in 2010)
Plasmapheresis: Rationale

- Removal of a circulating factor
  - Antibodies, monoclonal protein, immune complex, alloantibody, toxins
  - Removal of other inflammatory proteins
    - C3, C4, activated complement products, fibrinogen, cytokines
  - Shift in the antibody-to-antigen ratio
  - Cryoglobulinemia in HCV
  - Infusion of normal plasma
    - Replace a deficient plasma component (TTP)

Not all autoantibodies behave equally

<table>
<thead>
<tr>
<th>Glomerular Disease</th>
<th>Pathogenic autoantibody reacts with</th>
<th>Evidence based use of TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM (Goodpasture’s)</td>
<td>α chain non-collagenous domain of type IV collagen</td>
<td>TPE when Cr &lt; ~6 or with DAH</td>
</tr>
<tr>
<td>ANCA GN (Wegener’s)</td>
<td>Neutrophil lysosomal proteins (myeloperoxidase, proteinase 3)</td>
<td>TPE only if Cr &gt; ~6 or need for HD</td>
</tr>
<tr>
<td>Membranous GN (primary idiopathic)</td>
<td>M-type phospholipase A2 receptor on podocyte foot process</td>
<td>TPE almost never indicated</td>
</tr>
</tbody>
</table>

Sanchez & Ward, Seminars in Dialysis—Vol 25, No 2 (March–April) 2012, pp. 119–131 (modified)
Plasmapheresis as First Line Therapy  
(Category I ASFA Indication)

1. Thrombotic thrombocytopenic purpura (TTP)
2. Hyperviscosity in monoclonal gammopathies
3. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
4. Myasthenia Gravis (moderate-severe, and pre-thymectomy)
5. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
6. NMDA-R encephalitis
7. TMA associated with tirofiban and complement Factor H autoantibody
8. Paraproteinemis demyelinating polyneuropathies (IgG/IgA/IgM)
9. ANCA associated glomerulonephritis & DAH (Wegener’s, Microscopic Polyangiitis)
10. Anti-glomerular basement membrane disease (Goodpasture’s)
11. FSGS recurrent in transplant, aHUS, renal transplant Allo med rejection
12. Liver transplant, desensitization ABO iD; acute liver failure – HV TPE
13. Wilson disease (Fulminant)

Centrifugal Plasmapheresis: Mechanisms

More dense elements on bottom and less dense at top

Kits designed to remove specific cell layer based on specific gravity

Centrifugal Therapeutic Plasmapheresis in the USA

COBE SPECTRA  
Spectra OPTIA  
FENWAL AMICUS
Membrane Based Plasma Separators in the USA

LDL Apheresis on Kaneka Liposorber

Plasmapheresis Prescription: Calculating the Plasma Volume

1) Blood volume: Weight (kg) x 55-75 ml/kg
   - 70 kg man x 70 ml/kg = 4900 ml

2) Plasma Volume: Blood volume x (1-Hct)
   - If Hct 40% then:
     - 4900 x (1 - 0.4) = 2940 ml
     - or “a 3 Liter exchange” = one plasma volume
   - In general, exchanges range between 2L and 5.5L for adults

<table>
<thead>
<tr>
<th>Patient</th>
<th>Obesity</th>
<th>Sex</th>
<th>Height</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Gilcher’s Rule of Five

Removal Kinetics of Plasmapheresis

[Graph showing efficiency of immunoglobulin removal by TPE depending on plasma volume exchanged]

Frequency of Apheresis Treatments

- Distribution space of the substance
  - IgG: 50% intravascular
  - IgM: 80% intravascular
  - Red cells – only intravascular
- Size of substance
- Synthetic and catabolic rates
  - Half life
    - IgG ~21 days
    - Due to long half life, immunosuppression may take weeks to work
    - Fractional catabolic rate of IgG is not constant, and is lower at low plasma concentrations
  - IgM ~5 days

Plasmapheresis Prescription

- Frequency of Procedure

Two Compartment Model

Daily TPE, 1.2 x TPV, T½ = 21 days; 2-compartment

Other plasma constituents removed with TPE

- Immunoglobulins: IgG (large volume of distribution), IgM (largely intravascular)
- Coagulation factors (fibrinogen, etc)
- Platelets (small degree)
- Electrolytes (K, Mg)

***important caveat of patients undergoing TPE therapy: check all necessary labs PRIOR to therapy!!! (antibody levels, C3/C4, ADAM15 etc)

Plasmapheresis Prescription

Replacement Solutions:
- MUST be isotonic and isosmotic
- 5% albumin
- Can use some normal saline, but not more than ~1/3rd of total replacement
- Plasma replacement
  - Single-donor plasma (FFP), cryoprecipitate reduced plasma (cryosupematant plasma), solvent/detergent-treated pooled plasma (ie Octoplas)

Plasmapheresis Prescription

- Plasma replacement
  - Full plasma replacement if TTP
  - Removing an antibody/inhibitor
  - Replacing deficient ADAM15 enzyme
- Some amount of plasma
  - FFP contains similar concentrations of all clotting proteins except Factor VIII
  - 1 unit of FFP raises fibrinogen about 15mg/dL in a 70 kg man
  - DAH, imminent surgery or procedure
  - Low starting fibrinogen (case by case basis)
Plasmapheresis Prescription: Access & Anticoagulation

<table>
<thead>
<tr>
<th>Access</th>
<th>Centrifugal</th>
<th>Membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIV, dialysis</td>
<td>Dialysis</td>
<td>Heparin</td>
</tr>
<tr>
<td>catheter, port,</td>
<td>catheter</td>
<td>3000 unit LO,</td>
</tr>
<tr>
<td>or AVF/AVG</td>
<td>or AVG/AVF</td>
<td>1500 U/hr</td>
</tr>
</tbody>
</table>

Plasmapheresis Prescription: Citrate Anticoagulation

- Given at a ratio of incoming blood: ie 14:1 = WB to AC
- Anticoagulation-citrate-dextrose solution (ACD-A)
  - Most commonly used. ACD-A contains 3% citrate (112 mmol/L of citrate or 21.3 mg/mL)
  - AKA acid-citrate-dextrose-formula A
- ACD-B: 2% citrate (68 mmol/L or 12.8 mg/mL)
- Sodium citrate has 4% citrate (136 mmol/L, citrate or 25.6 mg/mL)
  - Used in continuous renal replacement therapy (CRRT) primarily

Plasmapheresis Prescription: Citrate Anticoagulation

- Citrate binds iCa that is necessary for clotting factors
- Citrate metabolized by liver almost immediately upon return
- Calcium given to patient peripherally so only the circuit experiences anticoagulation and low iCa
  - Continuous infusion
  - Periodic bolus
  - Chewable TUMS
Example TPE Prescription #1

- Diagnosis: Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barre)
- Access: PIVs
- Volume to remove: 3000 mL
- Replacement solutions: 3000 mL of 5% albumin
- Anticoagulation: ACD-A 12:1
- Calcium gluconate or calcium chloride via return line at ~8 meq/hr
- Frequency: every other day x 6 treatments
- Labs: CMP with Mg, CBC, fibrinogen prior to start
- Post Labs: K, Mg, Ca, fibrinogen

Example TPE Prescription #2

- Diagnosis: TTP
- Access: Tunneled or temporary catheter
- Volume to remove: 3000 mL
- Replacement solutions: 14 units FFP
- Anticoagulation: ACD-A 14:1
- Calcium gluconate or calcium chloride via return line at ~8 meq/hr
- Frequency: daily
- Pre-Labs: LDH, CMP, CBC with diff
  - Additional labs: ADAMTS 13 activity level AND inhibitor prior to 1st treatment
- Post Labs*: LDH, CBC, K/Mg/Ca

*Not fibrinogen as giving FFP

Cytapheresis

- RBC exchange, white cell depletion or collection, platelet depletion
- Must be done on a centrifugal system
- For white cell collections and depletions, often processing 2-3x TBV
- Citrate for anticoagulation: ACD-A

Cytapheresis

- Frequency
  - RBC exchange:
    - acute – may be 1 treatment
    - chronic - may be a monthly treatment
  - WBC depletion – typically 1-2 treatments
  - WBC collection, stem cell collection: 1-4 treatments typically
  - Platelet depletion: 1-2 treatments

Extracorporeal Photopheresis (ECP)

- FDA approved for CTCL, but useful in other cell-mediated immune disorders
- Mechanism:
  - Leukapheresis via a centrifugal machine (~10% of WBC)
  - 8 methoxypsoralen injected into WBC product
  - Photocytokinesis of WBCs by UV-A light in an external chamber
  - Treated leukocytes then returned to patient
ECP: A Unique Extracorporeal Therapy

- One size fits all treatment
- Process 1500ml of whole blood
- Collect ~10% circulating WBCs
- No replacement solutions
- Actual cell modification therapy – not a removal
- Extracorporeal volume is not set
- Lower the Hct the higher the extracorporeal volume

ECP: A Unique Extracorporeal Therapy

- Single or double needle access can be used
- Low blood flow rates: 25-30mL/min
- Heparin for anticoagulation
  - 10,000 units of heparin in 500mL of NS given at a rate of 10:1
  - Citrate protocols exist
- Generally, a pair of treatments are done weekly to every other week

LDL Apheresis

- Kaneka Liposorber FDA approved in 1996
- ONLY selective apheresis column available in the USA
- Process 1.5x plasma volume
- No replacement solutions
- PIVs, ports, AVF/AVG, catheters
- Heparin anticoagulation: loading dose 25 units/kg then repeat hourly
- Frequency: ~every 2 weeks
Thank You!

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UCSD Apheresis moving soon to the new Outpatient Pavilion in La Jolla
Apheresis Access and Complications

Robyn Cunard, M.D.

Access Options

- Peripheral Vein
- Subcutaneous Venous Access Device
- Arteriovenous fistula
- Arteriovenous graft
- Central Venous Catheter

UCSD Plasmapheresis: 2011-2016

- 834 inpatient and 12,100 outpatient TPE procedures
- Risk factors that increased need for central venous access (CVA):
  - Higher BMI
  - Female sex
  - Initiation as an inpatient
- Age, number of procedures, and duration of tmt did not significantly impact the successful use of peripheral venous access
Peripheral Veins

- 16-20 GA semi-rigid needles (angiocatheters)
- Provides BF 80-100mL/min
- Use warmer, supine position, tell patient to be well hydrated

Pros:
- Can be done immediately
- Low risk of serious complications (infections, bleeding)

Cons:
- Patient discomfort
- High risk of minor complications
- Venous infiltration
- Thrombosis and sclerosis of veins
- Cannot be used for filter based TPE

Trans-Illuminator Vein Finders

**Advantages**
- Increases the visibility of veins eligible for cannulation
- Does not require a significant investment of time to learn technology

**Disadvantages**
- Many studies show no significant difference in the rate of successful IV placement
- Does not show depth of vessel

Ultrasound guided PIV

**Advantages**
- Allows visualization of deep veins
- Distinguishes veins from arteries
- Can be used for peripheral access and return
- Improves vascular access success in black patients

**Disadvantages**
- Equipment is expensive
- Traditional apheresis needles may not be long enough
- Learning curve can be long and steep
A successful model to learn and implement ultrasound-guided venous catheterization in apheresis

- Danish study
- 6 nurses trained in median 48 days (17/18g)
- No CVC was placed because of failure of PIV access
- In post-implementation phase CVC's were placed
  - Central line already in place (in ICU)
  - US machine not available

<table>
<thead>
<tr>
<th></th>
<th>Pre-implementation</th>
<th>Post-implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of apheresis procedures, n</td>
<td>251</td>
<td>325</td>
</tr>
<tr>
<td>No failures for CVC, n (%)</td>
<td>120 (48.0)</td>
<td>36 (12.3)</td>
</tr>
<tr>
<td>Rate of difficult PIV placement, n (%)</td>
<td>16 (6.4)</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td>Bloodstream infections, n (%)</td>
<td>7 (2.8%)</td>
<td>14 (4.4)</td>
</tr>
<tr>
<td>Severe graft displacement, n (%)</td>
<td>12 (4.8%)</td>
<td>28 (9.0%)</td>
</tr>
</tbody>
</table>

The number of apheresis procedures and CVCs for apheresis procedures was counted over a 5 month period both in 2010 and 2011. In between the time periods the discussed problems were implemented in a central unit in the department. The number of CVCs was reduced noticeably after the implementation of ultrasound guidance and central skills.

Subcutaneous venous port

- Newer ports are MRI-compatible
- Pain
- Life of 150-200 accesses (16-18g) Vs. 2000 (Huber needle)
- Coring needles reduce the lifespan
- Bloodstream infections (0.15/1000 catheter days)
- Catheter-induced venous thrombosis (0.11/1000 cd)
- Catheter migration/flipping (0.04/1000 catheter days)
- Overall explant rate of 6.1%
- Flush with Heparin after each use and at least monthly
Use of a Dual Lumen Port for aRCE in adults with Sickle Cell Disease

- More complications
- Inlet speed was slower and duration longer than PV access

[Table]

Doc, my port feels squishy
Non-tunneled Central Vein Catheters
- Anticipated duration of treatment < 2 weeks (usu inpatient)
- May be inserted at the bedside
- 10-13.5F
- Usually polyurethane
- Soft silastic catheters not suitable → high likelihood of collapse due to negative pressure produced by the pump
- May be used in centrifugal or filter based TA
- Most often double lumen hemodialysis catheter
- Higher risk of infection c/w peripheral veins or TC
- Risk of central vein stenosis

Tunneled Central Vein Catheters
- Internal Jugular Vein
  - Preferred
  - Risk of venous stenosis 10-26%
- Femoral Vein
  - Potentially higher risk of infection (seems to be BMI dependent)
  - Highest risk of thrombosis * (25%)
  - Limits patient mobility
  - Higher risk of re-circulation
- Subclavian vein
  - Highest risk of central vein stenosis * (40%)
  - PTX (SCV>IJV)

Central Vein Catheter Dysfunction
- Early (< 2 weeks)
  - Poor tip orientation
  - Kinking
- Late (> 2 weeks)
  - Thrombosis:
    - 4-6.5 episodes/1000 days in HD patients
    - Catheter loss 1.8-3.6/1000 days in HD patients
    - R atrial thrombus (rare, but high mortality rate)
    - Fibrin sheath formation
- Preventing catheter dysfunction: catheter locks
  - Heparin
  - Citrate (lower bleeding risk, lower cost and no HIT)
  - TPA (reduces risk of infection and dysfunction, but $$$)
  - Colcemid (effective when INR 1.5-2.0)
Complications of Central Lines

- Central Vein Thrombosis
  - Prolonged use
  - Subclavian Vein
  - Increased risk with pacemakers/ICDs, PICCs

Tunneled Catheter: Blood Stream Infection

- If hemodynamically unstable
- If Staph aureus, Pseudomonas, Fungus
- If exit site or tunnel infection
- If blood cultures + after 72 hours of abx
- Catheter exchange over the wire
- Systemic antibiotics and catheter lock: overall success ~75%
  - 87-100% in GN infections
  - 75-84% in S. Epidermidies
  - 61% in Enterococcus infections
  - 46-50% in S. aureus
- Lock solution consists of antibiotic (same as systemic) + heparin
  - Continue for 2-3 weeks
  - If fever persists for >3 days or bacteremia persists → remove line
- Systemic antibiotics alone not sufficient to treat line sepsis
  - Cannot eradicate bacteria imbedded in biofilm

Prevention of catheter related bacteremia

- Protocol with aseptic technique to access catheter
- Chlorhexidine gluconate (different strengths) better than povidone-iodine in ICU Study
- No data comparing chlorhexidine gluconate with other solutions in dialysis patients
- Chlorhexidine gluconate-impregnated sponge dressing
- Topical antimicrobial agents: povidone-iodine ointment, mupirocin, polymyxin decrease risk of bacteremia but there is concern for development of high level of resistance to topical agent
- Lock solutions decrease risk of bacteremia but are associated with higher rate of antibiotic resistance
- Elimination of S. aureus nasal carriage associated with lower rate of bacteremia but emergence of resistance
Complications AVF

- Aneurysm: median rate (1.5% per year)
- Infection 0.02-0.11 per 1000 patient days
  - Button hole higher than rope ladder cannulation
- Steal 0.05 events per 1000 days
  - Worse with upper arm AVF
- Thrombosis 0.24
- Endovascular interventions: 0.82 events per 1000 pt days
- Surgical interventions 0.19 per 1000 pt days
- Bleeding
- High CO
- Hematomas

Failure of AVF in Apheresis

- 16 pts: Maturation rate 37.5%; patency rate at 1 year was 25%
- Mean primary patency was 236 days (range 10-878), with secondary patency achieved in three patients adding a mean of 174 days (range 2-517).
- Apheresis patients usu do not have platelet dysfunction
- Many of our apheresis patients are on steroids
- Difficulty in monitoring access issues
  - Transonic Hemodialysis Monitor/Preventix on-line clearance monitoring
AVF for aRBC exchange in patients with SCD...

- SCD patients
  - Prothrombotic
    - Endothelial dysfunction
    - Hypercoagulable
    - Leukocyte and platelet activation
- 26 pts with AVF, mean AVF lifespan 51 mos
- Nineteen patients (73%) had complications
  - 0.36 stenosis per 1,000 AVF days
  - 0.37 thrombosis per 1,000 AVF days
  - 0.078 infections per 1,000 AVF days

Adverse Events in Apheresis: An update of the World Apheresis Association Registry Date

- 50,846 procedures in 7142 patients (42% women)
- More AE during first procedures (8.4% vs. 5.5%)
- More than 50% of mild AE were related to access problems
- Hypotension most common if albumin used
- Urticaria most common if plasma used
- No death reported
  - Previous reports of 0.05% death rate (1994)
- Interruption of treatment for severe AE 168 procedures
- Therapeutic apheresis using filtration techniques had more complications than centrifugal (11% vs. 6%)
- Center experience

Severe AE in 4/1000 procedures

Effect of Diagnosis on AE

<table>
<thead>
<tr>
<th>Field of diagnosis</th>
<th>% of all proc.</th>
<th>Mild AE</th>
<th>Moderate AE</th>
<th>Severe AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinology</td>
<td>12.0</td>
<td>1.22</td>
<td>0.47</td>
<td>0.30</td>
</tr>
<tr>
<td>Neurology</td>
<td>17.0</td>
<td>0.05</td>
<td>0.17</td>
<td>0.45</td>
</tr>
<tr>
<td>Malignancy</td>
<td>14.7</td>
<td>0.16</td>
<td>0.45</td>
<td>0.22</td>
</tr>
<tr>
<td>Hematology</td>
<td>2.0</td>
<td>0.20</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Hematology</td>
<td>8.0</td>
<td>0.20</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Organ rejection</td>
<td>7.1</td>
<td>0.05</td>
<td>0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>Renal</td>
<td>2.5</td>
<td>0.05</td>
<td>0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>Transplantation &amp; donors</td>
<td>2.0</td>
<td>0.22</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>1.0</td>
<td>0.22</td>
<td>0.33</td>
<td>0.09</td>
</tr>
<tr>
<td>Neurology</td>
<td>1.8</td>
<td>0.15</td>
<td>0.39</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Total N = 47,556 (reference)

More than reference: **p < 0.001**, *p < 0.01, *p < 0.05, Less than reference: ***p < 0.001, **p < 0.01, *p < 0.05.
## Table 5
**Most common findings of mild specified AEs/10,000 procedures.**

<table>
<thead>
<tr>
<th>Symptom, reason</th>
<th>AE/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access problems</td>
<td>130</td>
</tr>
<tr>
<td>Hypotension</td>
<td>36</td>
</tr>
<tr>
<td>Tingling</td>
<td>19</td>
</tr>
<tr>
<td>Device problems</td>
<td>17</td>
</tr>
<tr>
<td>Urticaria</td>
<td>12</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Hemorrhage at procedure site</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Fuss</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
</tr>
<tr>
<td>Shivering, fever</td>
<td>2</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
</tr>
</tbody>
</table>

Access issues usually reinsertion of needle

## Table 6
**Most common findings of moderate specified AEs/10,000 procedures.**

<table>
<thead>
<tr>
<th>Symptom, reason</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tingling</td>
<td>174</td>
</tr>
<tr>
<td>Urticaria</td>
<td>45</td>
</tr>
<tr>
<td>Hypotension</td>
<td>30</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Technical problems</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
</tr>
<tr>
<td>Chills and fever</td>
<td>6</td>
</tr>
<tr>
<td>Flush</td>
<td>5</td>
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</tbody>
</table>

## Table 7
**Severe adverse events (primary reason is 198 procedures) resulting in un-**
**satisfaction of patients given as specified AEs/10000 procedures.**

<table>
<thead>
<tr>
<th>Symptom, reason</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, syncope</td>
<td>11</td>
</tr>
<tr>
<td>Urticaria</td>
<td>6</td>
</tr>
<tr>
<td>Access problems</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, intens</td>
<td>2</td>
</tr>
<tr>
<td>Tingling, intens</td>
<td>2</td>
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<td>Acne</td>
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<tr>
<td>Respiration, poor</td>
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<td>Quincke's release</td>
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<tr>
<td>Technical problems</td>
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<tr>
<td>Renal pain</td>
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<tr>
<td>Back pain</td>
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<tr>
<td>Epiglott</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Sphen</td>
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<tr>
<td>Acute neurovascular</td>
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<tr>
<td>TIA/MI-related pain</td>
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<tr>
<td>Acroanaphylax</td>
<td>0.2</td>
</tr>
<tr>
<td>Cerebrovascular bleeding</td>
<td>0.2</td>
</tr>
<tr>
<td>Acute respiratory distress</td>
<td>0.2</td>
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<tr>
<td>Adherence to drug</td>
<td>0.2</td>
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<tr>
<td>Pneumothorax</td>
<td>0.2</td>
</tr>
<tr>
<td>Anxiety + hyperventilation</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Citrate Induced Hypocalcemia: Risk Factors

- Distal extremity or perioral tingling and paresthesias
- Prolonged QT/Arrhythmias (? Need for baseline EKG)
- Higher risk:
  - Older age, females
  - Lower body wt (BV < 4L)
  - Pre-existing cardiac dysfunction (?loop diuretics)
  - Neuromuscular dysfunction: MG
  - Hepatic +/- renal insufficiency
- Low baseline albumin
  - Manufactured albumin is stripped of Ca, thus Ca-avid
- Patients receiving FFP as replacement fluid
  - 14% citrate by volume or ~7mmol citrate/unit or ~50 mmol citrate/h vs. 14 mmol/h
  - FFP has a 4.8% incidence of hypocalcemic symptoms
- Longer and larger volume procedures
  - Citrate line can become disengaged from pump

Citrate-induced Hypocalcemia: Treatment

- Mild
  - slow the blood flow rate (and citrate rate)
  - Increase calcium infusion rate
  - In future can use ACD-B
    - ACD-B: 3% citrate (68 mmol/L or 12.8 mg/mL)
  - ACD-A: 3% citrate (112 mmol/L of citrate or 21.3 mg/mL)
- Moderate or Severe,
  - IV calcium (gluconate 94 mg elemental Ca/g, calcium chloride 270 mg/g)
  - Need central line for calcium chloride push
  - pause treatment to allow catabolism of citrate
  - H~ hepatic metabolism: half-life of infused citrate is 36 ± 18 minutes
  - If not better, or if hypotension,
    - do not restart treatment (no more citrate) until recovered
    - measure ionized Ca~ and total Calcium
    - if ionized Ca~ < 0.9 mmol (3.6 mg/dl), no more citrate until corrected
    - Add heparin to citrate
      - WB:citrate ratios are lowered to 25 to 1:30 and heparin is given by bolus dosing (20-40 IU/kg) followed by continuous infusion (0.1-0.5 IU/kg/min)
      - heparin can be added to ACD solutions (5000 units in 500 mL, ACD-A bag) and infused at a WB:AC ratio of 1:25
**Metabolic Alkalosis**

- Induced by citrate esp when FFP used as replacement
- Liver metabolizes citrate to bicarbonate
- Bicarbonate is excreted by kidneys
- Metabolic alkalosis can occur in patients with CKD
- Metabolic alkalosis can worsen hypokalemia
- If patient undergoing dialysis, administer TPE first followed by HD

**Hypomagnesemia**

- Can be due to citrate or independent
- Mg⁺ has similar affinity to citrate as calcium
- Mg⁺ levels can decrease by as much as 30-50%
- Symptoms similar to those of hypocalcemia
- Muscle spasm, weakness, decreased cardiac contractility, and decreased vascular tone
- Fall in magnesium more rapid and lasts longer than Ca
- May be related to increased urinary excretion of Mg
- Coronary artery vasospasm → chest pain and arrhythmias
- Severe reductions (~50%) in Mg reported in liver failure patients within 30 minutes on TPE
- Levels recover to 80% 2 hours after treatment
- Treat with Magnesium Sulfate 2 gm IV

**Electrolyte Abnormalities**

- Hypokalemia
  - 5% albumin has <2mmol/L of potassium
  - NS has no potassium
  - 5% albumin will result in 25% reduction of serum K immediately post TPE
- Aluminum toxicity
  - 5% albumin has 4-24 mmol/L of aluminum
- Hyperglycemia (dextrose)
- Transient hyperparathyroidism
Hypotension

- Delayed or inadequate volume replacement
- Vasovagal episode
- Hypo-oncotic fluid replacement: at least 2/3-3/4 albumin
- Anaphylaxis
- Transfusion-related lung injury
- Bradykinin reactions (ACE inhibitors)
- Hemorrhage
- Cardiac arrhythmia: citrate/Ca/Mag/hypokalemia (digoxin)
- Anti-IgA Abs (IgA-deficient patient)
- Endotoxin-contaminated replacement fluids
- Sensitivity to ethylene oxide
- Pulmonary Embolus
- Disease-related hypotension
  - GBS: autonomic dysfunction
  - Waldenstrom macroglobulinemia – rapid decrease in plasma volume

Depletion coagulopathy

- After a single plasma exchange ↑PT by 30% and ↑PTT by 100%
- PTT returns to normal within ~ 4 hours and PT within ~ 24 hours
- After a single plasma exchange ↓fibrinogen and anti-thrombin III by 60%.
  - 2-5-4 days for recovery
- Rebound is biphasic, rapid initial increase in 4 hours followed by slower increase over the next day(s)
- With several daily TPE treatments, recovery time might take several days

Coagulation Abnormalities

- Depletion coagulopathy
  - Avoid high doses ASA/NSAIDs
- Thrombocytopenia
  - Loss of platelets in discarded plasma
  - Thrombosis within the plasma filter
  - Mild dilutional effect by the infusion of replacement fluid
  - Potential HIT with heparin
- Anemia
  - Treatment related hemolysis
  - High membrane pressure
  - Hypotonic priming solution in centrifugal system
  - Dilution of 25% albumin with distilled water
  - AKI, shock, death
- Thrombosis
  - Complications of heparin
    - HIT
    - Hemorrhage
Anaphylactoid Reaction

- Usually associated with FFP
  - FFP has a two-fold higher risk of adverse events than albumin
  - Underlying disease state is a confounding factor
- Symptoms: fever, rigors, urticaria, wheezing, hypotension, laryngospasm
- Incidence: 0.02-21% – similar with cryo
- Anaphylactoid reactions to albumin are rare
  - May be associated with the formation of antibodies to polymerized albumin created by heat treatment
- Complement-mediated membrane biocompatibility/sensitivity to ethylene oxide
- Premedicate: Diphenhydramine 25mg and Acetaminophen 650mg
  - If reaction to FFP, premedicate with extra Diphenhydramine and 100 mg of IV hydrocortisone, H2 blockers
  - Some centers use oral Prednisone 50mg given 13 hours, 7 hours, and 1 hour before each treatment
  - Epinephrine 0.3-0.5mL SQ (1/1000 solution) in life threatening reaction

Mokrzycki M et al, Am J Kidney Dis, 1994

Transfusion-Related Lung Injury (TRALI)

- Antibodies from plasma of a single donor react to antigens on leukocytes of the recipient
  - Leukoagglutination in pulmonary circulation → noncardiogenic pulmonary edema and hypotension
- Severe pulmonary damage
- Progresses over 6 hours after infusion of blood products
- Treatment is supportive
- Mortality 10-15%

Silliman CC et al., Blood Rev, 2009

Infections

- Immunoglobulin Depletion
- Viral Transmission in FFP
- Access Related
- Exacerbated by use of Rituximab/Ocrelizumab
- Hospital-related
**Immunoglobulin Depletion**

- One plasma volume exchange will reduce serum Immunoglobulin level by 60% and will ↓ net Immunoglobulin level by 20%

- Reduced Immunoglobulin levels from multiple treatments will persist for several weeks
  - Half life of IgG is 22 days

- Can restore normal immunoglobulin levels with single infusion of IVIG at 10-400mg/kg

  Kaplan-AS, Semin Dial, 2007

**Drug Removal with TPE**

- protein binding (>75%)
- Small volume of distribution (<0.3 L/kg)
- Better to administer after treatment

  J Clin Apher 2011, 26:243

**Summary**

- Most large registries report a relatively low incidence of adverse events (5-12%)
- Apheresis can be associated with minimal to potentially fatal adverse events
- Adverse reactions are substantially more common with FFP than with albumin
- The most frequent problems are access-related, citrate-induced paresthesias, hypotension, and urticaria
- More serious complications (anaphylactoid reactions) typically associated with FFP
- The overall incidence of death associated with apheresis is <0.05%
  - Higher risk with FFP (? Replacement vs. disease)
- The interdisciplinary collaboration between the iv team, apheresis and clinical hematology teams is paramount to optimize the safe care of patients
Centrifuges, Filters and Columns

David M. Ward, MD, FRCP, HP(ASCP)
Emeritus Professor of Clinical Medicine,
Division of Nephrology and Hypertension, UCSD

Thursday, February 22nd, 2018
9:20 – 9:45 am

6th Annual UC San Diego
Essentials and Advances in Apheresis Therapies

DISCLOSURES:
The speaker has the following potential conflicts
- TerumoBCT, Inc. – Honoraria, Consulting
- Fresenius Kabi, Inc. – Consulting

OUTLINE:
- Manual plasma exchange
- Continuous-flow centrifugation
- Discontinuous-flow centrifugation
- Membrane plasma separation
- Secondary plasma purification devices, columns, etc.
- Choice of plasmapheresis system
Yurevich VA and Rosenberg NK. On the question of cleansing the blood outside of an organism and the viability of red blood cells. *Russkiy Vrach (Russian Physician)*, Vol XIII, no. 18, page 637, 1914

**History of manual plasma exchange**

**In animals:**
- In France, circa 1902.
- Yurevich VA and Rosenberg NK (1914, Saint Petersburg)
- Abel JJ, Rowntree LG and Turner BB (1914, Baltimore)
- Whipple and others (1920-1940): 
  - Established safety of frequent plasma exchange in animals.

**In humans for plasma donation:**
- From volunteer plasma donors, a military need in wartime (1944)
- To establish a civilian plasma transfusion service (1950-1960)

**In humans for therapeutic purposes:**
- For a woman in renal failure (1909, Paris)
- For autoimmune hemolytic anemia (1955)
- For Waldenstrom’s macroglobulinemia (1960)

### Development of centrifugal apheresis systems

**Continuous-flow centrifuges**
- NCI-IBM prototype (1965) (became IBM 2990-6)
- Aminco Celltrifuge (1970)
- IBM 2997 (1978) (became Cobe 2997)
- Fenwal Celltrifuge II
- Cobe Spectra
- Terumo Optima
- Fenwal Amicus
- etc.

### Development of continuous-flow centrifugal apheresis

**Aminco Celltrifuge as used in Glasgow circa 1973**

- Reusable centrifuge bowl (sterilized between uses)
- Two circular ceramic plates with corresponding concentric grooves

---

**Diagram:**

- Underside of top ceramic plate
- Topside of lower ceramic plate
- Concentric grooves match up to convey fluids in and from the centrifuge
- Tubes connect to plasma pump, RBC pump, etc.
- Whole blood in
- Buffy coat out
- Red cells out
- Plasma out
- Saline injected between grooves to lubricate and separate channels
- Tubes connect to collection ports inside centrifuge bowl

---
IBM 2997 in use at UCSD in 1982

IBM 2997: ceramic plates attached to disposable centrifuge insert

Modern machines (starting with the Cobe Spectra):
Tubing set harness connects via the "omega-1 omega-2" principle
The Omega-1 Omega-2 principle in centrifugal apheresis machines involves the use of different components and orientations. In the Terumo Optia machine, "Omega-zero" (stationary) is shown, with "Omega-one" and "Omega-two" positioned at different angles. The Fresenius-Kabi (Fenwal) Amicus machine also demonstrates these principles, with "Omega-zero", "Omega-one", and "Omega-two" depicted in their respective positions. Blood lines are connected to these components, indicating the flow path.
Omega-1 Omega-2 principle in centrifugal apheresis machines

Fresenius-Kabi (Fenwal) Amicus

"Omega-1"

Separation by centrifugation

**Stoke's Law:**

\[ S_y = \frac{2 \cdot \omega^2 \cdot R \cdot (\rho_{\text{cell}} - \rho_{\text{plasma}})}{\mu} \]

Stoke's law says that the cellular velocity of sedimentation \((S_y)\) is proportional to:

- Centrifugal acceleration \((\omega^2 \cdot R)\) or \(g\)
- Square of the cell radius \((R^2)\)
- Difference between the density of cell and plasma \((\rho_{\text{cell}} - \rho_{\text{plasma}})\)
- Inverse of the fluid viscosity \((\mu)\)

Centrifugal separation is a function of:

- \(S_y\) and
- Dwell time (inverse of inlet blood flow rate)

Separation by centrifugation

**Specific Gravity**

- Plasma 1.027
- Platelets 1.04
- Mononuclear cells 1.06
- Blasts 1.085
- Erythrocytes 1.095

Terumo Optia
In the chamber, the opposing centrifugal force and flow rate causes separation of the cells according to their size.

- Platelets are pumped out of the top
- MNCs collect in the chamber and are periodically flushed by plasma into the collection bag
### Choice of anticoagulation

1. **Citrate**
   - Usual for centrifugal plasmapheresis (cTPE)
   - Continuous dosing proportional to blood flow
   - Short-acting and purely regional (extracorporeal) effect
   - Risk of citrate toxicity - reduced by calcium administration

2. **Heparin**
   - Usual for membrane plasmapheresis (mTPE)
   - Dosing proportional to body wt (+/- loading dose)
   - Long-acting and systemic
   - Risk of systemic bleeding (and HIT)

### Calcium during citrate anticoagulation

<table>
<thead>
<tr>
<th>Calcium regimen</th>
<th>Symptom rate</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No calcium</td>
<td>5.1%</td>
<td>Mokrzycki M, Kaplan A, Am J Kidney Dis 1994</td>
</tr>
<tr>
<td>I.V. 10% Ca²⁺ gluconate</td>
<td>1 %</td>
<td></td>
</tr>
<tr>
<td>Calcium added to Albumin before infusion</td>
<td>2.7%</td>
<td>Kantinkiewics et al, J Clin Apheresis 2007</td>
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<td>2.7%</td>
<td>Kenkawa et al. J Clin Apheresis 2007</td>
</tr>
</tbody>
</table>

Calcium “I.V.” meets blood here (close to patient)
Calcium mixed with albumin meets blood here (venous chamber)
Blood return line

Therapeutic Leukocytapheresis (white cell reduction)

- Hyperleukocytosis in acute myelogenous leukemia

Specific Gravity
- RBC's 1.095
- Lymph's 1.04
- Platelets 1.04
- PMN's 1.085
- Blasts
- Mono's 1.06
- Plasma 1.027

Therapeutic Leukocytapheresis (white cell reduction)

Position of interface is adjusted by altering ratio of plasma removal rate to RBC removal rate

Therapeutic Leukocytapheresis (white cell reduction)

- WBC pump collect rate determines breadth of cell selection
- Position of interface is adjusted by altering ratio of plasma removal rate to RBC removal rate

Therapeutic Leukocytapheresis

- QB ~ 50 ml/min
- QWBC ~ 2 ml/min
- Fractional removal 4%
- Removed only blasts
- Spared platelets, PMNs, etc.

Leukocytapheresis #1

- QB ~ 50 ml/min
- QWBC ~ 2 ml/min
- Fractional removal 4%
- Removed only blasts
- Spared platelets, PMNs, etc.

Leukocytapheresis #2

- QB ~ 50 ml/min
- QWBC ~ 5 ml/min
- Fractional removal 10%
- Removed blasts, myelocytes, metamyelocytes, etc.

Note rebound of more mature myeloid cells after the first leukapheresis.

The number of leukemic cells removed during each procedure exceeded the calculated number present in the circulation at the start of each procedure.

Red Cell Exchange (RBCX) for Sickle Cell disease

Hemoglobin SS disease = Sickle Cell Disease (SCD)

- Target reduction of HbS to <30%
- Target end-apheresis Hb to 10 gram/dl

ADVANCES

- Use of molecular antigen-matched RBCs
  - Reduces or eliminates antibody formation
  - Isovolemic hemodilution technique
  - In software of modern centrifugal machines.
  - "Deplete" phase: remove RBCs, replace with saline (or 5% albumin), reduces the circulating RBC mass.
  - "Exchange" phase is on a smaller mass of RBCs, i.e. more efficient.
  - Requires fewer units of transfused RBCs.
  - Achieves longer intervals between treatments.
  - More efficiently achieves primary targets (prevention of stroke, prevention of iron overload)
OUTLINE:
- Manual plasma exchange
- Continuous-flow centrifugation
- Discontinuous-flow centrifugation
- Membrane plasma separation
- Secondary plasma purification devices, columns, etc.
- Choice of plasmapheresis system

Centrifuges, Filters and Columns

Development of centrifugal apheresis systems

Discontinuous-flow centrifuges
Ancestry:
- DeLaval cream separator (Sweden, 1878)
- Cohn fractionator for in vitro separation of plasma from whole blood (1942)

Clinical apheresis machines:
- Bierman’s modification of the Cohn fractionator (1961) was used for on-line leukocyte depletion, mainly to study the kinetics of cell populations.
- Further development of the centrifuge bowl by Latham led to production of the Little/Abbott model 10 (1970).
- Haemonetics model 30 (1973), other Haemonetics models.
- Dideco, etc.
- Therakos UVAR, XTS, CellEx

Discontinuous-flow centrifugal apheresis systems

Discontinuous-flow centrifuges using the Latham bowl
ECP machines use Latham bowls

- In USA, FDA-approved machines all by Therakos (now Mallinkrodt)
- In Europe, also UV light-box added on to centrifugal machine (e.g. Optia)

CellEx machine uses modified Latham bowl

- Continuous removal of plasma from the top and RBCs from the bottom
- Accumulation of the WBC product within the centrifuge

OUTLINE:
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Development of membrane plasmafiltration

Flat-plate membrane plasmafiltration

COBE Centry-TPE machine circa 1980

Membrane materials:
1964: saponified cellulose triacetate
1973: polyacrylonitrile (PAN)
1985: polysulfone (PS)
... polymethylmethacrylate (PMMA)
... etc., etc.

Molecular size ranges:
Conventional dialyzer
High efficiency dialyzer
High flux dialyzer
Hemofilter
High molecular cut-off dialyzer
Plasma filter
Plasma fractionator
... etc.

Plasma separation by membrane filtration

Hollow-fiber plasma-filter
Pore size: ~0.3 microns
Cut-off: ~2000 kDa

Membrane specifications are those of Asahi products (Asahi Kasei Kuraray Medical Co., Tokyo Y741, Japan).
Plasmafilter in pediatric use at UCSD circa 1983

Curesis® plasmafilter

Some modern hollow-fiber membrane plasmafiltration machines

| Prismaflex | NxStage |

Centrifuges, Filters and Columns

**OUTLINE:**
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Secondary plasma purification devices, columns, etc.

- **DFPP (cascade plasmafiltration)**
- **Adsorption columns:**
  - Staphylococcal protein A
  - immobilized antibodies (Ab)
  - adsorption resins
  - immobilized antigen (Ag)
  - covalently-bound peptide ligands

Cascade Plasmafiltration (Double-Filtration)

- **#1 Plasma-filtrator**
  - Pore size: large
  - Cut-off: >2000 kD

- **#2 Plasma-fractionator**
  - Pore size: medium
  - Cut-off: ~ 100 kD
    - (Albumin ~ 67 kD)
    - (IgG ~ 140 kD)
    - (IgM ~ 970 kD)

Membrane specifications are those of Asahi products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8,101, Japan)

Protein-A Immunoabsorption (PA-IA)

- **Staphylococcal Protein A immuno-adsorption column**
  - Prosorba® (Immunosorba®)
  - Staph Protein A has high avidity for Fc portion of IgG (IgG₁, IgG₂, IgG₄)
  - Removal of antibody or antigen-antibody complexes

ITP: FDA-approved.
RA: Double-blind sham-controlled trial positive (Felson, 1999).
- **But columns no longer available.**
- **Also controversy: super-antigen (pharmacological) mechanism?**
Antibody Immunoadsorption with Anti-IgG

- Removes IgG (all subclasses)
- Used in Europe and Japan for:
  - autoimmune diseases
  - transplant alloimmunization
- Brands:
  - TheraSorb™ (Miltenyi Biotec)
  - others

LDL-Apheresis – Dextran adsorption (Kaneka Liposorber®)

- Removes LDL, Lp(a), and VLDL.
- Minimal effect on HDL or albumin.
- Effective LDL apheresis

LDL-Apheresis – Braun "HELP® System"
(Heparin-induced Extracorporeal Lipoprotein Precipitation)

- Acidity (pH 5.12) plus heparin causes precipitation of lipoprotein complexes
- Bicarbonate dialysis and ultrafiltration to correct pH and volume
- Precipitate filter captures lipoprotein complexes

Not FDA-approved

for SLE

Clinically unsuccessful due to Ag leaching.

Antigen (Ag) columns for Immunoadsorption (IA)

Blood return
Purified plasma
Whole plasma

Covalently-bound peptide ligands for Immunoadsorption (IA)

Blood return
Purified plasma
Whole plasma

Peptide ligands covalently linked to sepharose mimic the epitope and specifically immuno-adsorb pathogenic autoantibodies.

Effective in
Autoimmune type Idiopathic Dilated Cardiomyopathy due to autoantibodies to beta-1 adrenergic receptor and cardiac myosin.

But Ab's against different epitopes may cause similar disease.

Covalently-bound ligands for Immunoadsorption (IA)

Column containing synthetic terminal trisaccharide A or B blood group antigen linked to a Sepharose matrix

Glycosorb ABO column (Glycorex Transplantation AB).
Adsorption column presentations at EAAT

**EAAT 2015.**
“*A Case Study Using Lectin-Affinity Plasmapheresis in the Treatment of Ebola Virus Disease*”, Rodney Kenley, MS, MBA

**EAAT 2016.**
“Galectin-3 Removal by Apheresis: Significance and Clinical Applications”, Isaac Eliaz, MD

**EAAT 2017.**
“Selective Removal of C Reactive Protein (CRP): Clinical Advances”, Steffen Mitzner, MD

**EAAT 2018, Friday, at 10:30 am (Plenary session)**
“Selective CRP Apheresis as a New Treatment Option in Acute Myocardial Infarction: First Results of the CAMI1 Study”, Wolfgang Ries, MD

**EAAT 2018, Friday, at 1:15 pm (“Frontiers” session)**
“Soluble TNF Receptor Immunoadsorption: Progress Towards an Apheresis Treatment for Cancer”, Thomas E. Ichim, PhD

Centrifuges, Filters and Columns

**OUTLINE:**
- Manual plasma exchange
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Choice of plasmapheresis system

- **DFPP** - Double Filtration Plasmapheresis
- **IA** - Immunoadsorption
- **TPE** - Therapeutic Plasma Exchange

**Choice of plasmapheresis system**

<table>
<thead>
<tr>
<th>DFPP</th>
<th>IA</th>
<th>TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double Filtration Plasmapheresis</td>
<td>Immunoadsorption</td>
<td>Therapeutic Plasma Exchange</td>
</tr>
</tbody>
</table>

- Factor depletion, may need FFP
- Per liter of plasma treated, cannot remove more target molecule than TPE
- Factor depletion, may need FFP

---

**SUMMARY:**

- Manual plasma exchange
- Continuous-flow centrifugation
- Discontinuous-flow centrifugation
- Membrane plasma separation
- Secondary plasma purification devices, columns, etc.
- Choice of plasmapheresis system

---

**Centrifuges, Filters and Columns**

---

**Thank you for your attention**

Preparing for the opening of the 15-station Therapeutic Apheresis Unit in the new Outpatient Pavilion, UCSD La Jolla, planned for March, 2018
Apheresis Physicians’ College at UCSD

A 4-day immersion in the Apheresis Unit, with mentorship by experts. Round on 50+ procedures (TPE, EPC, RBCX-Aph, LDL-Aph, etc.). One-on-one discussions; lectures and workshops. Limited to 3-5 participants. Offered 4 or 5 times per year.

Next available APC courses: April 17th - 20th, 2018
May 29th - June 1st, 2018

Contact: nmgriffin@ucsd.edu
or dmward@ucsd.edu
Outline

1. Review the factors that affect drug removal by TPE/apheresis
2. Discuss timing of medication administration in relation to TPE/apheresis
3. Identify common medication management issues with TPE/apheresis

Pharmacokinetic Terms

- Absorption – process of a substance entering the blood circulation
- Distribution – dispersion of substances throughout fluid and tissues of the body
- Metabolism – irreversible transformation of compounds into metabolites
- Excretion – removal of substances from the body

\[ V_d = \frac{\text{drug amount}}{C_p} \]
Factors that Predict Drug Removal

**Drug Dependent Factors**
- Volume of distribution (Vd)
- Protein binding
- Rate constant for distribution
- Intrinsic clearance

**Therapy Dependent Factors**
- Duration
- Type
- Volume of exchange
- Replacement fluid
- Successive treatments


Volume of Distribution

Drugs with small Vd (< 0.2-0.3 L/kg) are located in the intravascular space

Drugs with large Vd are likely distributed at other tissue sites

Rebound phenomenon is due to distribution of drug from tissue back to vascular space
Protein Binding

Drugs with a high degree of protein binding (>80%) are more likely located in the vascular compartment and available for removal by apheresis. Unbound or free drug is not removed to the same extent because it is available for distribution to other tissue compartments.

Unbound Drug
Albumin

Medications Removed by TPE

Table 3: Medications reportedly removed by TPE

- Not a lot of pharmacokinetic studies
- Evaluate medications based on what we know:
  - $V_d < 0.2\,\text{L/kg}$
  - Protein binding > 80%


Immunosuppressants
Immunosuppressants and Apheresis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd</th>
<th>Pb</th>
<th>Removal by Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>3-5 L/kg</td>
<td>90%</td>
<td>Negligible removal by tpe or lipid apheresis</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.85-1.9 L/kg</td>
<td>99%</td>
<td>Negligible</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>12 L/kg</td>
<td>99%</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.4-1 L/kg</td>
<td>70%</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

Drug Vd Pb Removal by Apheresis

- Cyclosporine: 3-5 L/kg; Pb 90%; Removal by apheresis
- Tacrolimus: 0.85-1.9 L/kg; Pb 99%; Negligible
- Sirolimus: 12 L/kg; Pb 99%; Unlikely
- Prednisone: 0.4-1 L/kg; Pb 70%; Negligible

Drug Vd Pb Removal by Apheresis

- Cyclosporine: 3-5 L/kg; Pb 90%; Removal by apheresis
- Tacrolimus: 0.85-1.9 L/kg; Pb 99%; Negligible
- Sirolimus: 12 L/kg; Pb 99%; Unlikely
- Prednisone: 0.4-1 L/kg; Pb 70%; Negligible

Monoclonal antibodies (mAbs)

- Basiliximab Removal by TPE

Table 1. Plasma Concentration of Basiliximab in Relation to Plasmapheresis

<table>
<thead>
<tr>
<th>Time after commencement of plasmapheresis</th>
<th>Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Hours before commencement of plasmapheresis</td>
<td>0.1*</td>
</tr>
<tr>
<td>Sample drawn on admission at Apheresis unit</td>
<td>3.4</td>
</tr>
<tr>
<td>2 Hours after plasmapheresis</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Sample drawn 3 hours after administration of 20 mg Basiliximab.

References:
Case 1
- 39 yo F with TTP receiving daily to twice daily TPE, methylprednisolone, and vincristine
- Day 11: Rituximab 375 mg/m² once weekly started
- Day 12: Twice daily TPE resumed 24 hours after rituximab dose
- Day 15: blood specimen showed complete CD19+/CD20+ cell depletion by flow cytometry

Case 2
- 62 yo F with TTP
- No evidence of improvement after 42 days of plasma exchange and corticosteroids
- Blood sample showed 0.66% of all lymphocytes CD19+/CD20+
- Rituximab 375 mg/m² x 1 dose
- TPE resumed 36 hours later
- Blood sample drawn 12 hrs after TPE showed complete CD19+/CD20+ depletion (0 of 2,331 lymphocytes)
Rituximab and CD20 Depletion

Antimicrobials

Distribution Rate Constant Ceftriaxone Vd over Time

consider distribution time for antibiotic in relation to plasma exchange

Vd 0.1-0.2 L/kg 27 L
### Ceftriaxone Removal by TPE

<table>
<thead>
<tr>
<th>Administration Time</th>
<th>1 gram</th>
<th>3 gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q_{UL} (mg)</td>
<td>230.8±38.5</td>
<td>750±168.5</td>
</tr>
<tr>
<td>Fe(%)</td>
<td>23±3.9</td>
<td>24.9±5.6</td>
</tr>
<tr>
<td>Just prior to TPE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 hours prior to TPE</td>
<td>161±66</td>
<td>347±121</td>
</tr>
<tr>
<td>Q_{UL} (mg)</td>
<td>16.6±5.9</td>
<td>11.5±4</td>
</tr>
<tr>
<td>Fe(%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Ganciclovir is NOT removed by Plasmapheresis

<table>
<thead>
<tr>
<th></th>
<th>Day 4, with TPE</th>
<th>Day 8, without TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/L)</td>
<td>19.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Albunin (g/L)</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Haematoctict (%)</td>
<td>0.30</td>
<td>0.28</td>
</tr>
<tr>
<td>White blood cell count (× 10^9/L)</td>
<td>11.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Blow flow rate (mL/min)</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Dialysate rate (mL/h)</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>Post-dilution rate (mL/h)</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Ganciclovir K_{p} (h)</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Ganciclovir half-life (h)</td>
<td>18.5</td>
<td>9.2</td>
</tr>
<tr>
<td>%AVV</td>
<td>7.8</td>
<td>–</td>
</tr>
</tbody>
</table>


Antimicrobial Recommendations

### Table 4: Recommendations for Administration of Certain Antimicrobials in Plasma Exchange Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd or Pb</th>
<th>Removal by Pheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>IV</td>
<td>Administration after plasmapheresis</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>IV</td>
<td>Administration at least 1/2 hour before plasmapheresis</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>IV</td>
<td>Administration after plasmapheresis</td>
</tr>
<tr>
<td>Renogal</td>
<td>IV or IM</td>
<td>Administration after plasmapheresis or at least 1-2 hours before plasmapheresis</td>
</tr>
</tbody>
</table>

*IV, intravenous; IM, intramuscular. See text for additional information.
*Recommendations based on dosing required for systemic absorption following IV versus IM administration.

Miscellaneous agents

### Miscellaneous Medications and TPE

- **Atorvastatin**: 381 L, 98% Likely/ND
  - Unlikely/ND
- **Digoxin**: 5-8 L/kg, 25% Likely/ND
  - Digoxin Fab complexes documented
- **Glipizide**: 10-11 L, 98% Likely/ND
- **Metformin**: 1951.7 L, Negligible
  - Likely/ND
- **Metoprolol**: 5.6 L/kg, 12% Likely/ND
  - Likely/ND

*H, intravenous; IM, intramuscular. See text for additional information.
*Recommendations based on dosing required for systemic absorption following IV versus IM administration.


Therapeutic Drug Monitoring

- For drugs in which serum concentrations are available consider checking concentrations:
  - Pre-apheresis
  - Post-apheresis (delay a few hours)
  - Plasmapheresate (confirms actual clearance by procedure)
- Consider measuring free drug concentrations as protein binding may be affected
- Rebound phenomenon as seen in hemodialysis may also occur with pheresis
  - Drug levels drawn mid-apheresis or immediately following TPE will overestimate drug clearance

Conclusions

- Volume of distribution is the most important factor for determining removal by apheresis
- Most drugs should be administered after the apheresis procedure
- Monitor serum concentrations if available

Thank you!
Email: jkozuch@ucsd.edu
Treatments of Drug and Toxin Exposure by Apheresis

Linda Awdishu, PharmD, MAS
Associate Clinical Professor of Pharmacy

What will you learn today?
1. Brief overview of overdose guidelines
2. Review ASFA guidelines on use of apheresis for overdose, envenomation and poisoning
3. Drug toxicities
   a. Immunosuppressants
      i. Calcineurin inhibitors
      ii. Nataluzimab
      iii. Nivolumab
   b. Other interesting drugs
      i. Digoxin
      ii. Ibuprofen

Overdose: Know the ABCs
- Airway, Breathing, Circulation
- Supportive care
- Prevent GI absorption
  - Emesis
  - Activated charcoal – single or multiple dose
  - Whole bowel irrigation
- Antidote
  - N-acetylcysteine, Digibind, naloxone, flumazenil, snake antivenom
- Forced Excretion
  - Acid or alkaline diuresis
- Extracorporeal methods
  - Hemodialysis, hemoperfusion, therapeutic apheresis
  - Reserved for severe cases, specific ingestions/overdoses
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


• Ingestion of even small amounts present in a single mushroom (5-7 mg) can result in organ necrosis, acute hepatic failure
• Latency period of ~ 12 hours before symptoms appear when significant absorption has already occurred
• Mortality in the modern era estimated ~ 20%
• Over 250 case reports using TPE for Amanita phalloides ingestion
• ASFA Class II recommendation

Death Cap...as bad as it sounds...
• Retrospective study of 21 cases of mushroom poisoning in children and adults
• Symptoms appeared 7-23 hours post ingestion
• Gastric lavage performed in all patients
• All patients received some form of ancillary treatment (e.g. activated charcoal, penicillin, silibinin)
• TPE initiated after gastric lavage with an average exchange volume of 2.5 L
• Used commercial serum protein solutions, albumin or plasma
• 8 pts received TPE in first 36 hrs, 13 pts within 60-84 hrs
• 4.8% mortality vs ~20% mortality rate reported in literature

Amanita phalloides
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5000 snakes bites reported to Poison Control Centers annually
Most commonly occurring in men, with half of patients requiring hospitalization
Most common snakes include rattlesnakes, water moccasins and copperheads
Clinical manifestations include: local tissue damage, systemic effects (N/V/D), coagulopathy, hypotension, neurotoxicity, rhabdomyolysis with renal failure

Once bitten…

- Assess quantity of envenomation and degree of toxicity
- Identify offending animal species
- Prevent or slow absorption
- Neutralize venom
- Prevent and treat secondary and delayed toxic effects
- Manage complications of treatment

Envenomation: Basic Management Strategies

Snake and Insect Envenomation

![Image of a snake and a hand with a syringe]

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gender</th>
<th>Age</th>
<th>Species</th>
<th>Symptoms</th>
<th>Other Therapy</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>USA</td>
<td>Male</td>
<td>20</td>
<td>Rattlesnake</td>
<td>Pain, swelling</td>
<td>Bandage, Ice</td>
<td>Good</td>
<td>1</td>
</tr>
<tr>
<td>2002</td>
<td>USA</td>
<td>Male</td>
<td>30</td>
<td>Water Moccasin</td>
<td>Pain, swelling</td>
<td>None</td>
<td>Poor</td>
<td>2</td>
</tr>
<tr>
<td>2006</td>
<td>Mexico</td>
<td>Male</td>
<td>40</td>
<td>Copperhead</td>
<td>Pain, swelling</td>
<td>Ice, Hydrocortisone</td>
<td>Good</td>
<td>3</td>
</tr>
</tbody>
</table>

References:
Snake Envenomation

- N=37; Included only patients whose condition did not improve with snake antivenom and supportive care
- All patients given antivenom and supportive treatment for mean of 5 days before performing plasma exchange
- Mean 2.1 (1-4) plasma exchange sessions per patient, sessions performed daily
- FFP or albumin used for replacement fluid
- Hematologic parameters and swelling improved in 3 ± 1 days after plasma exchange
- All patients were discharged with good recovery with an average length of hospital stay of 12.2 (4-28) days
- No complications were seen during the 3 months following discharge

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before plasma exchange</th>
<th>After plasma exchange</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet</td>
<td>163 (127-212)</td>
<td>189 (148-235)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.87 ± 0.2</td>
<td>1.00 ± 0.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>27.9 ± 9.3</td>
<td>28.2 ± 10.9</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Drug toxicities

How Does PK Inform on Immunosuppressant TPE Removal?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd</th>
<th>Pb</th>
<th>Removal by Pheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>3-5 L/kg</td>
<td>90%</td>
<td>Negligible removal by apheresis or lipid apheresis</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>12 L/kg</td>
<td>99%</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.85-1.9 L/kg</td>
<td>99%</td>
<td>Negligible</td>
</tr>
</tbody>
</table>
Tacrolimus Overdose

60 yo F s/p OLT for HCV cirrhosis admitted with severe diarrhea and dehydration presents with BP 70/40 and altered mental status. The patient was found to have elevated LFTs (AST = 510 IU/L; ALT = 498 IU/L; total bilirubin = 9.6 mg/dL; INR 1.9) and AKI (Scr 5.31 mg/dL, GFR 10 mL/min/1.73 m²). Upon questioning of family, it was discovered that the patient had been taking tacrolimus 5 mg po BID for the past 6 days rather than her prescribed dose of 1.5 mg po BID. Patient became anuric and was transferred to ICU where she was intubated and started on CRRT.

Tacrolimus Toxicity
Removal by Red Blood Cell Exchange

Four daily RBC exchanges reduced FK to therapeutic levels.
Renal and neurological function improved with some residual kidney injury.

A Sticky Cyclosporine Mishap...

- 55 yo man s/p cardiac txp for end-stage HF from ischemic cardiomyopathy on CSA (111.0 to 190.2 ng/mL), mycophenolate mofetil and prednisolone.
- Day 16 developed immunosuppression associated leukoencephalopathy
- Day 17, received 50 fold overdose of CSA during dose conversion from oral capsules to syrup with levels of 8900 ng/mL.
- Whole blood exchange (instead of TPE) was employed since the distribution of CSA in circulating blood is 50% in RBC and 35% in plasma.
Whole Blood Exchange using Erythrocytapheresis and Plasma Exchange

- Therapeutic erythrocytapheresis followed by TPE were performed (COBE Spectra) consecutively for 3 days.
- Hct 39%, wt 48.2 kg, expected total BV 3,374 mL (RBC 1316 mL and PV 2,058 mL).
- Erythrocytapheresis: 7 units leukocyte-depleted RBCs were used in one exchange
- TPE: 1 PV exchanged with 15 units (about 2,100 ml) of FFP

Three Consecutive WBE Successfully Removes 95% CSA in Overdose

Natalizumab Associated PML

- Natalizumab (NTZ) is a humanized monoclonal Ab directed against cell adhesion molecule α4 integrin which reduces lymphocyte migration and CNS inflammation.
- NTZ is used to treat multiple sclerosis and is biologically active for up to 3 months after its infusion.
- Progressive multifocal leukoencephalopathy (PML) is syndrome associated with JC virus infection.
- 635 cases of NTZ-PML have been confirmed in patients with MS in the post-marketing setting.
- 24% mortality
Natalizumab Associated PML

- Rapid restoration of immune system is required by discontinuing the drug and using plasma exchange to remove NTZ.
- Category I, Grade 1C recommendation in AFSA guidelines.
- Serum natalizumab levels 1 week after final TPE were reduced by 92%.
- Although effective in removing NTZ, PLEX may increase the likelihood of immune reconstitution inflammatory syndrome (IRIS) and of inflammatory brain damage from the rapid restoration of immune system.

Use of Plasmapheresis for NTZ-PML

- Study by Landi and colleagues evaluated 219 cases of NTZ-PML.
- 193 cases were extracted from published case reports.
- 34 cases from Italian collaborators.
- Primary outcome: survival and post PML clinical status.
- Employed univariate, multivariate regression modeling and cox proportional hazard modeling.

Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>NTZ-PML</th>
<th>NTZ-PML</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.3</td>
<td>45.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Age of PML diagnosis (years)</td>
<td>26.8</td>
<td>27.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Age of PML diagnosis (years)</td>
<td>26.8</td>
<td>27.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Smokes (current)</td>
<td>Yes</td>
<td>No</td>
<td>0.06</td>
</tr>
<tr>
<td>Age of PML diagnosis (years)</td>
<td>26.8</td>
<td>27.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
</tbody>
</table>

Analysis of Clinical Outcome in NTZ-PML Using Multivariate Regression

Plasmapheresis is not associated with improved survival in NTZ-PML

PD-1 Inhibitors
- PD-1 antibodies
  - Nivolumab
  - Pembrolizumab
- PD-1 is expressed on activated T cells and plays an important role in immune tolerance and tumor escape from the immune system.
- PD-1 signaling is essential to tolerance of self antigens
  - PD-1 knockout mice develop GN
Nivolumab Associated Myasthenia Gravis

- Nivolumab is a human IgG4 checkpoint inhibitor antibody that binds to PD-1 receptors.
- Used to treat advanced melanoma, SCLC, renal cell carcinoma
- Numerous case reports of myasthenia gravis as an immune related adverse effect
- Bad prognosis in SCLC due to respiratory failure
- Treated with steroids, pyridostigmine, plasmapheresis, IVIG, mechanical ventilation.

Don’t hold your breath…

<table>
<thead>
<tr>
<th>Author</th>
<th>Case</th>
<th>Treatment/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loochtan</td>
<td>70 year old man with Stage 4 SCLC</td>
<td>Developed diplopia and ptosis 14 days after starting therapy AchRAb 1.64 nmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisone 1 mg/kg/day Plasmapheresis x 3 sessions Discharged, readmitted 1 week later</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylprednisolone 80 mg IV Plasmapheresis x 3 sessions 200 g IVIG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Care withdrawn</td>
</tr>
<tr>
<td>Kimura</td>
<td>80 year old man with melanoma</td>
<td>Developed dyspnea, muscle weakness, dysynchrony of left ventricle 17 days later CK 7740, CK-MB 120 AchRAb 28 nmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulse steroid 1000 mg x 3 days Prednisone 1 mg/kg/day Plasmapheresis x 7 sessions IVIG 400 mg/kg/day Recovery</td>
</tr>
</tbody>
</table>

Digoxin Overdose

- 70 yo M with history of cirrhosis 2/2 EtOH underwent right hemicolectomy for adenocarcinoma, developed anuric renal failure post operatively. Patient went into atrial fibrillation and was started on digoxin 250 mcg daily on post operative day 1. On day 4, he had partial loss of consciousness, developed cardiac rhythm/conduction disorders, and was found to have serum digoxin level of 4.4 mcg/L (reference range 0.9-2.2 mcg/L)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd</th>
<th>Pb</th>
<th>Removal by Pheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>5-8 L/kg</td>
<td>25%</td>
<td>Unlikely -- but removal of dig-fab complexes documented</td>
</tr>
</tbody>
</table>
79 yo patient admitted to ED 48h after ingestion of 30 mg of digoxin. Patient presented comatose, in junctional rhythm, hemodynamically unstable with oliguric acute renal failure. Plasma digoxin level was 16.7 ng/mL on admission.

- 48 yo M with intentional ingestion of 72 g of ibuprofen with development of circulatory failure refractory to aggressive fluid resuscitation and high dose vasopressors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd</th>
<th>Pb</th>
<th>Removal by Pheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>0.11-0.19 L/kg</td>
<td>90-99% likely</td>
<td></td>
</tr>
</tbody>
</table>
In summary...

- TPE can be used to treat mushroom poisoning with significant reduction in mortality (Category II)
- TPE has a Category III recommendation for envenomation and drug overdose
- Erythrosinapheresis should be employed for calcineurin inhibitors
- Currently plasmapheresis is a Cat I recommendation for natalizumab associated PML
  - This may change?
- Plasmapheresis may be an option for nivolumab associated MG
Special Considerations in Apheresis Anticoagulation

AMBER PARATORE SANCHEZ, MD
ASSOCIATE PROFESSOR OF MEDICINE
MEDICAL DIRECTOR OF UCSD THERAPEUTIC APHERESIS PROGRAM

Disclosures

- Consulting/Lecturing Honorarium
  - Terumo BCT
  - Fresenius Kabi
  - Angiodynamics

Overview

- Hemostatic Changes with TPE
- Anticoagulant Choices in Apheresis
- Management Patient on Concurrent Anticoagulation
Therapeutic Plasmapheresis

- Clinical situation dictates frequency of TPE and need for adequate hemostasis post procedure.
- TTP: daily therapy required, FFP needed.
- Other disorders: often every other day sufficient.
- Avoidance of FFP best.
- No recent or upcoming procedure, “no problem!”
- Intracranial hemorrhage, recent kidney biopsy, diffuse alveolar hemorrhage, etc. → special considerations must be given.

TPE with Albumin Replacement

- Removal of pro-coagulants
  - Fibrinogen
  - Factor II, X, VII, XI
  - Von Willebrand factor
- Removal of anti-coagulants
  - Antithrombin
  - Protein C.
- After a single plasma exchange PT by 30% and PTT by 100%
- PT returns to normal within ~4 hours and PTT within ~24 hours.

Helpful labs to monitor:
- PT/INR, & fibrinogen > aPTT
- aPTT more subject to variability especially in inpatient setting (heparin).

Fibrinogen

- During tissue & vascular injury it is converted by thrombin to fibrin to help clot blood.
- Affected the most by TPE & recovers the slowest.
- In 48h will be 50-65% of the pre treatment value.
- Most other coagulation factors will be close to pre TPE levels within 24-48h.
- Fibrinogen biosynthesis rate of 25-38 mg/dl/day & longer half life.
- Severe hypofibrinogenemia may last 3d post TPE.
- The larger the PV processed the larger the reduction in fibrinogen.
Add Some Plasma?

- Fibrinogen: risk for bleeding in pregnancy & surgery
- Bleeding post TPE is rare (<3%)
- INR > 1.5-2 and fibrinogen <100-125 mg/dL prior to procedure
- Consider giving some plasma
- Plasma has variable amounts of coagulation factors
- PT or INR for each bag of FFP can vary
- 1 unit FFP raises fibrinogen about 15mg/dL in a 70kg man

TPE Practice Habits

- Survey of 127 institutions
- 94% would use albumin alone if no h/o bleeding or clotting disorder
- Percentage that would use some plasma or cryo replacement:
  - 61% if liver disease & INR 1.5-2.0
  - 82% if active bleeding
  - 83% in a bleeding disorder due to a coagulation factor deficiency
  - 86% if fibrinogen <100mg/dL due to recent TPE

Vitamin K in Plasmapheresis

- Vitamin K: fat soluble vitamin required to make certain proteins necessary for blood coagulation (K from Koagulation, Danish)
- Vitamin K dependent factors:
  - Factors II, VII, IX, X
  - Lesser degree: proteins C & S
- Vitamin K (phylloquinone) is present in leafy green vegetables
- No literature available on its use in plasmapheresis
- Won’t change fibrinogen
- Not Vitamin K dependent factor
Anticoagulants Used in Apheresis in the USA

- Citrate: ACD-A
- Heparin
- Combination of citrate & heparin

Citrate Anticoagulation

- Citric acid has been used as an anticoagulant since 1914
- Anticoagulation-citrate-dextrose solution (ACD-A)
- Ideal in low blood flow circuits where load is offset by clearance
- Shorter half life than heparin (30-60 min vs 23 min to ~3 hours)
- More favorable safety profile
- Effects can be rapidly reversed with calcium

If symptoms of citrate toxicity occur: slow blood flow rate, give more calcium, or halt the procedure

- Mainly metabolized by liver but still safe in ESLD as 10-35% is excreted by the kidneys
- Does not affect the INR & aPTT in vivo
- Plasma also contains citrate – more symptoms of low Ca in procedures utilizing plasma (ie TTP)
  - FFP contains ~7 mmol citrate/unit
  - RBC contains ~2-3mmol/unit
Case Example

- 56yo man in status epilepticus. Seizures continue on EEG despite anti-epileptics. Neuro-critical care team places him on a ketogenic diet and considers autoimmune etiology for the seizures. They ask for plasmapheresis while the autoimmune antibody panel is pending.
- After the first plasmapheresis they call us frantically as the glucose increased post procedure.
- Anticoagulation-citrate dextrose solution (ACD-A) was used
- What do you do?

Case example

- Sodium citrate (4%) was used instead
- Used in continuous renal replacement (CRRT/CVVHD) circuits
- Consider using if dextrose is to be avoided (e.g. ketogenic diet in refractory status epilepticus)
- Concentration of citrate similar (4% vs 3%)
- 16:1 roughly equal to 14:1 of ACD-A

Heparin anticoagulation in Apheresis

- Can be used with TPE but given ease of citrate, use is limited
- Membrane based plasma exchange
- LDL apheresis
- Photopheresis
- Longer ½ life than citrate
- Risk for heparin-induced thrombocytopenia
- Risk for bleeding complications
Photopheresis considerations

- Manufacturer рекs for heparin are based on body weight:
  - >40 kg: 10,000-15,000 units/500mL of 0.9% normal saline
  - <40kg: 150-250 units/kg in 500mL of NS
- Can alter the ratio of delivery or the concentration of heparin:
  - Typically given at a ratio of 10 parts whole blood to 1 part heparin (10:1)
  - 1 or 2 ratio depending on patient's clinical need

Available A/C ratios on Cellex:

- 8:1, 10:1, 12:1, 14:1, 16:1, 25:1, 30:1 and 50:1
- In a patient already on anticoagulation (Coumadin, heparin, etc) the ratio of heparin should be significantly reduced
- For excessive clotting, the lowest ratio is 8:1
- Combined A/C strategies published (citrate + heparin bolus)
- No published guidelines

Consider ECP with Citrate

- History of heparin induced thrombocytopenia
- Delayed hypersensitivity reaction to heparin (occurs in 7.5%)
- Active bleeding
- Inherent or recent invasive procedure
- Thrombocytopenia
- Other bleeding disorders

Protocols exist*
- UCLA published protocol in Journal of Clinical Apheresis 2008

*ECP with ACD-A not FDA approved
Combination of Heparin & Citrate

- Issues with circuit clotting / platelet clumping
  - Add a loading dose of heparin at the start + ACD-A
  - Strategy reported in both TPE & ECP
- Decrease citrate reactions
  - Add heparin to ACD-A and give at a ratio of 30:1 (for example)
  - Reduces citrate reactions, but does not eliminate them
- Minimize volume of citrate & calcium in long procedures
  - Stem cell collections / leukapheresis
  - ESKCM

Pediatric apheresis

- Reduces citrate reactions, but does not eliminate them
- Minimize volume of citrate & calcium in long procedures

- Stem cell collections / leukapheresis
- ESKCM

Management of Anticoagulants in Patients Undergoing TPE

- A.Fib, mechanical valves, thrombois, DVT prophylaxis, etc
- Patient on a heparin drip
- Direct oral anticoagulants
  - Coumadin
  - Others
- If withholding any of these medications for TPE the risk-benefit ratio must be weighed

TPE in the Patient on Heparin: "It’s Complicated"

- Heparin binds to antithrombin, enhancing inactivation of coagulation factors (thrombin/factor IIa, Xa, Xla, & Xla)
- Half life of heparin is longer the higher the IV dose
  - T1/2 30min with 25 U/kg, 60 min with 100 U/kg, 150 min with 400 U/kg
  - Unpredictable subject-to-subject variation, must monitor PTT or anti-Xa
- Low Vd, largely intravascular (= TPE removal)
TPE in the Patient on Heparin: “It’s Complicated”

- TPE may remove the drug, change levels of antithrombin & its targets
- Some people would increase rates predicting heparin will be removed
- However, the anticoagulant antithrombin is also removed. PT & PTT known to go up after single TPE
- What to do with citrate, since blood is already anticoagulated (1:25: 1:30)?
- Not a lot of data

TPE in the Patient on Heparin

- A Retrospective review of TPE pts on continuous IV UFH
- Heparin levels were monitored by anti-Xa level; PT and antithrombin were checked infrequently
- Included in review if anti-Xa done pre and post TPE, and if all albumin or all plasma used as replacement (but not combo)
- Small study
  - 5 patients in albumin only group
  - 14 in plasma replacement group

TPE with Albumin in Patient on Heparin

- With albumin, there was no clear pattern of change in anti-Xa levels in this small study
TPE with Plasma Replacement in the Patient on Unfractionated Heparin (UFH)

- UFH rate unchanged
- UFH stopped
- UFH decreased by 25%
- UFH increased by 65%


TPE in the Patient on Heparin

If no change in UFH rate or held UFH, net effect = less anticoagulation

Authors changed their practice habits:
- If FFP replacement, they increase heparin gtt 65% during TPE
- If patient transitioning to warfarin, they recommend DC warfarin during TPE if receiving FFP (use heparin during this time)
- If albumin replacement: heparin rate not changed unless pre TPE level would dictate based on protocol
- Small retrospective study


TPE in the Patient on Warfarin

- Warfarin (Coumadin) – Vitamin K antagonist
  - Blocks the enzyme vitamin K epoxide reductase that reactivates vitamin K
  - Required co-factor \( \downarrow \) factor II, VII, IX, & X, and proteins C & S
  - INR is monitored
  - Risk of bleeding increases with higher INR
  - Reversed with vitamin K and FFP
  - Important in the patient who may need plasma during TPE
TPE with Albumin in the Patient on Warfarin

- INR will go up after TPE (can nearly double)
- Returns to prior value in 2 days
- Pre procedure INR predictive of post procedure INR if 1 PV exchange using albumin

Author conclusions: “TPE with albumin replacement appears to be safe to perform in patients who are therapeutic on warfarin”

- Check pre and post INR, and only advise adjustment in warfarin dose if post procedure INR >6
- Hold that night and recheck the next day
TPE with Plasma in the Patient on Warfarin

- Using 1/3rd or more of plasma will decrease INR at end of procedure
- Further decrease is seen the next day
- Cryoprecipitate will improve fibrinogen levels, but have less impact on warfarin related coagulopathy
- Consider changing patient to a different anticoagulant, if feasible
  - Heparin drip
  - LMWH

Other Oral Anticoagulants

- Direct oral anticoagulants
  - Dabigatran (Pradaxa) – inhibits thrombin
  - Apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa) - direct Factor Xa inhibitors
- No studies in TPE, bleeding risk unknown
- Current standard coagulation tests not useful in determining bleeding risk
- No data to guide management in TPE

Thank You!
a6sanchez@ucsd.edu

Suggested reading:

Submit a challenging case by the end of today for consideration for Saturday’s “Cases For the Experts”: a6sanchez@ucsd.edu
Transfusion Reaction

• Any unfavorable transfusion-related event occurring in a patient during or after transfusion
• Occur in 1–2% of transfusions
• Symptoms can be highly variable
Complications of Transfusion

- Acute Transfusion Reactions
  - Occur within 24 hours of transfusion
- Delayed Transfusion Reactions
  - Can occur up to months after transfusion
- Infectious Complications of Transfusion

Transfusion Reactions

- Therapeutic apheresis is different than the usual setting of transfusion
- Red cells and plasma are usually transfused over a couple of hours
- During therapeutic apheresis a unit of red blood cells or plasma is transfused in a couple of minutes
- When symptoms of a transfusion reaction occur during therapeutic apheresis, they are often related to a unit of blood that has already been completely transfused

Acute Transfusion Reactions

- Acute Immune Mediated Hemolytic Transfusion Reactions
  - Intravascular hemolysis caused by transfusion of incompatible blood
  - Usually ABO incompatible red blood cells
  - Can be caused by non-ABO incompatible red blood cells
- Nonimmune Mediated Hemolysis
  - Intravascular hemolysis caused by infusion of hemolyzed red blood cells
  - Improper heating of red blood cells
  - Improper shocking of red blood cells
  - Rapid infusion of red blood cells through small needle
- Transfusion Related Sepsis
  - Transfused unit contains bacteria
  - Most common with platelet transfusion (room temperature storage)
  - Rarely seen with red blood cells (cold storage)
Acute Transfusion Reactions

- **Transfusion-Associated Circulatory Overload (TACO)**
  - Circulatory overload secondary to transfusion
  - Small patients and patients with heart failure are most susceptible
  - Small volumes can precipitate TACO

- **Massive Transfusion**
  - Fluid shifting, coagulopathy and metabolic effects of massive transfusion

- **Febrile Nonhemolytic Transfusion Reactions (FNHTR)**
  - Febrile reaction to blood transfusion not associated with hemolysis
  - Usually caused by cytokines or HLA antibodies in blood products
  - Leukocyte reduction of cellular blood products decreases risk

What signs and symptoms should make me concerned that the patient may be experiencing a serious transfusion reaction?
Patients can experience significant transfusion reactions during therapeutic apheresis. If any of these signs and symptoms occur, the apheresis procedure should be halted and the physician overseeing the procedure should be notified:

- Fever (>1°C rise in temperature)
- Shortness of breath/difficulty breathing
- Hypotension
- New onset of hemoglobinuria
- New onset of abdominal pain
- “I feel awful” (new onset)

Transfusion Reactions can be caused by:

- Hemolytic Transfusion Reaction (fever, hypotension, hemoglobinuria, abdominal pain, feeling of impending doom)
- Allergic Transfusion Reaction (hypotension, dyspnea)
- Septic Transfusion Reaction (fever, hypotension)
- Transfusion-Related Acute Lung Injury (TRALI) (fever, dyspnea, hypotension)

Transfusion Reaction Investigation:

- Bedside clerical check:
  - Compare paperwork sent with unit, unit labeling and patient identification to make certain that the correct unit was transfused to the correct recipient
- Blood bank clerical check:
  - Compare unit returned to the blood bank with information regarding unit issued from blood bank and unit ordered
  - Confirm that the correct unit was issued and the correct unit was returned to the blood bank
**Transfusion Reaction Investigation**

- Send sample to blood bank for testing
- Repeat ABO and Rh
  - Confirms that the ABO and Rh post-transfusion matches the pre-transfusion ABO and Rh
  - If they do not match there could be a problem with patient identification or transfusion of incompatible red blood cells
- Check for visual hemolysis
  - Confirms that hemolysis is not present after transfusion
  - Most serious cause of hemolysis in a post-transfusion specimen is traumatic draw
- DAT
  - Confirms that unexpected antibodies are not present

**Delayed Transfusion Reactions**

**Delayed Hemolytic Transfusion Reactions**
- Extravascular hemolysis
- Typically caused by non-ABO antibodies
- Can occur weeks after transfusion
- Usually asymptomatic

**Transfusion-Associated Graft Versus Host Disease**
- Graft versus host disease caused by viable lymphocytes in the transfusion in a susceptible patient
- Almost uniformly fatal
- Prevented by irradiation of blood components

**Delayed Transfusion Reactions**

- **Post Transfusion Purpura**
  - Profound thrombocytopenia 5 – 10 days after transfusion
  - Usually caused by human platelet antibodies
  - Patient destroys their own platelets in addition to transfused platelets
  - Most common in females
- **Iron Overload**
  - Red blood cell exchange decreases iron overload due to removal of red blood cells during the procedure
Zika Virus Update

Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components – August 2016

• Due to the limited number of tests available at the time testing was phased in by the location of the collecting blood center
  - If the blood center was located in an area with locally acquired cases of Zika Virus (Florida and Puerto Rico), testing was implemented immediately – 8/26/16
  - If the blood center was located near areas with locally acquired cases or in an area with a high number of travel-associated cases (AL, AZ, CA, GA, HI, LA, MS, NM, NY, SC and TX) implemented within four weeks – 9/23/16
  - If the blood center was located in the remainder of the US or territories, testing was implemented within 12 weeks – 11/18/16

Zika Virus Update

• Blood Products Advisory Committee (BPAC) met on December 1, 2017 to discuss options for continued testing of the blood supply for Zika Virus
  - The committee voted to recommend to the FDA to use minipool nucleic acid testing to screen all blood donations
  - If there is a local transmission of Zika virus the blood supplier would switch to individual donor testing
  - The blood supply is currently tested in this manner for West Nile Virus
Resolution of NAT Positive Triplex Test

- Start with positive pool (16 samples, 1 test)
- Resolve to positive unit (16 samples, 16 tests)
- Determine which virus is present in unit (1 sample, 3 tests)

Zika Virus Update

- FDA usually implements BPAC recommendations, but is not required to do so
- Expect draft guidance document in 2018
- Until the guidance is finalized, all blood donation (except pathogen reduced blood products) will be tested by individual NAT for Zika Virus

Transfusion Storage and Transport Options for Therapeutic Apheresis
In August of 2017 UCSD implemented portable refrigerators to support liver transplant and massive transfusion.

- Case for equipment purchase was made based upon anticipated reduction in blood wastage for patients requiring large volumes of blood transfusion.
- If blood is kept in a portable refrigerator, it will remain in temperature and will not need to be discarded when it is returned to the blood bank.
- Since implementation, therapeutic apheresis has been the most frequent user of the portable refrigerators.

### Portable Refrigerator Use (Four Months)

- Therapeutic Apheresis: 63
- Liver Transplant: 21
- Trauma: 18
- MTP: 17
- ED: 6
- Other: 2

![Portable Refrigerator Use Chart]
Pediatric Apheresis Overview

Nadine Benador MD, Professor of Pediatrics
Medical Director of Dialysis and Apheresis
Pediatric Nephrology
University of California, San Diego
Rady Children’s Hospital, San Diego
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Apheresis procedures at Rady Children’s Hospital, San Diego over the past 5 years

Population San Diego county 2017: 3,095,313
RCHSD: 551 beds

<table>
<thead>
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<td>56</td>
<td>78</td>
<td>37</td>
<td>114</td>
<td>89</td>
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<td>5</td>
<td>5</td>
<td>7</td>
<td>11</td>
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<tr>
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<td>(12 pts)</td>
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<tr>
<td>allo</td>
<td>12</td>
<td>(9 pts)</td>
<td>9</td>
<td>(7 pts)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
<td>138</td>
<td>88</td>
<td>138</td>
<td>115</td>
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Outline

- Indications of TPE: what is the evidence in pediatric patients?
- Pediatric Physiological considerations
- Apheresis prescription
- Complications
- Example of Apheresis therapies:
  - TPE
  - Red cell exchange
Indications

• Over 21 years (1995-2016): 1198 pediatric apheresis publications. Only 370 articles for treatment of specific pediatric disease. 98%: single-center, case report or case series, 2%: prospective or randomized controlled trials

Indications for TPE

Renal Diseases
- Other Conditions
  - Renal transplant conditions
  - ABO incompatible kidney transplant
  - ABO incompatible stem cell transplant
  - Pre-transplant desensitization
  - Aplastic anemia (pure red cell aplasia)
  - Antibody mediated rejection
  - Autoimmune hemolytic anemia (Cold agglutinin)
  - Recurrent focal segmental glomerulosclerosis
  - Catastrophic antiphospholipid antibody syndrome
  - Immune mediated glomerular disease
  - Hypersensitivity purpura
  - Post-transfusion purpura
  - ANCA associated rapid progressive GN
  - IgA Nephropathy
  - Neurologic
    - Henoch Schonlein Purpura nephritis
    - Acute disseminated encephalomyelitis
    - Other immune mediated glomerulonephritis
    - Chronic inflammatory demyelinating polyneuropathy
    - Cerebral palsy
    - Myasthenia gravis
  - Other
    - Chronic inflammatory demyelinating polyneuropathy
    - Myotonic dystrophy
    - Myotonia congenita
    - Myasthenia gravis
    - Myotonia muscularum
    - Other neuromuscular diseases
    - Inflammatory myopathy
    - Other muscle conditions
  - Metabolic
    - Refsum's disease
    - Wilson's disease
  - Other
    - Solid organ transplant
      - ABO incompatible heart transplant
      - Familial hypercholesterolemia (homozygotes, small blood volume)
      - Thombotic thrombocytopenic purpura
      - Lupus cerebritis
      - Multiple myeloma
      - Multiple myeloma cast nephropathy
      - Neuromyelitis optica
      - Multiple sclerosis
      - Sepsis with multiorgan failure
      - Sjogren's syndrome
      - Systemic lupus erythematosus
      - SLE
      - Other conditions
        - PANDAS, Syndenham's chorea
        - Solid organ transplant
          - Paraproteinemic polyneuropathies (IgG/IgA/IgM)
          - Antibody mediated heart transplant
          - Familial hypercholesterolemia (homozygotes, small blood volume)

What’s so special about a small patient compared to adults? Size of the patient determines the blood volume

ECV should not exceed 10 to 15% of patient blood volume to avoid hypotension and acute blood loss anemia

<table>
<thead>
<tr>
<th>Patient size</th>
<th>Blood volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>100 mL/kg</td>
</tr>
<tr>
<td>Infants + small chld</td>
<td>80 mL/kg</td>
</tr>
<tr>
<td>Older chld + adults</td>
<td>70 mL/kg</td>
</tr>
</tbody>
</table>

Importance of patient blood volume vs extracorporeal volume

- 12 months old - 10 kg
- Blood volume 80 ml/kg = 80 x 10 = 800 ml
- ECV of 200 ml is 25% of his blood volume
- For a 70 kg adult male, 400 ml (largest circuit) is only 8% of TBV
- For a small adult, 40 kg, TBV is 40 x 70 = 2800 ml
- Prime circuit with PRBCs (diluted to Hct of 35%). If borderline, can prime with albumin 5%
- May need blood prime or albumin 5% prime if patient is critically ill or unstable

Other pediatric issues

- Volume issues lead more easily to possible hypotension or hypertension
- Small size: vascular access more difficult to establish
- Dose of anticoagulation
- Hypothermia (Blood warmer!)
- Cooperation

Apheresis prescription

- Vascular access: Blood flow rate?
- What do I need to prime circuit with? (ECV and clinical state of patient)
- What is my anticoagulation?
- What am I removing?
- What am I replacing with?
- What do I need to watch for?
- How often?
Blood flow rate: about 1 ml/kg/min

- 6-20 kg: 8-20 ml/min
- 20-30 kg: 10-40 ml/min
- 30-50 Kg: 20-50 ml/min
- Adult size: 30-90 ml/min

Vascular Access

- Small patients (<30kg, double lumen HD catheter- cuffed versus non cuffed)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>7 Fr.</td>
</tr>
<tr>
<td>3 to 7-10 kg</td>
<td>7 Fr.</td>
</tr>
<tr>
<td>7 to 15-20 kg</td>
<td>8 Fr.</td>
</tr>
<tr>
<td>15-30 kg</td>
<td>9 Fr.</td>
</tr>
<tr>
<td>&gt; 30 kg</td>
<td>10-12.5 Fr.</td>
</tr>
</tbody>
</table>

Vascular Access
In children > 30 kg, consider peripheral access

17-18 Ga draw
18-22 Ga return (max flow rate for 22Ga = 38 ml/min)
Vascular access: Double chamber vortex portacath

Anticoagulation

- Citrate ACD-A (21 g citrate/L)
- Calcium: CaCl : 8 Gm/L NS
- Ca Gluconate: 23 Gm/L NS

Calcium ratio 14:1

- Check patient ionized calcium
- To maintain normal (or at least above 1.0)
- Check PTT (40-60 sec) or ACT (180-210)

Removal/Replacement - Fluid balance

Removal
- TPE: plasma
- WBCD and PBSC
- RBCX

Replacement
- Albumin: autoantibody removal
- FFP (TTP/ANCA associated vasculitis with pulmonary hem.
- aHUS, before surgery
- Albumin 5% or saline: be careful in small children, as volume removed with cells often large
- PRBCs
Monitoring - Clinical

- Blood pressure, Heart rate, Temperature, O2 saturation
- Observe vascular access for bleeding, infection, thrombosis
- Citrate toxicity: acute abdominal pain, pallor, bradycardia, hypotension, restlessness, sour taste in mouth, tingling around lips or extremities
- Allergic reactions

Monitoring - Chemistry/Hematology

- Ionized calcium
- Mag, K, (may need supplementation-oral or i.v.)
- CBC: RBCs and platelets are lost
  Do not start with Hgb < 8 or 9, Platelets < 20,000.
  (Transfuse before)
- Clotting factors: depleted progressively if no FFP replacement
  Check fibrinogen (may need to give FFP)

Complications

- Access related: line infections, thrombosis, malfunction
- Citrate toxicity (hypocalcemia)
- Allergic reactions: urticaria, hypotension. FFP related.
- Hypotension, hypertension (fluid balance!)
- Hemorrhage (from clotting factor depletion)
- Infections (removal of IgG and complement- patients on immunosuppression)
- Air embolism and blood leak
An example of long term therapy with TPE

- Weakness in legs, arms, falls. Diagnosed at age 6 with CIDP (immune mediated disorder - damage to the myelin sheath causing weakness)
- Some response to steroids and ivIG but dependent. Abdominal TB
- Decided to start on TPE
- Weight: 29 kg
- Access: more than a few treatments → cuffed R IJ double lumen Cath
- Blood volume: 29 x 70 = 2030 ml.
- Prime? What equipment? Cobe Spectra 170 ml ECV.
- Clinical status? Good BP. OK to prime with saline

A case of long term plasmapheresis for CIDP

- Hct 35% - Plasma volume = 65% (29 kg; blood volume is 2000 ml)
- 5 x plasma volume = 1300 ml
- Replacement: Albumin 500 ml; saline 400 ml
- Citrate: 1:1 - Calcium chloride (8g/L) = 40 ml/hour
- Stable during treatment.
- Wean: 3 x/week, then 2 x weekly, Q2 weeks

- After 6 months of TB therapy, Cell Cept treatment and trial to wean her off TPE but unable to space more than Q 2 weeks. Also getting intermittent ivIG
- Treatment of iv cyclophosphamide (6 monthly infusions)
- Resumed Cell Cept.
- Increased ivIG dose again
- Able to come off plasmapheresis after 5 years.

Access issues

May 2013 Vortex Port

Aug 2013 to April 2014
Erythrocytapheresis

- Removal or replacement of RBC
- Used for complications of sickle cell disease: defective RBC replaced with normal RBC
  - Acute stroke
  - Acute chest syndrome
  - Prevention of iron overload
- Other indications (rare)
  - Hemochromatosis
  - Malaria
  - Polycythemia vera

An example of PRBCX for complications of sickle cell disease

- Multiple complications from sickle cell disease.
- Chronic blood transfusion since 2006 (8yo) - CNS vasculopathy, chronic infarcts, Moya Moya disease (neurovascular complication).
- Iron overload: spleen, liver, heart despite oral iron chelation
- Started PRBCX 2014 (15 yo).

Access

Had regular Portacath, tried peripheral vein for access and Port for return → then 2 portacaths.

L EJ Petite Port (placed at age 8)
R IJ Vortex 9.6Fr
Access: Double vortex

R LJ Vortex 11.4Fr. Needs to be accessed with 16 Ga non-coring needle for apheresis.

Prescription

- Weight: 46 kg
- 1x red cell volume exchange (1200 ml). End Hct of 30%
- Blood flow usually ~ 40 ml/min (limited by access)
- Citrate 13:1
- Calcium Chloride (8 mg/ml at 600 mg/hour = 75 ml/hour)
- Since June 2016, started depletion/exchange (lowest Hgb 25% during procedure)

FCR %: fraction of cells remaining = Post HgbS/Pre Hgb S

- The percentage of the original RBC remaining in the patient’s body at the end of the procedure
- If starting Hbs (Pre Procedure) = 30% and desired Hbs (Post) = 10%
  FCR = 10/30 = 33%
- A lower FCR results in a lower final Hbs% and a greater volume of RBC exchanged
Monitoring of Hgb S

- Goal to maintain pre-procedure Hgb S ≤ 30%
- Post procedure Hgb S of 10% is optimal

Hgb S pre: 20 to 39, Average 30.5
Hgb S post: 7 to 17, Average 11.0

FERRITIN

Ferritin before starting PBBCX was 7620 and is now 995

Started depletion/exchange in June 2026
Thank you for your attention.

Any questions?

nbenador@ucsd.edu
Pediatric Apheresis Concurrent with Extracorporeal Membrane Oxygenation (ECMO) or Continuous Renal Replacement Therapy (CRRT)

Peter Yorgin, MD

6th Annual UC San Diego Essentials and Advances in Apheresis Therapies

1:40-2:00 PM
Thursday, February 22, 2018

Objectives

- Discuss indications for concurrent apheresis therapy.
- Demonstrate the technique for concurrent apheresis with both CRRT and ECMO.
- Review the technical challenges of concurrent apheresis therapy
  - Blood volumes/primes
  - Anticoagulation challenges
  - Continuous versus discontinuous apheresis flow
- Explain how we have applied this technique in children.
Indications

- Continuous renal replacement therapy (CRRT) patients who need apheresis, where discontinuation of CRRT would cause:
  - Hemodynamic instability
  - Fluid problems
  - Fever
  - Problematic new blood exposure
  - Any ECMO patient who needs apheresis

Concurrent Technique

- Adjust citrate to optimize circuit ionized calcium values. Maintain ionized calcium ~0.25 mmol/L.

Concurrent Technique

- Bring in the plasmapheresis machine.
Connect plasmapheresis access and return lines.

How does this work? Parallel circuits!

Turn stop cocks on, start both machines.

CRRT ON, but with reduced blood flow equal to 30-40 mL/min.

Plasmapheresis ON, with a blood flow of 30-40 mL/min.
At conclusion of plasmapheresis, return plasmapheresis circuit blood, if ordered.

Concurrent Technique

Disconnect plasmapheresis lines and increase CRRT blood flow by 30-40 mL/min.

Concurrent Technique

Blood prime

- No more than 10% of the patient’s blood volume should be extracorporeal.
- Priming volume for:
  - Cobe Optia: up to 185 mL
  - Prismaflex: 165 mL
  - Total = 350 mL
- Blood volumes for children:
  - Male Blood Volume = (Weight (kg) x 63.11) + 312 mL
  - Female Blood Volume = (Weight (kg) x 62.34) + 351 mL
- Patients with blood volume <3.5 L will probably need a blood prime (~50 kg)

Raes et al. BMC Pediatrics 2006, 6:3
**Normalized blood**

- Problems with PRBC
  - Potassium: 20.5 ± 7.8 mEq/L
  - Lactic acid: 9.4 ± 4 mmol/L
  - Calcium: <0.2 mmol/L
  - Glucose: 24.1 ± 6.1 mg/dL
- RCHS priming protocol for children <10 kg
  - Normalized blood
    - PRBC: 80 mL
    - 5% albumin: 55 mL
    - Heparin: 150 units
    - Sodium bicarbonate 1mmol/mL: 22 mL
    - Calcium gluconate 10% (100 mg/mL): 2 mL
- With patients larger than 10 kg
  - 1:1 PRBC and Normal saline

---

**Citrate comparison**

- Less ACD-A citrate is used with CRRT when compared to apheresis
  - CRRT = 33:1 ACD-A to blood ratio
  - Apheresis = 14:1 ACD-A to blood ratio
- If circuit ionized calcium <0.25 mmol/L risk of clotting is minimal.
  - Quantities of LR were added to citrated blood to determine conditions when blood would clot.
  - Risk of clotting is <1% when ionized calcium is >0.33 mmol/L.
- Blood were recalcified. No sample with a Ca²⁺ < 0.33 mmol/L showed any clot formation. Normal coagulation measures were obtained in almost all samples in which the Ca²⁺ was >0.36 mmol/L.
- Dilution of citrate concentration by 1/3 with apheresis with albumin replacement.

---

**ECMO + apheresis**

[Diagram of ECMO + apheresis process]

---

3) King WH, Patson ED. Anesthesiology 1988, 68:115-121
ECMO + apheresis

- High (arterial-like) pressure to plasmapheresis machine access.
- ECMO circuit is heparinized
  - ACD-A citrate + 8% calcium chloride needed.
- Monitor ionized calcium values carefully
- Priming and plasma replacement affect activated clotting times. More heparin is often needed.

Anticoagulation issues
- Since heparin was used for ECP, the anticoagulation was held and no heparin calcium chloride infusion rate was based.
- The patient was noted to be well anticoagulated before starting heparin - activated clotting time (ACT) 210 seconds. ACT ranged from 193-239 seconds during treatment.
- After ECP, ACT was not maintained immediately. ACTs were between 191-239 seconds during treatment. When the ACT was 200 seconds, heparin was ordered and the calcium chloride infusion was increased.
- The patient’s ionized calcium values during the procedure ranged from 1.2 to 1.26 mmol/l.

Variable CRRT machine pressures with ECP
- Occasional access pressure on CRRT machine became positive when the ECP machine returned the patient’s blood.
- When the patient’s blood was being returned during the fifth cycle, there were wide access pressure fluctuations on CRRT machine. This led to a minor interruption in ECP that required decreasing the return rate on the ECP machine further to 20 ml/min and increasing the blood flow rate on the CRRT machine from 150 to 140 ml/min to stabilize circuit pressures.
- Six cycles of ECP over four hours were completed without stable patient vital signs.
Thanks!

- Peter Yorgin, MD
- pyorgin@ucsd.edu
Initial presentation: History
April 2005

- 6 yo boy of Samoan descent presents with “brown urine” x 2-3 days
- 3 weeks prior treated with amoxicillin for AOM, stopped abx early due to diarrhea
- 2 days prior complained of abdominal pain, nausea, vomiting
- 1 day prior decreased appetite and decreased energy, seen by PMD who recommended labs and referred for admission once labs resulted
- ROS: no recent febrile illness, no swelling, no rash, no joint complaints.

PMHx: Term infant, SVD, no complications; recurrent AOM
Immunizations: UTD
SHx: Family intact, no tobacco exposure
FHC: Dad has history of vach s/p defibrillator
  - Paternal grandmother died of ESRD complications, had DM on insulin
  - Paternal cousin s/p nephrectomy for unclear reasons
  - Paternal aunt CKD of unclear etiology
Initial presentation: Physical exam

- Vitals: T: 98.3, HR 96, BP: 126/73 (95th %ile 125/84), RR: 18, O2: 98 RA
- Height 131 cm (95th %ile) weight 41.2 kg (95th %ile)
- Overall well appearing, unremarkable physical exam

Initial presentation: Labs

- WBC 8.9, Hgb/Hct: 5.4/17.8, Pt 28
- Na: 143, K: 4.8, Cl: 102, CO2: 16, BUN: 150, Cr: 3.4, Glucose 86
- UA: 1.0/5.5/4+ blood, 3+ protein, 10-20 RBC/hpf
- RBC casts on urine microscopy
- RUS: Bilateral enlarged echogenic kidneys (R 11.4 cm, L 10.9 cm)
- Haptoglobin <14, retic 4%, LDH 12, 500
- Peripheral smear showed schistocytes and spherocytes
- AST 238, ALT 39, Tbil 3.2
- C3 59 (75-175), C4 23 (14-40)

Initial presentation: Diagnosis?

- Thrombotic microangiopathy
  - HUS
    - Shiga toxin mediated
    - Pneumococcal
  - Atypical HUS
  - Acquired
  - Inherited
- TTP
Initial management

- Hospital course complicated by:
  - PRBC transfusion every other day
  - Difficult to control hypertension
  - Pancreatitis requiring TPN
- Dialysis started hospital day 6: decreased urine output, persistent anemia requiring multiple transfusions (BUN 153/Cr 7.1), fluid overload
  - HD chosen over PD due to consideration for therapeutic plasmapheresis
  - FFP (20 mL/kg) given with first dialysis recommended by hematology

Dialysis day 6 through HD 19

- ADAMTS13 normal 91% (nl >67%)
- Factor H low 120 (nl 180-220), supports diagnosis of aHUS
- No improvement in renal function or hematologic parameters so TPE started on HD 19
  - Cobe Spectra with blood warmer, ECV 170 mL
  - Blood volume 2520 mL (weight 36 kg x 70 mL/kg)
  - Primed with saline
  - Remove 2L plasma and replace with 2L FFP (approximately 1 plasma volume)
  - BFR 30-50 ml/min as tolerated (~1 mL/kg/min)
  - ACDA 13:1; CaCl 8 mg/mL 65 mL/hour
- HD 20: Pediatric nephrology attending writes, “He looks like a new man!!!!”
Hospital course

- 8 TPE during hospitalization, well tolerated except for CONS line infection
  - Days 19, 20, 23, 25, 27, 29, 33, 35, 41
  - All exchanges were 2L (~1 plasma volume), replacement fluid FFP
- Discharged from the hospital on day 42 (June 2005)
  - 3 x/week hemodialysis
  - 1 x/week TPE

Follow up

- Hemodialysis-dependent for ~5 weeks after hospital discharge
  - Recovered kidney function to nadir of 0.8 mg/dL, eGFR ~70 ml/min
- Admitted July 2005 for hypoxia ~3 weeks after stopping dialysis
  - Pleural/pericardial effusions
  - Discharged after 2 days of good response to diuretics
- Admitted 5 days later with AUC requiring intubation in outside ED
  - Hypertensive emergency (SBP >200 mmHg)
  - Brain MRI: Multiple occipital lobe lesions, cerebellar lesions, parietal lesions consistent with hypertensive encephalopathy
  - Platelets, hemoglobin, renal function were all at baseline, received usual TPE
- Weekly TPE with FFP for 7 months, weaned off in December 2005
Follow up: February 2007

- Admitted with 2 weeks of n/v, decreased urine output, facial swelling
- Hgb: 8.3, Cr: 2.5, platelets 55, LDH 3241, C3: 40, C4 26
- Treated with FFP infusion 10 mL/Kg on hospital day 2, 3 but renal function worsened to Cr 5.2, platelets fell to 27
- Dialysis and TPE resumed on hospital day 4
  - TPE daily x 6 then every 2-3 days for total of 14 treatments over 3 weeks
- Discharged on dialysis and weekly TPE

Kidney biopsy July 2007

- 1/5 glomeruli obsolescent
- Variable periglomerular fibrosis and segmental sclerosis, mesangial expansion
- Small fibrous crescents
- Diffusely widened interstitium with fibrous tissue, edema, lymphocytic infiltration
- IF: C3: 2+ granular capillary, 1+ granular TBM, vessel wall
- IGM/ IgA: 2+ tubular casts
- EM: Subendothelial deposits in process of reabsorption
- Overall thought to be a combination of acute reversible tubular injury with some irreversible degenerative changes

Follow up

- Required dialysis for 6 months before renal recovery, new baseline Cr 1.5-1.6
- TPE q week for 7 months, then slowly weaned over the next 5 months to q 3-4 weeks at lower volume of plasma infused
- Plasma infusion (20 ml/kg) started every 3 weeks, weaned to every 4-6 weeks
- Dialysis catheter removed April 2008
Genetic testing 2012

- **CFH, CFI, CD46, THBD, C3**: 2 normal alleles
- **CFH-CFHR5**: heterozygous deletion of CFHR1-CFHR4
- **PKD1** nucleotide substitution, **PKD2** frameshift mutation (by this time father is on dialysis due to ADPKD)
Evolving management

- Transformed to eculizumab in August 2014
  - 900 mg IV weekly x 4 in August 2014
  - 1200 mg IV q 2 weeks since then
- Transitioned care to Kaiser at age 18 (5/2017)
- Remains in remission with creatinine ~2.2, hypertension, epo dependent anemia

Thank you.
LDL-Apheresis: Evolving Indications and the New Anti-Cholesterol Drugs

David M. Ward, MD, FRCP, HP(ASCP)
Emeritus Professor of Clinical Medicine,
Division of Nephrology and Hypertension, UCSD

DISCLOSURES:
The speaker has the following potential conflicts
- TerumoBCT, Inc. – Honoraria, Consulting
- Fresenius Kabi, Inc. – Consulting

OUTLINE:
- Case report
- History
- Methods
- Standard indications
- Efficacy
- New anti-cholesterol drugs
- Evolving indications:
  - in pregnancy
  - for Lp(a) (an independent coronary risk factor)
  - for pediatric FSGS (Focal Segmental Glomerulosclerosis)
  - others
16 year old boy.
- Age 4: nodules on his tendons.
- Age 9: cholesterol >600 mg/dl.
- Genetics: compound heterozygote (2 loci on LDL-R gene).
- Rx: atorvastatin, Zetia, Welchol. Niacin not tolerated.
- On meds, diet and exercise: LDL >300 mg/dL.
- Negative cardiac stress and carotid U/S.
- Rx: LDL-apheresis (Kaneka) at UCSD:

![Graph showing LDL levels](image)

**Case Report**

**LDL-Apheresis**

- Developed for treatment of severe homozygous Familial Hypercholesterolemia (FH) resistant to lipid lowering therapy
  - Rare disorder (1:1,000,000).
  - Virtual absence of cell-surface receptors that remove LDL from circulation
  - LDL often 500-1000 mg/dl
  - Severe atherosclerosis & CHD in 1st decades of life
- More common is heterozygous FH (1:500): 2x normal LDL, CHD in middle decades
- Other severe cases presenting in childhood are double heterozygotes

**History**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Method</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Gueyes</td>
<td>1967</td>
<td>Plasmapheresis</td>
<td>Quick, considerable elimination of cholesterol, minimizes atherogenic substances</td>
</tr>
<tr>
<td>Thompson et al.</td>
<td>1967</td>
<td>Plasmapheresis</td>
<td>Quick, considerable elimination of cholesterol, minimizes atherogenic substances</td>
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<tr>
<td>Agishi et al.</td>
<td>1980</td>
<td>Consolodilation</td>
<td>Selective, effective, minimizes atherogenic substances</td>
</tr>
<tr>
<td>Stoffel et al.</td>
<td>1981</td>
<td>Immunoabsorption</td>
<td>Selective, effective, minimizes atherogenic substances</td>
</tr>
<tr>
<td>Bubersch et al.</td>
<td>1983</td>
<td>Immunoabsorption</td>
<td>Selective, effective, minimizes atherogenic substances</td>
</tr>
<tr>
<td>Wehrle and Loch</td>
<td>1983</td>
<td>Hyperpolarized LDL adsorption (HLP)</td>
<td>Selective, effective</td>
</tr>
<tr>
<td>Nair et al.</td>
<td>1992</td>
<td>Thermodilution</td>
<td>Selective, effective</td>
</tr>
<tr>
<td>Boucher et al.</td>
<td>1987</td>
<td>Dextran sulfate LDL adsorption</td>
<td>Selective, effective</td>
</tr>
<tr>
<td>Mahieu et al.</td>
<td>1999</td>
<td>LDL-apheresis</td>
<td>Selective, effective, simple technology, simple technology</td>
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<tr>
<td>Ose et al.</td>
<td>2002</td>
<td>LDL-apheresis</td>
<td>Selective, effective, simple technology, simple technology</td>
</tr>
</tbody>
</table>

Sibling as control subject. All on nicotinic acid & lovastatin.

TPE (Plasma Exchange) q 2 weeks for 6-9 years:
- peak cholesterol decreased by 37%.
- regression of xanthomas & coronary lesions.
- survived 5.5 years longer than controls (p = 0.03).


LDL Apheresis - systems available worldwide

**LDL removal from separated plasma**

1. Adsorption
   - Liposorber (Dextran sulfate adsorption)
   - TheraSorb LDL (Anti-ApoB immunoadsorption)

2. Precipitation
   - H.E.L.P. (Heparin-induced precipitation)

3. Filtration
   - Double Filtration Plasmapheresis (DFPP)

**Direct LDL adsorption from whole blood**

- Liposorber D (Dextran sulfate adsorption)
- Direct Adsorption of Lipoprotein (DALI)
  (Polyacrylate adsorption)


*FDA approved in USA
Whole plasm a
Precipitate filter captures lipoprotein complexes

Heparin Adsorber
Hemodialyzer
Bicarbonate dialysis and ultrafiltration to correct pH and volume

Acetate - Acetic acid buffer + heparin
from patient blood
return

Purified plasma

- Processes 3 liters of plasma (capacity of precipitate filter)
- First developed in 1983
- FDA approved
  - 1997: Secura (no longer in use)
  - 2007: Plasmat® Futura

B.Braun HELP Plasmat Futura
Kaneka Liposorber MA-03
Heparin-induced Extracorporeal Lipoprotein Precipitation
Dextran Sulfate Adsorption

- Processes 1.5 x plasma volume
- Extracorporeal volume: 170ml blood + 230 ml plasma
- First described in 1987
- FDA approved
  - 1996

- Cost: $2,000 to $2,200
- Time 2 - 3 hours
- Anticoagulation: heparin

B.Braun HELP Plasmat Futura
Kaneka Liposorber MA-03
Heparin-induced Extracorporeal Lipoprotein Precipitation
Dextran Sulfate Adsorption

- Cost: $2,000 to $2,200
- Time 2 - 4 hours
- Anticoagulation: heparin

Advantages
- No bradykinin effect (patient can be on an ACE inhibitor)

Disadvantages
- LDL elimination limited by capacity of precipitate filter
- Non-selective removal of C3, C4, fibrinogen, plasminogen, and factor VIII
- Some removal of HDL (6 - 21%)
- Complex system
Kaneka Liposorber MA-03  
Dextran Sulfate Adsorption

**Advantages**
- No binding of HDL
- Low extracorporeal volume: 170ml blood + 230 ml plasma

**Disadvantages**
- Bradykinin effect: patient must not be taking ACE inhibitor.
- Can’t use citrate (disrupts dextran sulfate binding)
- Reduction of platelets (17%) and fibrinogen (29%)

Comparison of B.Braun (HELP) and Kaneka Liposorber (DS)

**Comparison:**
1) Braun (heparin precipitation) 3 liters "HELP"
2) Kaneka (dextran sulfate) at 3 liters "DS3"
3) Kaneka (dextran sulfate) final volume "DSF"

**Reduction of Cholesterol:**

<table>
<thead>
<tr>
<th></th>
<th>HELP 3 liter</th>
<th>DS3 3 liter</th>
<th>DSF 1.5 PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>-63%</td>
<td>-60%</td>
<td>-70% *</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-65%</td>
<td>-65%</td>
<td>-71%</td>
</tr>
<tr>
<td>HDL</td>
<td>-21%</td>
<td>-6% *</td>
<td>-6% *</td>
</tr>
</tbody>
</table>

* DS significantly better than HELP


**LDL Apheresis**

**Indications for hypercholesterolemia:**
- Homozygous FH . . . . . . . absolute indication.
- Heterozygous FH + CHD . . . relative indication.

**Insurance standards for LDL apheresis . . .** if after 6 months of diet and maximum tolerated cholesterol-lowering drug therapy:
- LDL-C >160 mg/dl with documented CHD . . . every 2 weeks.
- LDL-C >300 mg/dl . . . . . . . every week.

**LDL Apheresis:**
- Life-long therapy
- Continue statins, resins, niacin, fibrates, and diet (to slow rebound and prolong intervals between LDL-Apheresis sessions).
Clinical successes

- Cardiac survival
- Cardiovascular event rates
- Regression of coronary atherosclerosis
- Regional myocardial perfusion
- Exercise stress testing
- Endothelium-dependent coronary vasodilation
- Cerebral blood flow
- Carotid artery atherosclerosis
Increased myocardial perfusion

Aengevaeren et al. JACC 28:1696-704, 1996

ST-depression on bicycle stress test


Cerebral blood flow

Rubba et al. Stroke 24:1154-1161, 1993
Renal deterioration after vascular interventions (35 cases):

- 11 (control group) received steroids
- 24 received steroids and LDL-apheresis (mean 4.3 +/- 1.8 apheresis treatments)
- eGFR rose from 15.0 to 19.6 in LDL-A group (p<0.05).
- At 1 year, eGFR higher in LDL-A versus controls (median 7.5 versus 2.2, p=0.019)
Follow-up series

The German Lipoprotein Apheresis Registry (SLAR) - almost 5 years on.

- 1435 patients, 15527 LDL-apheresis procedures.
- LDL reduction 67.5%.
- Major cardiovascular events reduced by 78%.

- TPE and later LDL-apheresis for up to 38 years (53 patients).
- 28 patients had a major event.
- 4 died due to complications of major surgery
- 3 died of acute MI
- 1 died of stroke.

LDL-Apheresis

OUTLINE:

- Case report
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- Standard indications
- Efficacy
- New anti-cholesterol drugs
- Evolving indications:
  - in pregnancy
  - for Lp(a) (an independent coronary risk factor)
  - for pediatric FSGS (Focal Segmental Glomerulosclerosis)
  - others

New anti-cholesterol drugs

- **Lomitapide**
  - FDA-approved 2012. Orphan drug (adjunctive) for Ho-FH.
  - Inhibits VLDL assembly.
  - Poorly tolerated (LFT elevations and fatty liver).

- **Mipomersen**
  - FDA-approved 2013. “Black box” warning (LFTs & fatty liver)
  - Antisense nucleotide – inhibits synthesis of Apo-B, so lowers LDL, VLDL and Lp(a).

- **PCSK9 inhibitors**
  - Are monoclonals, well-tolerated in many patients:
    - alirocumab = Praluent (Sanofi) (FDA-approved July 2015)
    - evolocumab = Repatha (Amgen) (FDA-approved August 2015)
  - Reduce plasma LDL levels by increasing density of LDL-R.
Mipomersen added to LDL-Apheresis

The "MICA" Study:
- 15 patients on LDL-apheresis Q2W were randomized to
  - mipomersen 200mg (sc injection) Q1W (n=11)
  - or control (n=4)
  (Some pts dropped out and were replaced*)
  (All continued LDL-apheresis and all other meds.)
- In the mipomersen group at 12 wks:
  - LDL down by 22.6 ± 17.0% (significant)
  - Lp(a) down by 16% (not significant)

*Side effects were severe injection site reactions (5), flu-like symptoms (2) and elevated liver enzymes (1).


PCSK9 (Proprotein convertase subtilisin/kexin type 9)

- LDL-receptors LDL-R bind LDL, then internalized
- LDL-R recycled to cell surface.
- A high density of LDL-R lowers plasma LDL levels.

Addition of PCSK9 Inhibitor in Homozygous FH

The "TAUSSIG" Study:
- 106 patients with Ho-FH – Interim analysis
- On treatment (including LDL-apheresis in 34 cases)
- Evolocumab (Repatha) q 2 wks*
- Significant cardiovascular events in
  - 1 patient on apheresis
  - 3 not on apheresis
  (Mean follow-up of 1.7 years. No deaths.)
- LDL reduction at 12 weeks was 20.6% (similar in apheresis
  and non-apheresis groups).
- * Some non-apheresis pts started injections q 4 weeks
  - those who switched to q 2 weeks (doubling dose)
  - had additional 8.3% reduction after 12 weeks.

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  - for pediatric FSGS (Focal Segmental Glomerulosclerosis)
  - others
LDL Apheresis – in Pregnancy

- Statins and newer LDL drugs are contraindicated in pregnancy.
- 12 pregnancies with 10 deliveries in 7 patients with Ho-FH:
  - One patient who refused LDL-apheresis died from Acute MI.
  - Another poorly adherent patient also died from Acute MI.
  - One had to discontinue LDL-apheresis because of angina.
  - Another had bradykinin syndrome (nausea, hypotension, bradykinin) during dextran sulfate LDL-apheresis.
  - The other 3 (including 2 with CAD before pregnancy)
    - continued LDL-apheresis with good adherence
    - delivered healthy infants with no adverse effects.
- Conclusion: LDL-apheresis essential for pregnant Ho-FH patients.


“Lipoprotein little a” – Lp(a)

Lp(a) is an independent risk factor for CVD.
- Mortality, MI, stroke, and PAD still under investigation.
- Atherogenic levels >25-30 mg/dL.
- No FDA-approved drugs that specifically lower Lp(a)
- PCSK9 inhibitors sometimes lower Lp(a), unpredictably.
- LDL-apheresis is the most effective way to lower Lp(a). (1,2)
  - Lp(a) not an FDA-approved indication for LDL-apheresis.
  - Lp(a) >60 mg/dL (in absence of high LDL) approved in Germany (2008) (2)
- Device specific for Lp(a) – Lipopak® (Pocard, Moscow). (2,3)


LDL-apheresis for Lp(a) - UCSD case

- 65yo woman, diagnosed age 27, negative cath age 49, MI age 50.
- Intolerant of statins, on Zetia, Niaspan & fish oil.
- Baseline LDL of 309 mg/dL.
- Baseline Lp(a) of 140 (“atherogenic” if >25 or 30).

[Graph of LDL and Lp(a) levels over time]

Slide courtesy of Amber P. Sanchez MD
Major Adverse Coronary Events ("MACE")

- 170 cases of isolated Lp(a)-elevation + progressive CV disease
- Followed before and after starting LDL-apheresis

LDL-apheresis for Lp(a)

- 118 patients with elevated LDL or Lp(a) or both (>36,000 treatments)
- Overall MACE decrease 79.7%
- In Lp(a) only elevation (35 patients), MACE decreased by 90.4% (p<0.001)

LDL-apheresis for Lp(a)

- 170 consecutive Lp(a) patients.
- 154 completed 5-year follow-up.
LDL-apheresis

In Germany (written in 2016):

- 2,000 to 2,500 patients currently on LDL-apheresis.
- About 1,000 are for elevated LDL only.
- Of the remaining 1,000–1,500 subjects:
  - approx half for elevated Lp(a) only,
  - the other half for combined elevations of LDL and Lp(a).
- PCSK9 inhibitors will "most likely decrease the number of patients being treated for elevated LDL-C only very significantly (by approximately 80–90%)".

Focal Segmental Glomerulosclerosis (FSGS)

- FSGS causes
  - heavy proteinuria
  - nephrotic syndrome
  - kidney failure
- Recurrence after kidney transplant
  - responds to TPE
  - TPE is first line therapy (ASFA Category 1).
- Use of TPE for native disease (before transplant) is less well documented
- LDL-apheresis (dextran sulfate adsorption) for FSGS, reported 2003.


Focal Segmental Glomerulosclerosis (FSGS)

- Will be discussed Saturday at 11 AM in "Apheresis for renal diseases".

FDA letter granting "Humanitarian Use Exemption" for Kaneka Liposorber to treatment pediatric FSGS.

(page 1 of 5)
Other applications of LDL-apheresis

• One will be discussed at 2:15 PM on Friday:
  “Chylomicronemia syndrome and its management with LDL-Apheresis”
  by Wolfgang Ries, MD

SUMMARY:

LDL-Apheresis:

- Effectively reduces atherosclerosis in patients with severe hypercholesterolema.
- Particularly useful in patients intolerant of statins.
- New anti-cholesterol drugs have reduced the number of patients receiving LDL-apheresis.
- Evolving indications:
  - in pregnancy
  - for Lp(a) (an independent coronary risk factor)
  - for pediatric FSGS (Focal Segmental Glomerulosclerosis)
  - others

Thank you for your attention

Preparing for the opening of the 15-station Therapeutic Apheresis Unit in the new Outpatient Pavilion, UCSD La Jolla, planned for March, 2018
Apheresis Physicians’ College at UCSD

A 4-day immersion in the Apheresis Unit, with mentorship by experts. Round on 50+ procedures (TPE, EPC, RBCX-Aph, LDL-Aph, etc.). One-on-one discussions; lectures and workshops. Limited to 3-5 participants. Offered 4 or 5 times per year.

Next available APC courses: April 17th - 20th, 2018
May 29th - June 1st, 2018

Contact: nmgriffin@ucsd.edu
or dmward@ucsd.edu