Therapeutic Plasma Exchange: principles and practice in pediatric nephrology

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1394
References


8) Plasmapheresis;principles ,Methods and Clinical use. www.ibto.ir

- Apheresis: Definition & History; Principles and practice
- TPE: key points
- Pediatric considerations
- TPE in Pediatric Nephrology Diseases
Apheresis: Definition & History
Definitions

- **Apheresis**: [in Greek] “to carry away”
  - Cytapheresis; Plateletpheresis; Plasmapheresis
- **Plasmapheresis**: plasma is removed and replaced w/plasma substitute (N.S. and/or 5% albumin)
- **Plasma exchange**: plasma is removed and exchanged w/allogeneic plasma
- **TPE**: therapeutic plasma exchange
Use of Apheresis

- **Collection**
  - facilitate collection of a blood component (plt, wbc) from an allogeneic donor
  - collection of hematopoietic progenitor cells

- **Therapy** (therapeutic apheresis):
  - removing undesired substances like antibodies, lipids from the circulation, which are:
    - present in plasma
    - tightly bound to plasma proteins
  - reducing excess wbc/plt in pts w/myeloproliferative disorders
  - automated exchange of sickled rbc
Abnormal Substances Removed From the Circulation by TPE

1) Paraproteins (Waldenstorm’s Macroglobulinemia)
2) Autoantibodies (Myasthenia Gravis, Goodpasture’s syn.)
3) Lipids (LDL in familial hypercholesterolemia; phynatic acid in refsum’s disease)
4) Toxins or drugs (that are bound to albumin)
5) Circulating immune complexes (CIC)
6) Soluble mediators of inflammatory response (activated complement component, vasoactive substances)
History:

- Plasmapheresis (removal of plasma with return of RBC) first performed 1914 John Abel at Johns Hopkins University in a dog in context of artificial kidney research.

- 1959 Skoog and Adams used manual plasmapheresis in patient with Waldenstrom’s to reduce serum viscosity.

- Developed manual plasmapheresis was major method of collecting source plasma from paid donors until early 1980’s.
History

- Earliest work in early 1950’s by Dr. Edwin Cohn at Harvard
  - Devised fractionation scheme for plasma and important in providing albumin for WWII
  - Blood into conical centrifugal separation chamber

- 1962 IBM engineer son dx with CML
  - Together with Dr. Emil Freireich and IBM developed NCI-IBM (2990) at National Cancer Institute
  - Initially process 11L of blood from CML patients for leukopheresis

- 1964 studies on CLL patient leukopheresis

- 1969 1\textsuperscript{st} automated plasma exchange procedures
Apheresis: Principles of Separation & Methods
Centrifugal separation based on special gravity

- Plasma (1.025-1.029 specific gravity)
- Platelet (1.040)
- Mononuclear (lymph, mono, PBSC, blast) (1.070)
- Granulocyte (neut, baso, eos) (1.087)
- Neocyte RBC
- RBC (1.093-1.096)
METHODS

1) Centrifugation
   A- manual:
   B- automatic:
   – Intermittent Flow Centrifugation [IFC]
   – Continuous Flow Centrifugation [CFC]

2) Filtration: based on size, not gravity
   Smaller; less EV

3) Combined Centrifugation & Filtration

4) Affinity Adsorption Apheresis: based on physical, chemical or immunological properties
Manual vs Automatic:

- Cheaper & Simpler
- No machine
- Less dependent to size of IV access
- Less volume/slow
- Error in RBC return
- Alternative to automatic method
Intermitent Flow Centrifugation [IFC]:

- Intermittent flow
  - Blood processed in discrete batches
  - Separation until container filled with dense component (RBC)
  - Needs to empty before next batch

*Haemonetics MSC plus, V50, V30*
Continuous Flow Centrifugation [CFC]

– All fractions can be removed in ongoing manner
  • Do not need to empty container until end of procedure

*Cobe spectra, CS 3000, Fresnius AS 104*
Intermittent vs. Continuous Flow

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

- **Continuous flow**: blood withdrawn, processed and reinfused simultaneously
  - **Pro**: smaller ECV, hemodynamic stability, faster
  - **Con**: 2 venipuncture sites for peripheral access
  - Examples: **COBE Spectra**, Fenwal C3000 Plus, Fresenius AS104
Membrane Filtration

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

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

- In contrast to conventional plasma-exchange therapy, immunoadsorption removes harmful agents while retaining natural plasma components, enabling the patient’s own modified plasma to be used as a replacement solution.

- Perfuse plasma through a selective removal column/filter
  - Dextran sulfate column: removes LDL
  - Staphylococcal protein A: removes IgG by binding to the Fc portion
immunoabsorption

- Maximum rate of 50ml/min
- 2.5 - 3 plasma volume are processed in each session
- Treatment period: 2 days, allowing overnight equilibrium
- The same columns can be kept refrigerated (in 0.1% Thiomersal) and used again for the same patient
Main Questions about TPE

- Characteristics of pathogen for uptake
- Expectation for success
- Plasma Volume for Exchange in each session
- TPE intervals
- Fluid substitutions
- TPE and interactions
- Lab tests needed before and during TPE
- Where and by Whom it should be done
Characteristics of pathogen for the most efficient uptake

- Macromolecules (>15000 D)
- Long half life: IgG with 21 days hl
- Slow synthesis rate
- Intravascular compartment
- Toxic OR refractory to conventional less complicated treatments
Expectation for success

- The correlation will be correct if pathogen is:
  - totally intravascular;
  - not produced;
  - not consumed.

- Accordingly the success rate could be sorted descendingly:
  1. Fibrinogen, C3
  2. IgM, Cholestrol, ALP
  3. IgA, IgG, LDH, CK
  4. Small molecules & minerals

- Little advantage beyond 1.0-1.5 volumes:
  - Decrease efficiency:
    - 1 pv = 63%,
    - 2 pv = 86%,
    - 3 pv = 95%
  - More time (2Hr for each PV)
  - More cost
Removal of IgG and IgM by plasma exchange:

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular amount</td>
<td>45%</td>
<td>76%</td>
</tr>
<tr>
<td>“total body” removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PV Ex.</td>
<td>28%</td>
<td>48%</td>
</tr>
<tr>
<td>1.5 PV Ex.</td>
<td>35%</td>
<td>59%</td>
</tr>
<tr>
<td>2 PV Ex.</td>
<td>39%</td>
<td>65%</td>
</tr>
</tbody>
</table>

- Rebound effect & Neg Feedback:
  - less IgG level leads to more synthesis
  - Immunosuppressive treatment has agonistic effect on TPE
- IVIG blocks FcRn: more free Intravascular pathogen IgG; more pathogen IgG catabolism and more pathogen IgG available for TPE
- TPE is more efficient for natural IgG than Paraprotein IgG (due to more plasma volume)
TPE intervals & sessions

- Depends on:
  - Type of pathogen particle
  - Severity of disease & clinical status
  - Regeneration of pathogen
  - Redistribution of pathogen
  - Adjuvant Rx: Immunosuppressive Rx; IVIG
TPE intervals & sessions

- **GBS**: continue 1-2 times/W until clinical improvement
- **TTP**: daily until clinical improvement: normalization of LDH and Platelet level for at least 2-3 days
- **GPS**: daily for at least 2 weeks
- **Combination with immune suppressives**: continue for 5-10 times until drug response expectation

<table>
<thead>
<tr>
<th>Substance to Remove</th>
<th>Treatment Volume (ml/kg)</th>
<th>Treatment Interval (in hours)</th>
<th>Treatment Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td>40-60</td>
<td>24-48</td>
<td>Four to six treatments</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>40-60</td>
<td>24-48</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>40-60</td>
<td>24</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Cryoproteins</td>
<td>40-60</td>
<td>24-48</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Toxins</td>
<td>40-60</td>
<td>24-72</td>
<td>Treat for response</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome</td>
<td>40</td>
<td>24</td>
<td>Treat to establish remission</td>
</tr>
<tr>
<td>Immunologic rebound</td>
<td>40-60</td>
<td>24-48</td>
<td>Two to three treatments followed by immunosuppressive medication</td>
</tr>
</tbody>
</table>
# Fluid substitutions

<table>
<thead>
<tr>
<th>Replacement solutions</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloids</td>
<td>• Low cost • Hypoallergic • No viral risk</td>
<td>• Rapid exit to EVC: 2-3 volumes required • No Coaglation • No Immunoglobulins</td>
<td>• &lt;500-1000 cc TPE • Hyper viscosity</td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>• Iso/mild hyper-oncotic • No inflammatory mediators • No viral risk</td>
<td>• High cost • No Coaglation • No Immunoglobulins • Dilutional anemia • <strong>Drug cross reaction:</strong> ACEI</td>
<td>• Rare reactions due to pre-kalirein and pyrogens</td>
</tr>
<tr>
<td>Plasma:</td>
<td>• Low cost • Maintain levels of: • Immunoglobulins • Complements • Antithrombin • proteins</td>
<td>• Viral transmission risk • ABO compatibility test • Allergic reaction • TRALI • Sensitization • Citrate load</td>
<td>• First choice in: • TTP • Repeated TPE • Bleeding tendency • Liver failure • <strong>Cryo-poor plasma is indicated for TTP refractory to TPE with plasma</strong></td>
</tr>
<tr>
<td>FFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDT-plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QR-Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>• Moderate cost • Isotonic • No inflammatory mediators</td>
<td>• No Coaglation • No Immunoglobulins • Long-term residual of HES • <strong>Contraindicated in renal failure</strong></td>
<td>• Indicated in patients with severe reactions to albumin and plasma</td>
</tr>
</tbody>
</table>
Recommended method

- Due to Hypo-oncotic characteristic of crystalloids which may lead to intravascular fluid deficit, usually used in combination with albumin: start procedure with NS replacement, then finish with albumin replacement.

- Albumin 4-4.5% (Albumin 5% 60-70% + N/S 30-40%)

- TTP: FFP or CPP 60-70% + 20-30% N/S

- Repeated TPE (prevention of coagulopathies): last cycle of each session 10-15 cc/kg FFP
Patient History and Medications

- Does patient have a disease which is amenable to treatment by the requested apheresis procedure
- Does the patient/donor capable of sustaining the fluid shifts associated with apheresis
- Certain medications, most notably antibiotics and anticoagulant can be removed by apheresis - should be given immediately after the procedure
- Angiotensin-converting enzymes (ACE) inhibitors
ACE inhibitors and Apheresis

1- Activation of XII
2- Inhibition of Kinase II

ACE Inhibitor
Kinase I & II
Bradykinin

Prekallikrein → Kallikrein → H.M.W.K → Bradykinin

Vasodilatation
TPE and interactions: Drug clearance

- No change needed:
  Digixin; prednisolone; propranolol; valporic acid; phenobarbital; cyclosporine; ceftriaxone; ceftazidim

- Added dose needed:
  Salicylates; aminoglycosides; phenytoin (?)

- Should be omitted immediately after TPE (partial enzyme deficiency)
  - Choline esterase: neuromuscular blocking drugs (succinylcholine)
  - Catabolic Enzymes for bradykinins: ACEI (captopril, enalapril)
Normal Constituents Removed

- **Coagulation factors:**
  - Most coagulation factors are lost at the same rate
  - Rapidly synthesized; replacement usually is 2-3 days following exchange (VIII; X; VWF: RCO after 4 h)
  - Practical: measure PT/PTT/Fibrinogen every 2-3 days (rather than daily)

- **Platelets:**
  - 25-30% per procedure
  - Endogenous synthesis replaces lost platelets within 2-4 days (except hypoplastic/aplastic marrow)

- **Lab work (esp. chemistry):** not immediate post-procedure; allow equilibrium intra/ extravascular space
## Alteration in Blood Constituents by a 1-PV Exchange

<table>
<thead>
<tr>
<th>Constituent</th>
<th>% decrease</th>
<th>% recovery 48 hrs post exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factors</td>
<td>25 – 50</td>
<td>80 – 100</td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>20 – 30</td>
<td>Variable</td>
</tr>
<tr>
<td>Liver Enzymes</td>
<td>55 – 60</td>
<td>100</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>C3</td>
<td>63</td>
<td>60 – 100</td>
</tr>
<tr>
<td>Platelets</td>
<td>25 – 30</td>
<td>75 – 100</td>
</tr>
</tbody>
</table>

Modified from: Weinstein, in McLeod, Apheresis, Principles and Practice, 3rd edition, AABB press, 2010
• Routine supplementation with FFP not necessary for most patients

• Fibrinogen replaced most slowly (but this is variable depending on patient – Fg is an acute phase reactant, elevated in many patients)

• If consecutive TPE’s with albumin replacement are performed, check fibrinogen. If falls <100mg/dL, consider increasing interval between exchanges, or supplement with FFP/cryoprecipitate
Lab tests needed before and during TPE

- Pathogen particle or element
- CBC:Hct; Platelet
- PT;PTT
- Electrolyte
- Serum Albumin & Globulin

Some hours after session or just before the next session
Site & persones

- Expert persons: Nurse and physician
- CPR and Cardiac monitoring and assist set
- In severe cases, and frequent, high volume TPE: in hospitals with ICU
Pediatric Apheresis - Considerations

- How Small Is Too Small?
- Vascular Access
- TBV Calculation
- Blood Prime
- Anticoagulation
- Pump Flow Rates
- Collect Flow Rates
- Volumes Processed
- Adverse Effects
Background

The use of therapeutic apheresis in paediatric patients is still very limited:

- **technical difficulties**:
  - The choice of a suitable machine and method;
  - The choice of suitable vascular access and the insertion site (jugular vein, subclavian vein, femoral vein),
  - and the type of central venous catheter to be used (tunnelling, percutaneous, long-term, short-term)

- **psychological aspects** (Admission to hospital, extracorporeal treatment)

- **physiological response/standards**:
  - Greater difficulty in metabolising citrates
  - Blood volume vs ECV
Pediatric Apheresis - Considerations

Adverse Effects
Pediatric Apheresis - Considerations

Adverse Effects

- Citrate toxicity
- Hypotension/Vasovagal
- Access related complications
  - Infection
  - Hematoma
  - Pneumothorax
  - Air emboli
  - etc
- Platelet loss
- Hemoglobin level drop
- Hypofibrinogenemia
- Transfusion reactions
- Allergic reactions
### TABLE II. Adverse Reactions of Therapeutic Apheresis

<table>
<thead>
<tr>
<th>Reaction</th>
<th>% of procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD Toxicity</td>
<td>3.0</td>
</tr>
<tr>
<td>Vasovagal Reactions</td>
<td>0.5</td>
</tr>
<tr>
<td>Vascular Access Complications</td>
<td>0.15</td>
</tr>
<tr>
<td>FFP Related Reactions</td>
<td>0.12</td>
</tr>
<tr>
<td>Hepatitis B (from FFP)</td>
<td>0.06</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>0.01</td>
</tr>
<tr>
<td>Single death (from underlying disease)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Total</td>
<td>3.856</td>
</tr>
</tbody>
</table>

### TABLE III. Severity of Adverse Reactions (%)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD toxicity</td>
<td>85</td>
<td>12</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vasovagal reactions</td>
<td>1</td>
<td>73</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Vascular access complications</td>
<td>39</td>
<td>49</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>FFP related reactions</td>
<td>36</td>
<td>53</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
paediatric patients are particularly subject to the toxicity of citrates, they have greater difficulty in metabolising citrates in critical situations

Symptoms of citrate toxicity are nonspecific and can be difficult to detect in young children: Abdominal pain, vomiting, pallor, bradycardia, hypotension, anxiety, sweating, agitation, licking their lips (tingling)...

In infants and critically ill, semi-conscious patients, hypotension may be the first sign of hypocalcemia
Pediatric Apheresis - Considerations
Adverse Effects - Hypocalcemia

Differences in patient sensitivity to lower calcium levels may be due, in part, to differences in:

- Magnesium levels
- Serum protein levels
- Decreased serum glucose levels
- Drop rate of ionized calcium
Strategies to prevent Hypocalcemia according to the literature:

- In small children, obtain an ionized calcium level before and during the treatment.
- High volume (>1-2V) frequent & repeated TPE: Check Serum Ca hours after session or just before the next session.
- Supplement calcium.
- Limit the amount of citrate delivered to 1 - 1.5 mg/kg/min².
- Wash RBCs used for priming.
- Avoid transfusions on the same day.
- Use a blood warmer.
- *heparin or ACD associated heparin* may be used as an anticoagulant, (In the absence of any clotting disorders).
Calcium-Supplementation Options according to the literature:

- Bolus dosing of calcium gluconate 0.5 g/10 kg at 1. and 2. hour of collection\(^5\) OR Calcium gluconate 10% 10cc+1000 cc N/S as replacement solution
- Infusion from different vein
- Simultaneous reinfusion of calcium solution into the return line just before it reenters the patient\(^1\)
- Older patients with vague symptoms can be treated with oral calcium carbonate, 10 mg/kg\(^2\)
**Pediatric Apheresis - Considerations**

**Adverse Effects – allergy & anaphylaxis**

- Plasma proteins (IgA, complements, etc.)
- HES: Alternative complement activation (C3a & C5a)
- Ethylen Oxide in plasmapheresis tube set: hapten formation
- ACEI medicines: no inactivation of bradykinin by kininase I & II
  - Plasmapheresis tube sets and patient’s plasma
  - Rapid Albumin infusion increase pre-kalikrein and consequently bradykinin

*(ACEI should be discontinued 48 h before TPE)*
Pediatric Apheresis - Considerations
Adverse Effects - Hypotension

● Decreased Intravascular Volume:
  – High extracorpular Volume (>10.5 cc/kg)
  – Clinical condition: neurologic disorders; severely sick patients, etc
  – Intermittent method of TPE
  – Fluid shift:
    • When blood is removed in the beginning of a procedure
    • Crystalloid replacement
  – Negative Fluid balance:
    • Anticoagulant + Replacement Fluid < Plasma Removed

● Vasovagal reflex
To minimize the risk of hypovolemia and fluid shift:

- Limit the patients extracorporeal (ECV) to <15% of patients TBV at all times:
  - ECV: the “dead spaces” (tubing, chambers) of an instrument. (Range 150-500ml) that need to filled to complete the apheresis circuit

- Priming the instrument with colloid solution or RBCs (washed RBCs diluted with 5% albumin ) may be necessary for a pediatric/small pt

- Hct during TPE should be ≥ 24%

- Start at a slow inlet flow rate of 10 ml/min, then increase flow rate in increments of 5 ml/min²
Pediatric Apheresis - Considerations

Adverse Effects – catheter complications

- Infection
- Thrombosis
- Nerve insults
- Hematoma and bleeding
- AV fistula
- Air emboli (acute dyspnea, cyanosis, tachycardia, and hypotension)
Pediatric Apheresis - Considerations

Adverse Effects – hypokalemia

- Albumin: 35% dilutional decrease in serum potassium
Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

Joseph Schwartz,1 Jeffrey L. Winters,2 Anand Padmanabhan,3 Rasheed A. Balogun,4 Meghan Delaney,5 Michael L. Linenberger,6 Zbigniew M. Szczechowizki,7 Mark E. Williams,8 Yanyun Wu,9 and Beth H. Shaz10,11*

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Aphresis Indication Categories (ASFA/AABB)

- **Category I:** First line therapy – proven to be effective
- **Category II:** Adjunct therapy – proven to be beneficial in some instances
- **Category III:** May be - evidence is conflicting but there is some suggestion of benefit, can be considered if conventional therapy is failing
- **Category IV:** 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.
- **Category P:** Pending
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment (TPE)</th>
<th>Clinical Course</th>
<th>Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; Wegener’s Granulomatosis)</td>
<td>TPE</td>
<td>Dialysis dependence</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>DAH</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Dialysis independence</td>
<td>III</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>TPE</td>
<td>Dialysis dependent and no DAH</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>DAH</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Dialysis independence</td>
<td>I</td>
</tr>
<tr>
<td>Anlastic anemia: pure red cell anlasia</td>
<td>TPE</td>
<td>Anlastic anemia</td>
<td>III</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>TPE</td>
<td>Recurrent in transplanted kidney</td>
<td>I</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome, atypical</td>
<td>TPE</td>
<td>Complement gene mutations</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Factor H antibodies</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>MCP mutations</td>
<td>IV</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome, infection-associated</td>
<td>TPE</td>
<td>Shiga toxin associated</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>S. pneumoniae associated</td>
<td>III</td>
</tr>
<tr>
<td>Henoch-Schonlein purpura</td>
<td>TPE</td>
<td>Crescentic</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Severe extrarenal disease</td>
<td>III</td>
</tr>
<tr>
<td>Immunoglobulin A nephropathy</td>
<td>TPE</td>
<td>Crescentic</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>TPE</td>
<td>Chronic progressive</td>
<td>III</td>
</tr>
<tr>
<td>Nephrogenic sytemic fibrosis</td>
<td>ECP</td>
<td></td>
<td>III</td>
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<tr>
<td></td>
<td>TPE</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td>Stage</td>
<td>Category</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Renal transplantation, ABO compatible</td>
<td>TPE</td>
<td>Antibody mediated rejection</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desensitization, living donor, positive crossmatch due to donor specific HLA antibody</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desensitization, high PRA deceased donor</td>
<td>III</td>
</tr>
<tr>
<td>Renal transplantation, ABO incompatible</td>
<td>TPE</td>
<td>Desensitization, live donor</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Humoral rejection</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group A2/A2B into B, deceased donor</td>
<td>IV</td>
</tr>
<tr>
<td>Thrombotic microangiopathy, drug associated</td>
<td>TPE</td>
<td>Ticlopidine</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clopidogrel</td>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>Cyclosporine/Tacrolimus</td>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quinine</td>
<td>IV</td>
</tr>
<tr>
<td>Thrombotic microangiopathy, HSCT associated</td>
<td>TPE</td>
<td>Refractory</td>
<td>III</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>TPE</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>TPE</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>General</td>
<td>Description</td>
<td></td>
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<td>---------------------------------------</td>
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<td></td>
<td></td>
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<tr>
<td>Rationale(^a)</td>
<td>Based on the established/presumptive diagnosis and history of present illness the discussion could include the rationale for the procedure, brief account of the results of published studies, and patient-specific risks from the procedure.</td>
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<tr>
<td>Impact</td>
<td>The effect of therapeutic apheresis on comorbidities and medications (and vice-versa) should be considered.</td>
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<tr>
<td>Technical issues(^a)</td>
<td>The technical aspects of therapeutic apheresis such as type of anticoagulant, replacement solution, vascular access, and volume of whole blood processed (e.g., number of plasma volumes exchanged) should be addressed.</td>
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<tr>
<td>Therapeutic plan(^a)</td>
<td>Total number and/or frequency of therapeutic apheresis procedures should be addressed.</td>
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<tr>
<td>Clinical and/or laboratory end-points(^a)</td>
<td>The clinical and/or laboratory parameters should be established to monitor effectiveness of the treatment. The criteria for discontinuation of therapeutic apheresis should be discussed whenever appropriate.</td>
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</tr>
<tr>
<td>Timing and Location</td>
<td>The acceptable timing of initiation of therapeutic apheresis should be considered based on clinical considerations (e.g., medical emergency, urgent, routine etc). The location where the therapeutic apheresis will take place should be also addressed (e.g., intensive care unit, medical ward, operating room, outpatient setting). If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient.</td>
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</tbody>
</table>

NOTE: The above issues should be considered in addition to a routine note addressing patient’s history, review of systems and physical examination.

\(^a\) ASFA Fact Sheet for each disease could be helpful in addressing these issues.
Rationale for therapeutic apheresis:

- TPE can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators
- TPE over PLx: benefits without risk of volume overload, development of hyperproteinemia, or refractoriness to regular plasma infusion

Duration and discontinuation/number of procedures:

- no standardized approach: based upon patient response and condition
- vascular access, RBC prime, and calcium supplementation are of special concern.
- 5 times per week for 2 weeks, then 3 times per week for 2 weeks with outcome evaluated at day 33 (Sanchez)
- neither continued treatment after initial therapy failure nor ongoing prophylactic treatment for patients with remission
THROMBOTIC THROMBOCYTOPENIC PURPURA

Duration and discontinuation/number of procedures:

- TPE is generally performed daily until the platelet count is above $150 \times 10^9/L$, and LDH is near normal for 2 to 3 consecutive days.
- The median number of TPE procedures to establish hematologic recovery is 7–8 days.
- The 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.
- plasma ADAMTS13 protease levels are not severely deficient nor are ADAMTS13 inhibitors detectable in patients with TATMA. Therefore, a therapeutic rationale is undefined and consistent with the uncertain clinical efficacy.
Pediatric Apheresis - Considerations

Any Questions?