Therapeutic Plasma Exchange Indication and Prescription

Pediatric CRRT Workshop

Pediatric Nephrology Seminar

Marissa DeFreitas, MD

University of Miami/Holtz Children's Hospital

Therapeutic Plasma Exchange (TPE)

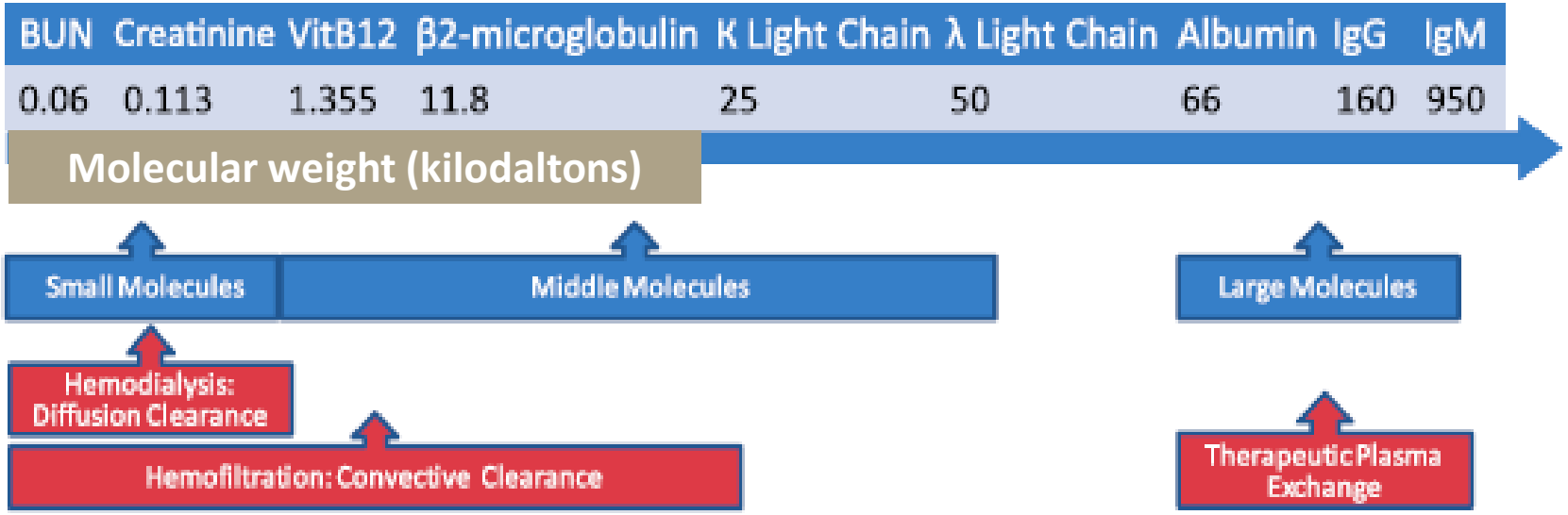
- An extracorporeal treatment modality that removes circulating pathologic factors from plasma.
- Plasma is removed and replaced with a colloid solution (albumin, plasma or a combination solutions).
- Technology and advancements in understanding of disease processes have made TPE an important and safe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



Williams. Clin J Am Soc Nephrol, 2014.

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

J Clin Apher. 2013 Jul;28(3):145-284

ASFA guidelines for TPE in children

Disorders	ASFA Category
Immune-medicated glomerulonephritis:	
ANCA-Associated rapidly glomerulonephritis	1
Anti-glomerular basement membrane disease	1
SLE, severe (cerebritis, pulmonary hemorrhage)	2
Henoch-Schönlein purpura: - Crescentic or Severe extrarenal disease	3
Immunoglobin A nephropathy: - Crescentic or Chronic progressive	3
Immune complex rapidly progressive glomerulonephritis	3
Atypical Hemolytic-uremic syndrome (aHUS)	
- aHUS associated with Autoantibody to factor H - aHUS associated with Complement gene mutations* - aHUS associated with Streptococcal pneumoniae	1 2 3

**Use FFP as replacement; Modified from J Clin Apher. 2013*

ASFA guidelines for TPE in children

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

**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 erythematosus**

- Nephritis

Modified from J Clin Apher. 2013

Techniques

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

Modified from Clin J Am Soc Nephrol, 2014.

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

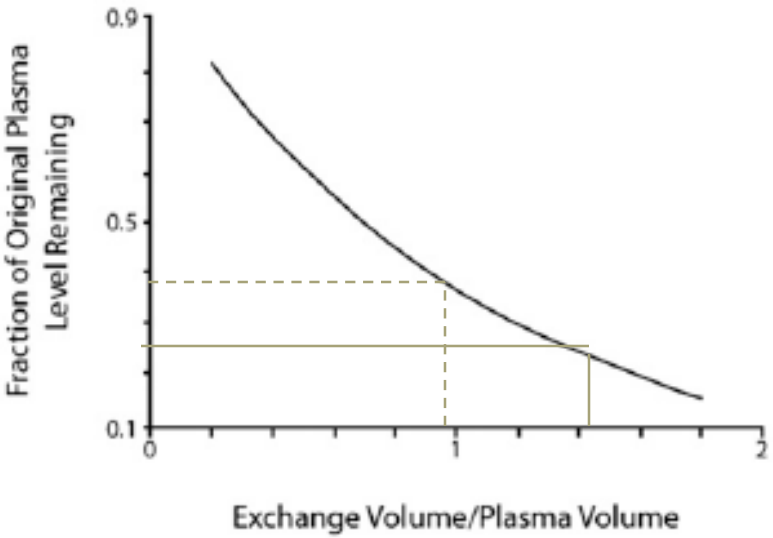
Advantage:

- 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

Williams. Clin J Am Soc Nephrol, 2014.

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.

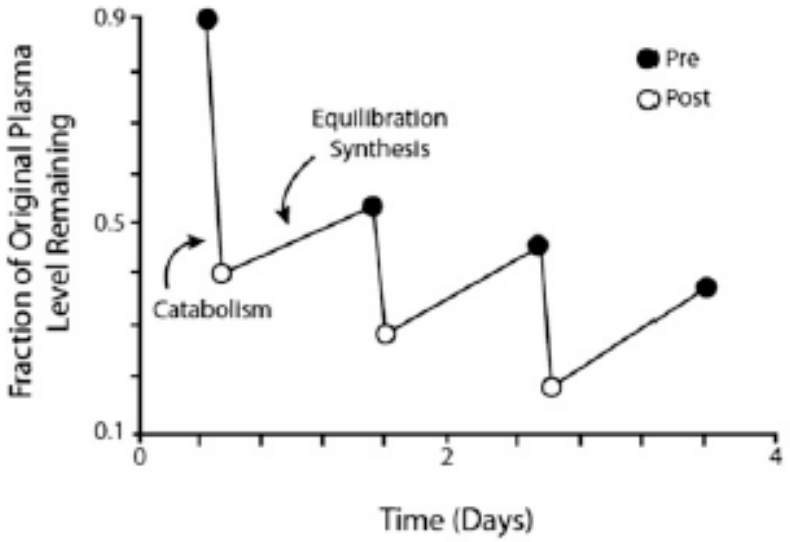
Example:

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



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

- IgM:
  - 75% intravascular; half life 5 days.
    - Only 1-2 TPE will be required to reduce IgM levels.
- IgG:
  - 45% intravascular, half-life 21days; 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.

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:

- Carter CE. Therapeutic plasma exchange for the treatment of pediatric renal diseases in 2013: Pediatr Nephrol (2014)
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- Schwartz et al. 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. J Clin Apher (2013)
- Friday JL, Kaplan AA. Therapeutic plasma exchange. Up to date. (Updated: Jan 2014)