Principles of Plasma Exchange, Applications, & Practical Issues

Workshop G07

March 8th, 2017
Principles of Plasma Exchange, Applications, & Practical Issues

11:00 Principles of Plasma Exchange - Eisei Noiri, MD, PhD.
11:35 Practicalities of Plasma Exchange: Case Based Discussion – Amber P. Sanchez, MD
12:05 Vascular Access Considerations for Plasma Exchange – Sarek Shen
12:20 Question & Answer Session for the Panel

Lunch

2:00 Introduction of Combined Circuits – Amber P. Sanchez, MD
2:15 Concurrent Treatments and Live Demo – Isagani Marquez, MSN, RN, QIA & Noel Oabel, BSN, RN, CNN
3:15 Question & Answer Session
Case 1

- 26yo woman who presented with chest tightness x 4 days and acute R facial droop and difficulty speaking. +Weakness and tingling of right arm. Stroke code called in ER, had negative stat head imaging and symptoms resolved. Only med an OCP.

- Further questioning revealed “red dots” on lower extremities x 4 days, HA, SOB, orange colored urine and non-productive cough

- Exam: T 97.9, BP 126/82, P 109 R 16 100 RA wt: 55kg
  Petechiae on lower extremities, back and chest

- Labs:
  - Platelets: 6K, Hgb: 6.8 hct 21
  - Creatinine: 0.7
  - LDH: 1096, haptoglobin: <10

- Hematology concerned for thrombotic thrombocytopenic purpura (TTP) & request plasma exchange
Case 1

- As the provider of plasma exchange now what do you do?
  - Is it indicated?
  - Informed consent: procedure plus blood products
  - Vascular access assessment
  - Labs to send before plasmapheresis begins
  - Plasma exchange prescription
    - Volume to remove
    - Replacement solution given
    - Machine: membrane vs centrifugal
    - Access
    - Anticoagulation
    - Frequency
Case 1

As the provider of plasma exchange now what do you do?

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<table>
<thead>
<tr>
<th>Disease name</th>
<th>TA Modality</th>
<th>Indication</th>
<th>Category Grade</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>TPE</td>
<td>Steroid Refractory</td>
<td>II</td>
<td>2C 163</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome</td>
<td>TPE</td>
<td>Primary Treatment</td>
<td>I</td>
<td>1A 165</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome</td>
<td>TPE</td>
<td>After IVIG</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>TPE</td>
<td></td>
<td>III</td>
<td>2B 167</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>TPE-HV</td>
<td></td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Age-related macular degeneration, dry</td>
<td>Rheophoresis</td>
<td></td>
<td>I</td>
<td>1B 169</td>
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<tr>
<td>Amyloidosis, systemic</td>
<td>β2-microglobulin column</td>
<td>TAPE</td>
<td>II</td>
<td>2B 171</td>
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<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis, and Microscopic Polyangiitis)</td>
<td>TPE</td>
<td>Dialysis dependence</td>
<td>I</td>
<td>1A 173</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture's syndrome)</td>
<td>TPE</td>
<td>Dialysis dependence, no DAH</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture's syndrome)</td>
<td>TPE</td>
<td>DAH</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture's syndrome)</td>
<td>TPE</td>
<td>Dialysis independence</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Aplastic anemia, pure red cell aplasia</td>
<td>TPE</td>
<td>Disease</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Atopic (neuro-) dermatitis</td>
<td>TPE</td>
<td></td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia; WAHA; cold agglutinin disease</td>
<td>TPE</td>
<td>Severe WAHA</td>
<td>III</td>
<td>2C 181</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>RBC exchange</td>
<td>Severe</td>
<td>II</td>
<td>2C 183</td>
</tr>
<tr>
<td>Burn shock resuscitation</td>
<td>TPE</td>
<td></td>
<td>III</td>
<td>2B 185</td>
</tr>
<tr>
<td>Cardiac neonatal lupus</td>
<td>TPE</td>
<td></td>
<td>III</td>
<td>2C 187</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>ECP</td>
<td>Cellular/recurrent rejection</td>
<td>II</td>
<td>1B 189</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>ECP</td>
<td>Rejection prophylaxis</td>
<td>II</td>
<td>2A</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>TPE</td>
<td>Desensitization</td>
<td>II</td>
<td>1C</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>TPE</td>
<td>Antibody mediated rejection</td>
<td>II</td>
<td>2C</td>
</tr>
</tbody>
</table>
**TABLE II. Category Definitions for Therapeutic Apheresis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV</td>
<td>Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>

**Description of the disease**

Thrombotic thrombocytopenic purpura (TTP), also known as TMA-ADAMTS13 deficiency, is a systemic thrombotic illness affecting mostly small vessels. Originally defined by the triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), mental status changes, renal failure, and fever, currently clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Because TIP is potentially fatal if left untreated, there should be a low threshold to treat presumed TIP. Treatment is usually initiated urgently within 6-8 h of diagnostic suspicion. After other causes of systemic TMA such as disseminated intravascular coagulopathy, severe malignancy hyperviscosity, primary antiphospholipid syndrome, and post-transplant TMA have been considered unlikely and without clinical evidence of TIP is made. TIP is associated with a severe (<10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of VWF multimers. Severe ADAMTS13 deficiency becomes a cornerstone for making a diagnosis of TIP; however, lacking so does not exclude TIP. Congenital TIP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Antibodies to TIP are present in the majority of patients with idiopathic acquired TIP and severe ADAMTS13 deficiency suggest an acquired autoimmune disorder. IgG is the most common anti-ADAMTS13 IgG subclass and appears to be related to disease recurrence. Pregnancy, connective tissue disease, medications, infections, cancer, and transplantation are associated with TIP, HUS, and TMA syndromes. Diagnostic criteria to differentiate TIP from different types of HUS (characterized by TMA, thrombocytopenia, and renal failure) are still evolving.

**Current management/treatment**

TIP has a high mortality rate and idiopathic TIP is unlikely to be less than 10% TIP should be initiated urgently once TIP is recognized. If TIP is not immediately available, plasma infusions may be given until TIP can be initiated. Convalescent plasma is often used as an adjunct at 1 mg/kg/day; however, no definitive trials proving their efficacy have been performed. Remission is now often used to treat refractory or relapsing TIP and recent studies have described incorporation of immunosuppression as an additional agent with initial TIP. Since remission immediately leads to CD59-bearing lymphocytes, a 14-24 h interval between its infusion and TIP is used in practice. Other adjuncts include cyclophosphamide, methotrexate, vincristine, and other immunomodulatory agents. Splenectomy was used in the past. Although platelet counts can be very low, patients with TIP have therapeutic rather than hemorrhagic bleeding. If present, is typically limited to skin and mucous membranes. Platelets should only be transfused for severe clinical indications only potentially life-threatening bleeding. Because congenital TIP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10-15 ml/kg) or cryoprecipitate (which contains ADAMTS13) or plasma derived von Willebrand factor concentrates (used in von Willebrand disease) have been used. Most recently the use of anti-CD59 anti-CD59 antibody is being evaluated.

**Rationale for therapeutic apheresis**

TIP with plasma replacement has significantly improved patients’ clinical outcomes. One hypothesis is that TIP removes anti-ADAMTS13 antibody, while replacing ADAMTS13 plasma activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

**Technical notes**

Transfusion of RBCs, when medically necessary, may be given emergently around the time of apheresis. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma is drawn as an anticoagulant, ACD-A can be used in a higher ratio (to whole blood) to minimize citrate reactions, especially for patients with moderate to severe thrombocytopenia. Hemoglobin levels may decrease following apheresis procedures with cryoprecipitate poor plasma in replace ment. One recent study showed that the use of cryoprecipitate poor plasma as replacement may be associated with more frequent acute exacerbations. In patients with severe allergic reactions to plasma proteins or limited supply of ABO-compatible plasma, 5% albumin may be substituted for the whole portion up to 50% of replacement. Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma (O’Connor, 2013). Albumin alone with any plasma replacement or infusion however has never shown efficacy.

**Duration and discontinuation/number of procedures**

TIP is generally performed daily until the platelet count is >150 x 10^9/L, and LDH is near normal for 2-3 consecutive days. Role of apheresis over longer duration has not been studied prospectively but is used frequently. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TIP, does not preclude discontinuation of treatment.

**2016 ASFA Guidelines**
THROMBOTIC THROMBOCYTOPENIC PURPURA

<table>
<thead>
<tr>
<th>Disease of interest</th>
<th>Literature available</th>
<th>Disease description</th>
<th>Current management</th>
<th>Rationale for apheresis</th>
<th>Typical apheresis prescription</th>
</tr>
</thead>
</table>

**Description of the disease**

Thrombotic thrombocytopenic purpura (TTP), also known as TMA-ADAMTS13 deficiency, is a systemic thrombotic illness affecting mostly small vessels. Originally defined by the period of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), renal status changes, mental and behavioral changes, and fever, currently, clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4-6 h of diagnostic suspicion, after other causes of systemic TMA such as disseminated intravascular coagulopathy, severe sepsis, severe sepsis hypotension, primary or secondary anemia (vitamin B12 deficiency), HUS, and post-transplant TMA have been considered unlikely and working clinical diagnosis of TTP is made. TTP is associated with a severe (≤10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of VWF multimers. Severe ADAMTS13 deficiency becomes a cornerstone for making a diagnosis of TTP; however, lacking so does not exclude TTP. Congenital TTP is associated with somatic mutations resulting in a severely diminished ADAMTS13 function. Autoantibody presence in the majority of patients with idiopathic acquired TTP and severe ADAMTS13 deficiency suggests an acquired autoimmune disorder. IgG4 is the most common auto-ADAMTS13 IgG subclass and appears to be related to disease recurrence. Pregnancy, connective tissue disease, infections, injury, cancer, and transplantation are associated with TTP, HUS, and TMA syndromes. Diagnostic criteria to differentiate TTP from different types of HUS (characterized by TMA, thrombocytopenia, and renal failure) are still evolving.

**Current management/treatment**

TPE has decreased overall mortality of idiopathic TTP from nearly uniformly fatal to <10%. TPE should be initiated urgently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Concomitant use of an antithrombotic agent is recommended. TPE is now often used to treat refractory or relapsing TTP and recent studies have described incorporation of streptococcal eDNA as an adjunctive agent with initial TPE. Since tirofiban immediately leads to CD62P-bearing platelets, a 12-24 h interval between its infusion and TPE is used in practice. Other adjuncts include cyclosporine, methyprednisolone, vincristine, and other immunosuppressive agents. Splenectomy was used in the past. Although plasmapheresis can be very low, patients with TTP have thrombotic microangiopathy, thrombosis, or both, and it is typically limited to the skin and mucous membranes. Plasmapheresis should be considered for significant clinical indications such as potential life-threatening bleeding. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10-15 mL/kg), or cryoprecipitate (which contains ADAMTS13) or plasma derived von Willebrand factor concentrates (used to treat von Willebrand disease) have been used. Most recently the use of anti-von Willebrand factor antibody is being evaluated.

**Rationale for therapeutic apheresis**

TPE with plasma replacement has significantly improved patients’ clinical outcomes. One hypothesis is that TPE removes anti-ADAMTS13 antibodies, while replacing ADAMTS13 or plasma levels. TPE has been used in higher volumes (100% whole blood) to eliminate citrate reactions, especially for patients with moderate to severe thrombocytopenia. Plasmapheresis levels may decrease following serial TPE procedures with cryoprecipitate plasma as replacement. One recent study showed that the use of cryoprecipitate poor plasma as replacement may be associated with more frequent acute exacerbations. In patients with severe allergic reactions to plasma proteins or limited supply of ABO-compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma (O’Toole, 2013). Albumin alone without any plasma replacement or infuson however has never shown efficacy.

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**Duration and discontinuation/number of procedures**

TPE is generally performed daily until the patient count is > 150 × 10^9/L, and LDL is near normal for 2-3 consecutive days. The rate of correct TPE over a longer duration has not been studied prospectively but is used frequently. Prevention of anemia alone on peripheral blood smear is in the absence of other clinical features of TIP does not preclude discontinuation of treatment.
Pathogenic Substances Removed by Plasmapheresis

- Antibodies
- Probable antibodies
- Ag-Ab complexes
- Paraproteins
- Endogenous toxins
- Exogenous poisons

Principle Disease Treated with TPE

**Removal**
- **Autoantibody:** TTP, Myasthenia gravis (MG), Neuromyelitis Optica (NMO), Anti-GBM, ANCA-associated vasculitis, etc.
- **Probable autoantibody:** Multiple sclerosis, Guillain-Barré, CIDP, etc.
- **Antigen-Antibody complexes:** HCV vasculitis, S.L.E., etc.
- **Alloantibody:** Transplant sensitization, Transplant rejection (humoral), Transfusion reactions, etc.
- **Paraproteins:** Waldenstrom’s, Hyperviscosity, Light-chain neuropathy, Light-chain glomerulopathy, Myeloma cast nephropathy, etc.
- **Non-Ig proteins:** Focal Segmental Glomerulosclerosis (FSGS).
- **Endogenous toxins:** Hyperlipidemia, Liver failure, Sepsis, etc.
- **Exogenous poisons:** Amanita, drugs, etc.

**Replenishment**
- **FFP:** TTP (ADAMTS13), MPGN subtype (complement factor H).
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>a chain non-collagenous domain of type IV collagen</td>
<td>TPE only if Cr &lt; 6 or to treat 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 DAH</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>
Plasmapheresis as First Line Therapy
(Category I ASFA Indication)

1. ANCA associated glomerulonephritis (on HD or DAH)
2. Anti-glomerular basement membrane disease (dialysis indep. Or DAH)
3. FSGS recurrent in transplant
4. **Thrombotic thrombocytopenic purpura (TTP)**
5. Thrombotic microangiopathy associated with ticlopidine
6. Hyperviscosity in monoclonal gammopathies
7. Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
8. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
9. Myasthenia Gravis (moderate-severe, and pre-thymectomy)
10. NMDA receptor encephalitis
TTP: ADAMTS 13 and vWF

**ADAMTS13:** A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13
- vWF synthesized in endothelial cells and assembled in larger multimers (ULVWF)
- Rapidly degraded in circulation by vWF cleaving protease (ADAMTS13)
- Deficiency leads to accumulation of ULVWF and platelets & thrombi

Case 1

As the provider of plasma exchange now what do you do?
- Is it indicated?
- **Informed consent: procedure plus blood products**
- Vascular access assessment
- Labs to send before plasmapheresis begins
- Plasma exchange prescription
  - Volume to remove
  - Replacement solution given
  - Machine: membrane vs centrifugal
  - Access
  - Anticoagulation
  - Frequency
Informed Consent: Complications

- Access related issues
  - Catheter vs PIV
- Hypotension
- Anti-coagulation related issues
  - Citrate-induced hypocalcemia
  - Metabolic alkalosis
  - Heparin: bleeding, HIT
- Depletion coagulopathy
- Infections
- Electrolyte abnormalities
- Anaphylactoid reactions
- Air embolism

- Common complications occur in <10%
- Rare occur in <1.5%
Complications of Citrate Anticoagulation - Hypocalcemia

<table>
<thead>
<tr>
<th>Calcium regimen</th>
<th>Symptom rate (%)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No calcium</td>
<td>9.1%</td>
<td>Mokrzycki M, Kaplan A. Am J Kidney Dis 1994</td>
</tr>
<tr>
<td>I.V. 10% Ca(^{++}) gluconate</td>
<td>1 %</td>
<td></td>
</tr>
<tr>
<td>Calcium added to Albumin before infusion</td>
<td>2.7%</td>
<td>Kankirawatana et al. J Clin Apheresis 2007</td>
</tr>
</tbody>
</table>

UCSD: we run a constant infusion of calcium chloride during the treatment via the return line: CaCl\(_1\)g/135mL of NS, running at 80-100ml/hr.
Case 1

- As the provider of plasma exchange now what do you do?
  - Is it indicated?
  - Informed consent: procedure plus blood products
  - **Vascular access assessment**
  - Labs to send before plasmapheresis begins
  - Plasma exchange prescription
    - Volume to remove
    - Replacement solution given
    - Machine: membrane vs centrifugal
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TTP: urgent treatment should begin - Likely needs a temporary or tunnelled line, but can assess for PIV if using centrifugal TPE
Case 1

- As the provider of plasma exchange now what do you do?
  - Is it indicated?
  - Informed consent: procedure plus blood products
  - Vascular access assessment
  - Labs to send before plasmapheresis begins
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ADAMTS13 activity level and ADAMTS13 inhibitor

Any other labs (antibody, complement, complement genetic panel, etc)
Case 1

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      - Volume to remove
      - Replacement solution given
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      - Anticoagulation
      - Frequency
Plasmapheresis Prescription

- Volume to remove
  - Depends on patient size and Hct
  - 1-1.5x plasma volume

\[ y = e^{-x} \]
Calculating the Total Blood Volume (TBV) & Plasma Volume

Gilcher’s Rule of Fives
Blood Volume (mL/kg of Body Weight)

<table>
<thead>
<tr>
<th></th>
<th>Obese</th>
<th>Thin</th>
<th>Normal</th>
<th>Muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>60</td>
<td>65</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
</tbody>
</table>

One Plasma Volume = TBV x (1-Hct)

Case: 55kg woman with Hct of 21% → TBV = 55kg x 65ml/kg = 3,575 mL
PV = 3,575 x (1-0.21) = 2824.25 mL → 3L exchange
Replacement Solutions

- Fresh Frozen Plasma
  - Full FFP replacement in TTP
  - Partial FFP replacement if diffuse alveolar hemorrhage (DAH), bleeding, procedure, severe depletion coagulopathy etc.
    - ANCA associated vasculitis s/p renal biopsy or with DAH
- 5% Albumin
  - MOST procedures (Myasthenia, Guillain-Barre, NMDA-R encephalitis etc)
- Combination of saline and albumin
  - Never more than 1/3rd saline, risk for hypotension
- Plasma regeneration
  - Patient’s own plasma is purified on-line and re-infused as the replacement volume
  - Selective procedures / columns (LDL apheresis)

We calculated a 3L exchange
Each unit of FFP ~250mL, so 12 units of FFP ordered
Case 1

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Centrifugal Plasmapheresis

Can perform separation of all blood compartments: plasmapheresis, leukapheresis, RBC exchange, platelet depletion
Membrane Based Plasmapheresis

Dialysis equipment that has additional functionality – PLASMAPHERESIS ONLY

PrismaFlex

NxStage
Plasmapheresis: Centrifugal Based Separation

- Kits designed to remove specified cell layer based on specific gravity
- Blood flow rates can range 10-100ml/min
- ACD-A (citrate) anticoagulant (heparin occasionally used)
- Packs RBCs to Hct of 80% or higher
  - Remove 80% or more of plasma \( \rightarrow \) ~1.5xTBV processed to achieve 1.2xTPV
Plasmapheresis: Membrane Based Separation

- Plasma is separated from other cellular components based on size.
- Whole blood flows through the hollow fibers in the filter & the plasma flows through the pores (0.2-0.6 µm) in the fiber walls.
- Blood flow typically ~150ml/min
- Heparin typical anticoagulant
- Extracts 30-35% plasma, so 3-4x TBV processed to achieve target plasma removal

Optimal TMP = Good Separation
## Comparison: Centrifugal vs Membrane TPE

<table>
<thead>
<tr>
<th></th>
<th>cTPE = Centrifugal Plasmapheresis</th>
<th>mTPE = Membrane Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement volume for 3-liter exchange</td>
<td>3 liters of 5% Albumin</td>
<td>3 liters of 5% Albumin</td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>~ 35 ml/min</td>
<td>~ 35 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>~ 85% (75 - 85%)</td>
<td>~ 35% (30 - 35%)</td>
</tr>
<tr>
<td>Plasma flow rate</td>
<td>~ 42 ml/min</td>
<td>~ 100 ml/min</td>
</tr>
<tr>
<td>Blood flow rate (Hct 40%)</td>
<td>~ 70 ml/min</td>
<td>~ 165 ml/min</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Needles in arm veins or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Citrate (ACD-A at ~1:12 ratio with whole blood)</td>
<td>Heparin (usually) or Citrate (at ~1:20)</td>
</tr>
<tr>
<td>If citrate used</td>
<td>6 ml/min (to machine), minus 85% (extraction) = 1 ml/min to patient</td>
<td>8 ml/min, minus 35% = 5 ml/min</td>
</tr>
</tbody>
</table>
## Comparison: Centrifugal vs Membrane TPE

<table>
<thead>
<tr>
<th></th>
<th>cTPE = Centrifugal Plasmapheresis</th>
<th>mTPE = Membrane Plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement volume for 3-liter exchange</td>
<td>3 liters of 5% Albumin</td>
<td>3 liters of 5% Albumin</td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>~ 35 ml/min</td>
<td>~ 35 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>~ 85% (75 - 85%)</td>
<td>~ 35% (70 - 85%)</td>
</tr>
<tr>
<td>Plasma flow rate (ml/min)</td>
<td>~ 42 ml/min</td>
<td>~ 100 ml/min</td>
</tr>
<tr>
<td>Blood flow rate (ml/min)</td>
<td>~ 70 ml/min</td>
<td>~ 165 ml/min</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Needles in arm veins or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Citrate (ACD-A at ~1:12 ratio with whole blood)</td>
<td>Heparin (usually)</td>
</tr>
<tr>
<td>If citrate used</td>
<td>Some risk of citrate symptoms</td>
<td>Higher blood flow limits use of peripheral veins</td>
</tr>
<tr>
<td></td>
<td>6 ml/min (to machine), minus 85% (extraction) = 1 ml/min to patient</td>
<td>Systemic a/c, but no citrate reactions</td>
</tr>
<tr>
<td></td>
<td>Higher risk of citrate symptoms if citrate used</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 ml/min, minus 35% = 5 ml/min</td>
<td></td>
</tr>
</tbody>
</table>

- **Flow rate limited by citrate load**
- **Citrate better anticoagulant**
- **... does not cause bleeding**
- **Hemolysis if ratio exceeded**
- **Longer treatment if flow rate has to be reduced**
- **Higher risk of citrate symptoms if citrate used**
## Considerations: Citrate Load

<table>
<thead>
<tr>
<th>Method</th>
<th>Citrate for a/c (mmol)</th>
<th>Citrate if FFP replacement* (+ extra = total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrifugal TPE using citrate</td>
<td>14 /hr</td>
<td>64 /hr</td>
</tr>
<tr>
<td>Membrane TPE using citrate</td>
<td>14-56 /hr</td>
<td>64-106 /hr</td>
</tr>
<tr>
<td>Membrane TPE using heparin</td>
<td>0</td>
<td>50 /hr</td>
</tr>
<tr>
<td>Continuous hemodiafiltration</td>
<td>20 /hr</td>
<td></td>
</tr>
<tr>
<td>(UCSD citrate-anticoagulated CRRT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFP (1 unit = ~250 ml) *</td>
<td>~ 7 /unit</td>
<td></td>
</tr>
<tr>
<td>Packed RBC’s (1 unit = ~300 ml)</td>
<td>2-3 /unit</td>
<td></td>
</tr>
</tbody>
</table>

*FFP at 30ml/min = 1800 ml/hr = 7+ units/hr ⇒ citrate at ~50 mmol/hr
Filtration vs. Centrifugation Apheresis

**Filtration**
- Minimal availability in the USA
  - Poor industry support
- Limited to plasma exchange
  - Low efficiency

**Centrifugation**
- The standard in the USA
  - Very good industry support
- Multiple procedures (cytapheresis)
  - Opportunity to provide cellular therapies
Case 1

- As the provider of plasma exchange now what do you do?
  - Is it indicated?
  - Informed consent: procedure plus blood products
  - Vascular access assessment
  - Labs to send before plasmapheresis begins
  - Plasma exchange prescription
    - Volume to remove
    - Replacement solution given
    - Machine: membrane vs centrifugal
    - Access
    - Anticoagulation
      - Frequency
Prescribing TPE: Frequency

Number and frequency of treatments depends upon:

- Pathogenic molecule
- Volume of distribution
- Disease characteristics

**Removal of IgM**

Monoclonal IgM (mg/dl)

- 5000
- 980
- 254

IgM

Plasmapheresis procedures

Waldenstrom’s macroglobulinemia
- IgM is large (~970,000 Daltons)
- 90% of IgM stays intravascular

**Removal of IgG**

IgG Autoantibody titer

- 1:20,480

IgG

Plasmapheresis procedures

Most antibody mediated diseases:
- IgG is smaller (~146,000 Daltons)
- Only 25%-30% is intravascular
Distribution of Body Water

Standard 70 Kg Adult

Total body water (TBW) = 50% - 60% of weight, say 57% = 40 liters

- Intracellular fluid = 60 - 65% of TBW, say 62.5% = 25 liters
- Extracellular fluid = 35 - 40% of TBW, say 37.5% = 15 liters

- Intracellular = 25 liters
- Interstitial fluid (third space) = 25 - 30% of TBW, say 30% = 12 liters
- Plasma ~8% = 3 liters
Number of TPE Procedures Needed

Removing IgM from plasma

\[ y = e^{-x} \]

1x = 3L

One TPE

2 hours

Intracellular
25 liters

No IgM in intracellular fluid

Interstitial (3rd space)
12 liters

IgM minimal in 3rd space

Plasma 3 liters

Removing IgG from extracellular fluid

\[ y = e^{-x} \]

1x = 15L

7 TPE procedures

11 days

Intracellular
25 liters

No IgM in intracellular fluid

Extracellular fluid
15 liters

IgG plentiful in 3rd space

IgG moves slowly from 3rd space

Plasma
Thrombotic Thrombocytopenic Purpura:

**Technical notes**
Transfusion of RBC, when medically necessary, may be given emergently around the time of apheresis. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio (to whole blood) to minimize citrate reactions, especially for patients with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with cryoprecipitate poor plasma as replacement. One recent study showed that the use of cryoprecipitate poor plasma as replacement may be associated with more frequent acute exacerbations. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma (O’brien, 2013). Albumin alone without any plasma replacement or infusion however has never shown efficacy.

<table>
<thead>
<tr>
<th>Volume treated</th>
<th>1–1.5 TPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement fluid</td>
<td>Plasma</td>
</tr>
</tbody>
</table>

**Duration and discontinuation/number of procedures**
TPE is generally performed daily until the platelet count is $>150 \times 10^9/L$, and LDH is near normal for 2–3 consecutive days. Role of tapering TPE over longer duration has not been studied prospectively but is used frequently. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

- Frequency: daily until platelet count $>150K$ and LDH near normal for 2-3 consecutive days
- Role of tapering not studied prospectively, but used frequently
Putting it All Together

- **Diagnosis:** TTP
- **Access:** temporary catheter
- **Machine:** Centrifuge or Membrane
- **Volume to exchange:** 3 Liters (1-1.5 x TPV)
- **Replacement Fluid:** all FFP – 12 units
- **Anti-coagulation:** ACD-A (cTPE) or heparin (mTPE)
- **Labs prior to start:** ADAMTS13 activity level and inhibitor
- **Frequency:** daily
Case 1: Response to Plasma Exchange

<table>
<thead>
<tr>
<th>Day 1:</th>
<th>Day 2:</th>
<th>Day 3:</th>
<th>Day 4:</th>
<th>Day 5:</th>
<th>Day 6:</th>
</tr>
</thead>
</table>

- Skipped TPE
- Skipped TPE
Case 1: Continued

Daily TPE from Day 7 to day 19, skipped day 20, then alternated days
• A 2½-day conference for MDs and RNs, from established practitioners to those starting a new program.
• Nationally prominent faculty.
• Didactics on the basics.
• Symposia on plasma exchange, cell apheresis, disease applications, special patient populations, new science, program management, etc.
• Hands-on workshops.
• cme.ucsd.edu/apheresis