Therapeutic Plasma Exchange
Indication and Prescription

Pediatric CRRT Workshop
Pediatric Nephrology Seminar

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Therapeutic Plasma Exchange (TPE)

- An extracorporeal treatment modality that removes circulating pathologic factors from plasma.
- Plasma is removed and replaced with a colloid solution (albumin, plasma or a combination solutions).
- Technology and advancements in understanding of disease processes have made TPE an important and safe treatment modality for children with renal and other immune-mediated diseases.
Objectives:

- To remove pathogenic circulating high molecular weight molecules eg. antibody, immune complex, toxin

- To replace deficient factors eg. ADAMTS13, complement regulation factors
Molecular Targets

- Effectiveness of extracorporeal therapies in relationship to the size of target substance.

Guidelines for TPE

• American Society for Apheresis (ASFA) guidelines
• Classification into 4 categories based on evidence of TPE efficacy in clinical disorders:
  - Category I: TPE is accepted as first-line therapy
  - Category II: TPE is accepted as second-line therapy
  - Category III: Optimum role of TPE is not established.
    • Decision making should be individualized
  - Category IV: Evidence suggests TPE is ineffective or harmful

## ASFA guidelines for TPE in children

<table>
<thead>
<tr>
<th>Disorders</th>
<th>ASFA Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune-mediated glomerulonephritis:</strong></td>
<td></td>
</tr>
<tr>
<td>ANCA-Associated rapidly glomerulonephritis</td>
<td>1</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease</td>
<td>1</td>
</tr>
<tr>
<td>SLE, severe (cerebritis, pulmonary hemorrhage)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Henoch-Schönlein purpura:</strong></td>
<td></td>
</tr>
<tr>
<td>- Crescentic or Severe extrarenal disease</td>
<td>3</td>
</tr>
<tr>
<td><strong>Immunoglobulin A nephropathy:</strong></td>
<td></td>
</tr>
<tr>
<td>- Crescentic or Chronic progressive</td>
<td>3</td>
</tr>
<tr>
<td><strong>Immune complex rapidly progressive glomerulonephritis</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Atypical Hemolytic-uremic syndrome (aHUS)</strong></td>
<td></td>
</tr>
<tr>
<td>- aHUS associated with Autoantibody to factor H</td>
<td>1</td>
</tr>
<tr>
<td>- aHUS associated with Complement gene mutations*</td>
<td>2</td>
</tr>
<tr>
<td>- aHUS associated with Streptococcal pneumoniae</td>
<td>3</td>
</tr>
</tbody>
</table>

*Use FFP as replacement; Modified from J Clin Apher. 2013
## ASFA guidelines for TPE in children

<table>
<thead>
<tr>
<th>Disorders</th>
<th>ASFA Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent focal segmental glomerulonephritis</td>
<td>1</td>
</tr>
<tr>
<td>Antibody-mediated rejection</td>
<td>1</td>
</tr>
<tr>
<td>Desensitization</td>
<td></td>
</tr>
<tr>
<td>- Living donor, + cross-match; ABO-incompatible</td>
<td>1</td>
</tr>
<tr>
<td>- Deceased donor, high panel reactive antibody</td>
<td>3</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TMA)*</td>
<td>1</td>
</tr>
<tr>
<td>- Autoantibodies to ADAMTS-13; ADAMTS-13 deficiency</td>
<td>1</td>
</tr>
<tr>
<td>- Drug-induced: Cyclosporine; Tacrolimus</td>
<td>3</td>
</tr>
<tr>
<td>- Hematopoietic stem cell transplant-associated</td>
<td>3</td>
</tr>
<tr>
<td>Wilson disease, fulminant</td>
<td>1</td>
</tr>
<tr>
<td>Antiphospholipid syndrome, catastrophic</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis with multi-organ failure</td>
<td>3</td>
</tr>
</tbody>
</table>

*Use FFP as replacement; Modified from J Clin Apher. 2013*
Disorders: TPE not indicated

ASFA Category IV:
Evidence suggests apheresis is ineffective or harmful
• **Hemolytic-uremic syndrome**
  - HUS associated with Shiga-like toxin
  - aHUS: membrane cofactor protein (CD64) mutations
• **Systemic lupus erythematous**
  - Nephritis

*Modified from J Clin Apher. 2013*
## Techniques

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Centrifuge TPE</th>
<th>Membrane TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Centrifugal force</td>
<td>Membrane filter</td>
</tr>
<tr>
<td>Separation</td>
<td>Specific gravity</td>
<td>Molecular Size</td>
</tr>
<tr>
<td>Blood volume in circuit (ml)</td>
<td>Approximate 180</td>
<td>110-125</td>
</tr>
<tr>
<td>Blood flow (ml/min)</td>
<td>10–150</td>
<td>10-200</td>
</tr>
<tr>
<td>Plasma extraction (%)</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Plasma removal (ml/min)</td>
<td>Variable</td>
<td>30</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Citrate</td>
<td>Heparin</td>
</tr>
</tbody>
</table>

Membrane filtration

- It can be performed using HD or CRRT equipment with a plasma filter.
- The transmembrane pressure forces the plasma through the membrane; blood components are separated by size.
- It is a more selective method than centrifugation and leads to less thrombocytopenia compared to centrifugation.
- The filtration rate is limited, and a smaller portion of plasma is removed, resulting in longer procedure times to achieve the same reduction in the target molecule.
Advantage and Disadvantage

Centrifugation:
- **Advantage:** Short procedure time
- **Disadvantage:** Large priming volume
  - Possible Citrate overdose
  - Thrombocytopenia, hemolysis

Membrane filtration:
- **Advantage:** Small priming volume
  - Equipment readily available
- **Disadvantage:** Long procedure time
Replacement Fluid

**Albumin**

*Advantage:*
- Minimize risk of anaphylaxis
- Avoid viral transmission

*Disadvantage:*
- Depletion of coagulation factors, immunoglobulin
- Electrolyte disturbance: Hypokalemia

**Fresh Frozen Plasma**

*Advantage:*
- Replace coagulation factors and immunoglobulins

*Disadvantage:*
- Hypothermia
- Infectious disease transmission
- Transfusion related acute lung injury
- Hypocalcemia (from citrate)
- Metabolic alkalosis (from citrate)
- Anaphylactoid reactions
Target molecule kinetics during TPE

- Single plasma volume exchange lower target molecule by 60%
- 1.4 times volume exchange lower target molecule 75%.

- In general, it is suggested to perform 1 to 1.5 plasma volume exchange per TPE session

TOTAL REPLACEMENT VOLUME

Estimated Plasma Volume = 80 x Wt x [1 - (Hct/100)]

- Plasma volume (mL)
- Wt: Body weight (kg)
- Hct: Hematocrit (%)
- In general, one to 1.5 plasma volume is exchanged.

Example:
Calculated volume for TPE for a 6 year old, 20-Kg child; Hct of 30%:
Estimated plasma volume = 80*20*[1 -0.3] = 1120 mL
Total plasma volume for exchange = 1.5*1120 = 1680 mL
TPE Schedule

- **IgM:**
  - 75% intravascular; half life 5 days.
  - Only 1-2 TPE will be required to reduce IgM levels.

- **IgG:**
  - 45% intravascular, half-life 21 days; within 48 hours of TPE, plasma IgG levels return to 40% of pre-TPE level.
  - More TPE procedures and the need of immunosuppressive therapy are required to significantly reduce IgG levels.

After TPE, target molecule levels rebound back in plasma due to the redistribution from the extravascular space, and ongoing synthesis.
Complications and Monitoring

• Extracorporeal circulation: Hypotension, Hypothermia
• Catheter-related issues: Thrombosis, Infection; Clotting circuit
• Anticoagulation: Bleeding, Heparin-induced thrombocytopenia
• Replacement fluid: FFP:
  • Citrate induced: Hypocalcemia, Metabolic alkalosis, Hypotension, Seizure
  • Transfusion related: Acute lung injury-hypoxemia, Infection transmission
• Replacement fluid: Albumin: Hypokalemia, Loss of coagulation factors, Hypogammaglobulinemia
• Plasma exchange: Removal of medications (high protein bound, low volume distribution (eg. IVIG, Rituximab, Vancomycin, anticonvulsants)
Monitoring:

• Laboratory tests before TPE:
  - Hematocrit, ionized calcium, coagulogram, fibrinogen;
  - If applicable: ADAMTS-13 for TTP, donor specific antibody for transplant rejection, immunoglobulin levels

• Monitoring during Procedure
  - Continuous cardiac monitoring and pulse oximetry
  - Record temperature, pulse and BP every 15 minutes
  - Monitor circuit pressures: Access, Filter, Return, TMP
  - Follow ionized Ca and activated clotting time as needed
References:

• Friday JL, Kaplan AA. Therapeutic plasma exchange. Up to date. (Updated: Jan 2014)