APHERESIS IN CRITICALLY ILL PATIENTS

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Therapeutic plasma exchange (TPE)

Objectives

1. To review what TPE is and isn’t
2. To discuss the potential risks of TPE
3. To discuss evidence-based categories for TPE
4. Review Category 1 and 2 indications
5. To examine important considerations before starting TPE
6. To understand the technical aspects of TPE
   - Centrifugal vs. Membrane TPE
   - Access
   - Prime
   - Anticoagulation
   - Type and Amount of Replacement Fluid
Blood components

 Plasma

 Water (91.5%)
 Proteins (7.0%)
 Other solutes (1.5%)

 ‘Buffy coat’
 WBC
 Platelets

 Lymphocytes
 Granulocytes
 Monocytes

 Basophils
 Neutrophils
 Eosinophils

 RBC

 Rodwig FR. Modern blood banking and transfusion practices. *Apheresis* 2005:Chapter 17
Apheresis – separation and removal of blood components

- Red cell pheresis (aka erythrocytapheresis)
  - Sickle cell crisis
- Stem cell collection
- Leukapheresis
  - Photopheresis
- Low-density lipoprotein (LDL) apheresis
- Plateletapheresis (aka thrombocytapheresis)
- TPE (aka plasmapheresis)

Rodwig FR. Modern blood banking and transfusion practices. *Apheresis* 2005:Chapter 17
Therapeutic plasma exchange (TPE)

• Rapidly and efficiently decreases pathogenic substances present in the plasma
  – Autoantibodies
  – Complement components
  – Cytokines

• As opposed to dialysis, TPE can:
  – Clear large particles
  – Can remove protein-bound particles

TPE does not stop underlying problem

Rodwig FR. Modern blood banking and transfusion practices. *Apheresis* 2005:Chapter 17
Who should get TPE?
How do we determine the potential benefits?

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, Anand Padmanabhan, Nicole Aqui, Rasheed A. Balogun, Laura Connelly-Smith, Meghan Delaney, Nancy M. Dunbar, Volker Witt, Yanyun Wu, and Beth H. Shaz

## Indications for TPE

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<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. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>

Examples of Category 1 indications for TPE

- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
- Acute liver failure*
- ANCA-associated rapidly progressive glomerulonephritis
- Anti-glomerular basement membrane disease (Goodpasture syndrome)
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Focal segmental glomerulosclerosis (recurrent)
- Hyperviscosity in monoclonal gammopathies
- Desensitization for liver transplant

- Kidney transplant – humoral rejection
- Myasthenia gravis
- N-methyl D-aspartate receptor antibody encephalitis
- Paraproteinemic demyelinating neuropathies (IgG, IgA, IgM)
- Progressive multifocal leukoencephalopathy†
- Thrombotic microangiopathy
  - Anti-factor H
  - Ticlopidine
- Thrombotic thrombocytopenic purpura
- Wilson’s disease – fulminant

*High-volume TPE
†Associated with natalizumab

Example of guidelines

THROMBOTIC THROMBOCYTOPENIC PURPURA

<table>
<thead>
<tr>
<th>Incidence: 0.37/100,000/yr (US)</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT</td>
<td>CT</td>
<td>CS</td>
</tr>
<tr>
<td>No. of reported patients: &gt;300</td>
<td>7(301)</td>
<td>2(133)</td>
<td>38(1541)</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 pentad 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 TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4–8 h of diagnostic suspicion, after other causes of systemic TMA such as disseminated intravascular coagulopathy, severe malignant hypertension, pernicious 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 severely deficient 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 anti-ADAMTS13 IgG subclass and appears to be related to disease recurrence. Pregnancy, connective tissue disease, medications, infection, 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 emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Corticoste-
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 antigen 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 autoantibody, while replacing ADAMTS 13 protease activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

**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>
<th>Frequency: Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement fluid:</td>
<td>Plasma</td>
<td></td>
</tr>
</tbody>
</table>

**Duration and discontinuation/number of procedures**

TPE is generally performed daily until the platelet count is >150 × 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
Randomized Groups
- 92 patients received High Volume Plasma (HVP)
  - 8-15% ideal body weight with FFP
- 90 patient received Standard Medical Therapy (SMT)
Primary Outcome – Liver Tx-Free survival
Secondary Outcome – Survival after Liver transplant
Fig. 1. Main results of the intention-to-treat analysis survival data in the standard medical treated group (SMT) compared to the high-volume plasma exchange (HVP) treated group (LogRank: \( p = 0.0058 \)).

Fig. 2. Survival in the groups, in the two groups receiving SMT (standard medical treated group) with and without emergency transplantation (−HVP +LTx vs. +HVP−LTx) and the two group receiving SMT with and without emergency transplantation (−HVP−LTx vs. +HVP−LTx) (LogRank: \( p = 0.0058 \)) and Cox proportional hazard: LTx: \( p < 0.0001 \); HVP: \( p = 0.0076 \).
Thrombocytopenia-Associated Multi-Organ Failure

- TAMOF is characterized by new-onset thrombocytopenia with progression to multiple organ failure (MOF) in critically ill patients.
- The decrease in platelet counts reflects their involvement in causing disseminated microvascular thromboses, which lead to organ ischemia and dysfunction.
- Autopsy studies from patients who died with TAMOF reveal widespread microvascular thromboses in all organs.
- With the current management strategy, mortalities from TAMOF remain high.
## NGUYEN 2008-RCT STUDY

<table>
<thead>
<tr>
<th>Control - 5 pt</th>
<th>PEx – 5 pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-18 yo, 5 males</td>
<td>1-16 yo, 3 females / 2 males</td>
</tr>
<tr>
<td>1 BMT, 1 HTx, 3 Sepsis</td>
<td>2 meningococcemia, 1 CGD, 1 BMT, 1 Liver Failure</td>
</tr>
<tr>
<td>5 with positive BCx</td>
<td>5 with positive BCx</td>
</tr>
</tbody>
</table>
Stop rule reached (5/5 survival in PEx vs. 1/5) after 10 patient review
- At least one PEx patient died later (PEx not re-initiated)
- ECMO and CRRT in one PEx pt, CRRT in 2 control patients
- PEx increased ADAMTS-13 levels and platelet counts and decreased ADAMTS-13 Inhibitor levels
Apheresis complications

- Types of apheresis complications:
  - Associated with the circuit/access
  - Associated with transfusion of blood products
  - Metabolic
  - Unintended removal of drugs

Incidence of non life-threatening complications (n=80) during 260 ICU plasma exchange procedures

- Hypotension
- Chills and fever
- Rash
- Agitation anxiety
- Chest pain – dysrhythmia
- Headache – dizziness
- Nausea
- Paresthesias
- Hypoxemia

Lemaire A et al. J Clin Apher 2017;ePub ahead of print
Apheresis complications

Circuit/access-related complications

Transfusion-related complications

- Transfusion reactions
- Hypocalcemia
  - High risk when fresh frozen plasma (FFP) is used as replacement fluid, as it contains approximately 15% citrate by volume
- Bleeding
  - Loss of platelets, Heparin, Low Fibrinogen (especially with multiple treatments)

Rodwig FR. Modern blood banking and transfusion practices. *Apheresis* 2005:Chapter 17
Apheresis complications

Metabolic complications with TPE

- When using albumin
  - Hypocalcemia
  - Hypokalemia

- When using FFP
  - Hypocalcemia
    - FFP contains approximately 15% citrate by volume
  - Metabolic alkalosis

Removal of drugs as a consequence of TPE

- General principles
  - If the drug stays mostly in the intra-vascular volume (low volume of distribution) it will be removed as much as any plasma product

- Need to think about timing of dosing most medications
  - Timing meds to be given after TPE will address many of the issues

- Guidelines for medications for TPE are available


Just Tell Me What to Do,

YEAH, IF YOU COULD GO AHEAD AND GET TO THE POINT ALREADY,

THAT'D BE GREAT.
Avoid the technician role … be a consultant!

Consultations help weigh potential benefits and risks of TPE specific to the patient, assure a plan is in place to halt the underlying process, and develop a therapeutic plan for TPE.

- Communication between family, team and consultant vital
- DEVELOP A PLAN before the first Treatment!
  - How many treatments, how much, how often?
  - How do we know its working?
  - How will we deal with calcium?
  - How will we deal with medications?
Centrifugal TPE

- Separate each blood component based on density
- Remove a certain part of the blood

![Diagram of blood components and centrifugation process]

Plasma

Buffy coat

Packed RBC

Platelet ± 1.040

Lymphocyte 1.050–1.061

Monocyte 1.065–1.06

Granulocyte 1.087–1.092

Centrifuge

RBC, WBC, and platelets return

Plasma out

Blood in

Kaplan AA. Am J Kidney Dis 2008;52:1180–96

Rodwig FR. Modern blood banking and transfusion practices. Apheresis 2005:Chapter 17
Centrifugal TPE

• Removes all nonsolid elements from the blood
  – Loss of cellular elements and platelets is unavoidable

• Net clearance of a substance by centrifugation is equal to the volume of plasma removed in a given time
  – Sieving coefficient = 1

• Citrate regional anticoagulation
  – Prescribed based on blood flow : citrate ratio

Rodwig FR. Modern blood banking and transfusion practices. Apheresis 2005:Chapter 17
Membrane TPE

Kaplan AA. Am J Kidney Dis 2008;52:1180–96
• Plasma removal is affected by:
  – Blood flow, hematocrit (Hct), pore size, trans-membrane pressure
  – Permeable blood filters
  – Separation is according to molecular size
  – Plasma filter membrane pores are up to 0.2 µm in diameter
    • 30 times the diameter of pores in conventional high-flux hemofilter membranes
    • Removal of substances up to a molecular weight of $3 \times 10^6$ Da
      • Immunoglobulins, immune complexes, complement factors, lipoproteins, and endotoxin
How does plasma separation compare between centrifugal and membrane TPE?

<table>
<thead>
<tr>
<th>Protein</th>
<th>Sieving coefficient</th>
<th>Size MW (daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.97</td>
<td>68,000</td>
</tr>
<tr>
<td>IgG</td>
<td>1</td>
<td>150,000</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.95</td>
<td>512,000</td>
</tr>
<tr>
<td>IgM</td>
<td>0.92</td>
<td>950,000</td>
</tr>
</tbody>
</table>

Centrifugal: 100% of given substance  
Membrane: almost 100% of given substance

MW, molecular weight
TPE prescription

Access

- Less flow needed than in hemodialysis / CRRT

- Choices
  - Central catheter
    - Femoral, IJ, subclavian
    - Tunneled or non-tunneled
  - Large IV x 2
    - Not recommended if multiple procedures planned
  - Double lumen port – needles
  - AVG/AVF

Rodwig FR. Modern blood banking and transfusion practices. Apheresis 2005:Chapter 17
What dose of TPE should I use?

Efficiency of removal is greatest early in the procedure and diminishes progressively during the exchange.

TPE prescription

What dose of TPE should I use?

• How much total blood volume (TBV) to exchange?
  – Between 1.0 and 1.5 total plasma volume (TPV)
    • These values represent the portion of plasma volume exchanged
  – There is only minimal benefit beyond 1.5, while risk increases significantly
    • 1.0 exchange removes ~63%
    • 1.5 exchange removes ~72%
    • Most protocols call for 1.0–1.2 for each exchange
    • In general, 1.2–1.5 is used for the initial treatment, followed by 1.0 volume exchange for subsequent treatments

In most situations, treatment is done daily or every other day

- Guidelines are available for specific diseases
  - Thrombotic thrombocytopenic purpura (TPP): perform treatment daily with 1.0–1.5 total plasma volume (TPV) until platelet count is $>150 \times 10^9/L$, and LDH is near normal for 2–3 consecutive days
  - Recurrent focal segmental glomerulosclerosis (FSGS): perform treatment with 1.0–1.5 TPV x daily x 3 days, then every other day

Why multiple exchanges?

- Antibody synthesis increases rapidly
- Rebound response occurs
  - Can only remove substances present in the intravascular space
  - Rapid substance redistribution into the intravascular space

Why do I need multiple TPE exchanges?

Reeves HM and Winters JL. Br J Haematol 2014;164:342–51
TPE prescription

- Smaller patients require blood priming to prevent hypotension/hemodilution
  - Circuit volume ≥10–15% patient blood volume

If treating someone with extracorporeal volume of >10%, consider an alternate to a saline prime

Goldstein SL. *Semin Dial* 2012;25:165–70
5% Albumin
- Calcium into albumin bottles are safe and help keep serum ionized calcium (iCa) levels normal

FFP
- Do you need to replace something from a therapeutic perspective?
- Monitoring fibrinogen levels
  - If low – use some or all FFP
- FFP has high citrate concentrations

Both FFP and albumin
Anticoagulation techniques in apheresis: From heparin to citrate and beyond

Grace Lee and Gowthami M. Arepally
TPE prescription

How do I anticoagulate the circuit with membrane TPE?

- Heparin
  - Bolus and infusion rate
  - Adjust using activated clotting time or prothrombin time (PTT)
  - Risks
    - Bleeding (<0.2%)
    - Serious complications (<0.03%)
    - Heparin-induced thrombocytopenia

Gavranić BB et al. J of Clin Apheresis 2017;00:1–7
Acid citrate dextrose A (ACDA)

CaCl (8 g/1 L)

Patient iCa = 1.1–1.3

Brophy PD et al. Nephrol Dial Transplant 2005;20:1416–21
TPE prescription

Citrate regional anticoagulation with membrane TPE (albumin replacement)

\[ Q_B = 100 \text{ mL/min} \]

\[ \text{ACDA} = 1.5 \times \text{BFR} 150 \text{ mL/hr} \]

\[ \text{CaCl} (8 \text{ g/1 L}) = 0.4 \times \text{citrate} 60 \text{ mL/hr} \]

Brophy PD et al. Nephrol Dial Transplant 2005;20:1416–21
TPE prescription

Citrate regional anticoagulation with membrane TPE (FFP replacement)

\[ Q_B = 100 \text{ mL/min} \]

\[ ACDA = 1 \times \text{BFR} = 100 \text{ mL/hr} \]

\[ \text{CaCl} (8 \text{ g/1 L}) = 1 \times \text{citrate} 100 \text{ mL/hr} \]

Brophy PD et al. Nephrol Dial Transplant 2005;20:1416–21
Summary

- TPE is a type of apheresis which can be performed using centrifugal and membrane machines.
- Before the first TPE, communications between the primary team, TPE team and family are critical:
  - A clear understanding of the potential benefits/risk.
  - A method to determine clinical response.
- TPE prescription:
  - Access is critically important.
  - Heparin and citrate anticoagulation are possible in membrane TPE.
  - Use FFP when fibrinogen is low.
  - 1.0–1.5 volume exchanges will maximize efficiency and minimize risk.