Therapeutic Plasma Exchange (TPE) in the ICU and in Nephrology

Amber P. Sanchez, MD
Medical Director of UCSD Apheresis
Associate Professor, Division of Nephrology
Overview

• Think about TPE as an additional tool
• Focus on ICU & renal indications
• Introduction to combined circuits
Indications –
American Society for Apheresis (ASFA)

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

ASFA “Special Issue” or ASFA Guidelines
Published every three years – next coming out this summer
ASFA Indications

• Category I: apheresis 1\textsuperscript{st} line therapy
  • Guillain-Barre & TTP
  • Myasthenia Gravis + immunosuppression

• Category II: apheresis 2\textsuperscript{nd} line therapy
  • Acute disseminated encephalomyelitis (ADEM) after high dose steroid failure
  • Photopheresis for refractory Graft Vs Host Disease

• Category III: role of apheresis unclear
  • Photopheresis for Nephrogenic Systemic Fibrosis; TPE for sepsis

• Category IV: apheresis ineffective or harmful
  • Acute rheumatoid arthritis, schizophrenia
<table>
<thead>
<tr>
<th>Disease name</th>
<th>TA Modality</th>
<th>Indication</th>
<th>Category Grade Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>TPE</td>
<td>Steroid Refractory</td>
<td>II 2C 163</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy/</td>
<td>TPE</td>
<td>Primary Treatment</td>
<td>I 1A 165</td>
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<tr>
<td>Guillain-Barre syndrome</td>
<td>TPE</td>
<td>After IVIG</td>
<td>III 2C</td>
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<tr>
<td>Acute liver failure</td>
<td>TPE</td>
<td></td>
<td>III 2B 167</td>
</tr>
<tr>
<td>TPE-HV</td>
<td>I</td>
<td>1A</td>
<td></td>
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<tr>
<td>Age related macular degeneration, dry</td>
<td>Rheopheresis</td>
<td></td>
<td>I 1B 169</td>
</tr>
<tr>
<td>Amyloidosis, systemic</td>
<td>β2 microglobulin column</td>
<td></td>
<td>II 2B 171</td>
</tr>
<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis</td>
<td>TPE</td>
<td>Dialysis dependence</td>
<td>I 1A 173</td>
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<tr>
<td>with polyangiitis; and Microscopic Polyangiitis)</td>
<td>TPE</td>
<td>DAH</td>
<td>I 1C</td>
</tr>
<tr>
<td>TPE</td>
<td></td>
<td>Dialysis independence</td>
<td>III 2C</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>TPE</td>
<td>Dialysis dependence, no DAH</td>
<td>III 2B 175</td>
</tr>
<tr>
<td>TPE</td>
<td></td>
<td>DAH</td>
<td>I 1C</td>
</tr>
<tr>
<td>TPE</td>
<td></td>
<td>Dialysis independence</td>
<td>I 1B</td>
</tr>
<tr>
<td>Aplastic anemia, pure red cell aplasia</td>
<td>TPE</td>
<td>Aplastic anemia</td>
<td>III 2C 177</td>
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<tr>
<td>TPE</td>
<td></td>
<td>Pure red cell aplasia</td>
<td>III 2C</td>
</tr>
<tr>
<td>Ateopic (neuro-) dermatitis (atopic eczema), recaleantir</td>
<td>ECP</td>
<td></td>
<td>III 2C 179</td>
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<tr>
<td>TPE</td>
<td>1A</td>
<td></td>
<td>III 2C</td>
</tr>
<tr>
<td>TPE</td>
<td></td>
<td></td>
<td>III 2C</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia; WAIHA; cold agglutinin disease</td>
<td>TPE</td>
<td>Severe WAIHA</td>
<td>III 2C 181</td>
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<tr>
<td>TPE</td>
<td></td>
<td>Severe cold agglutinin disease</td>
<td>II 2C</td>
</tr>
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<td>Babesiosis</td>
<td>RBC exchange</td>
<td>Severe</td>
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<td>Burn shock resuscitation</td>
<td>TPE</td>
<td></td>
<td>III 2B 185</td>
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<tr>
<td>Cardiac neonatal lupus</td>
<td>TPE</td>
<td></td>
<td>III 2C 187</td>
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<tr>
<td>Cardiac transplantation</td>
<td>ECP</td>
<td>Cellular/recurrent rejection</td>
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<tr>
<td>ECP</td>
<td></td>
<td>Rejection prophylaxis</td>
<td>II 2A</td>
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<tr>
<td>TPE</td>
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<td>Desensitization</td>
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<tr>
<td>TPE</td>
<td></td>
<td>Antibody mediated rejection</td>
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<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>TPE</td>
<td></td>
<td>II 2C 191</td>
</tr>
<tr>
<td>Chronic focal encephalitis (Rasmussen Encephalitis)</td>
<td>TPE</td>
<td></td>
<td>III 2C 193</td>
</tr>
</tbody>
</table>
Disease of interest →

Literature available →

Disease description →

Current management →

Rationale for apheresis →

Typical apheresis prescription →

2016 ASFA Special Issue
Plasmapheresis: Rationale

- Removal of a circulating factor
  - antibodies, monoclonal protein, immune complex, alloantibody, toxins
- Removal of other inflammatory proteins
  - C3, C4, activated complement products, fibrinogen, cytokines
- Shift in the antibody-to-antigen ratio
  - Cryoglobulinemia in HCV
- Infusion of normal plasma
  - replace a deficient plasma component (TTP)
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>α chain non-collagenous domain of type IV collagen</td>
<td>TPE when Cr &lt; ~6 or with 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 need for HD, or DAH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*prelim PEXIVAS data – no benefit</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>

Sanchez & Ward, Seminars in Dialysis—Vol 25, No 2 (March–April) 2012 pp. 119–131 (modified)
Plasmapheresis as First Line Therapy
(Category I ASFA Indication)

1. Thrombotic thrombocytopenic purpura (TTP)
2. Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
3. Myasthenia Gravis (moderate-severe, and pre-thymectomy)
4. ANCA associated glomerulonephritis & DAH (Wegener’s, Microscopic Polyangiitis)
5. Anti-glomerular basement membrane disease (Goodpasture’s)
6. NMDA-R encephalitis
7. Hyperviscosity in monoclonal gammopathies
8. Wilson disease (Fulminant)
9. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
10. PML associated with natalizumab
11. TMA associated with ticlopidine and complement Factor H autoantibody
12. Paraproteinemic demyelinating polyneuropathies (IgG/IgA/IgM)
13. FSGS recurrent in transplant, aHUS, renal transplant Ab med rejection
14. Liver transplant, desensitization ABOi LD; acute liver failure – HV TPE

Journal of Clinical Apheresis 2016
Quick Review: Calculating the Plasma Volume

1) Blood volume: Weight (kg) x 55-75 ml/kg
   - 70 kg man x 70ml/kg = 4900mL

2) Plasma Volume: Blood volume x (1-Hct)
   - If Hct 40% then:
     - 4900 x (1-0.4) = 2940mL
     - or “a 3 Liter exchange” = a one plasma volume
   - In general, exchanges range between 2L and 5.5L for adults

<table>
<thead>
<tr>
<th>Patient</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>

Gilcher’s Rule of Five

Alternatively, some use PV = 40ml/kg (= 2.8L)

Not to exceed 10-15% TBV extracorporeal
Quick Review: Other plasma constituents removed with TPE

- Immunoglobulins: IgG (large volume of distribution), IgM (largely intravascular)
- Coagulation factors (fibrinogen, etc)
- Platelets (small degree)
- Electrolytes (K, Mg)

****important caveat of patients undergoing TPE therapy: check all necessary labs PRIOR to therapy!!! (antibody levels, C3/C4, ADAMTS13 activity and inhibitor levels etc)
Quick Review: Replacement Solutions

• Plasma replacement
  • Full plasma replacement if TTP
    • Removing an antibody/inhibitor
    • Replacing deficient ADAMTS13 enzyme
  • Some amount of plasma
    • FFP contains similar concentrations of all clotting proteins except Factor VIII
    • 1 unit of FFP raises fibrinogen about 15mg/dL in a 70 kg man
    • DAH, imminent surgery or procedure
    • Low starting fibrinogen (case by case basis)
# Quick Review: Access & Anticoagulation

<table>
<thead>
<tr>
<th></th>
<th>Centrifugal</th>
<th>Membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access</strong></td>
<td>PIVs, dialysis catheter, port, or AVF/AVG</td>
<td>Dialysis catheter or AVG/AVF</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td>ACD-A (citrate) 14:1, 12:1, 10:1</td>
<td>Heparin 3000 unit LD, 1500 U/hr</td>
</tr>
<tr>
<td><strong>Blood flow</strong></td>
<td>50-80 ml/min</td>
<td>100-200 ml/min</td>
</tr>
</tbody>
</table>

- PIV: 18g in antecubital and a return (20g) - Angiocath and dialysis-type steel needles
- PICC and CVCs do NOT work!
Quick Review: Complications of TPE

- Hypotension
- Transfusion reactions
- Citrate toxicity / hypocalcemia
- Coagulation abnormalities
- Electrolyte abnormalities (K, Phos, Mag)
- Vascular access issues (thrombosis or infection)
- Mortality 0.03% - usually respiratory or cardiac
Most common ICU indications

• TTP / aHUS
• Pulmonary renal syndromes
• Acute Inflammatory Demyelinating Polyradiculoneuropathy / Guillain barre
• Myasthenia Gravis
• Autoimmune encephalitis
• Other (acute liver failure, sepsis, cryoglobulinemia, paraproteinemia)
Renal indications for TPE

- FSGS (post transplant)
- Anti GBM glomerulonephritis
- ANCA associated GN
- Cryoglobulinemia
- aHUS
- Multiple myeloma / cast nephropathy
- Transplant (antibody mediated acute rejection)
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence: 7/1,000,000

<table>
<thead>
<tr>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent in transplanted kidney</td>
<td>TPE</td>
<td>Grade 1B</td>
<td>I</td>
</tr>
<tr>
<td>Steroid resistant in native kidney</td>
<td>LDL Apheresis</td>
<td>Grade 2C</td>
<td>II</td>
</tr>
</tbody>
</table>

No. of reported patients: >300

<table>
<thead>
<tr>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3(48)</td>
<td>49(224)</td>
<td>15(17)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1(11)</td>
<td>4(4)</td>
</tr>
</tbody>
</table>

2016
Post-transplant FSGS

• 30-50% of patients with primary FSGS progress to ESRD in 5-10 yrs and risk of recurrence is 30-55% of patients who undergo renal transplant (hours to days after transplantation)
  • TPE in native kidneys has been disappointing, however post transplant typically responds in combo with increased IS (meta-analysis in 2016 response in 74%)
  • Rationale: removal of a yet to be confirmed permeability factor

• No RCT

• 3 daily exchanges then another ≥ 6 over the next 2 wks + concomitant immunosuppression

• Another approach: 3 x a week x 3 weeks, then 2 x a week x 3 weeks, then 1 x a week until month 3, then 2x a month, then 1x a month

• Tapering guided based on proteinuria, some will need prolonged course
LDL Apheresis for FSGS

- FDA approved in 2013 as HUD in pediatric FSGS
- FDA approval extended to pre-transplant adult patients in 2018

POLARIS trial
LDL Apheresis for FSGS – Case example

• 28yo woman with biopsy proven FSGS diagnosed in 2015, creatinine 0.8, who failed steroids, then CSA x 6 mos, then MMF, ACTHAR, rituximab was started on LDL Apheresis 10/2018. Albumin was 1.5 prior to starting LDL-A, and peaked at 3.1 on 1/7/19 after 17 treatments.
### ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE’S SYNDROME)

<table>
<thead>
<tr>
<th>Incidence: &lt;1/100,000/yr</th>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dialysis-dependent⁺; no DAH</td>
<td>TPE</td>
<td>Grade 2B</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>DAH</td>
<td>TPE</td>
<td>Grade 1C</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Dialysis-independent⁺</td>
<td>TPE</td>
<td>Grade 1B</td>
<td>I</td>
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</table>

<table>
<thead>
<tr>
<th># of reported patients*: &gt;300</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (17)</td>
<td>0</td>
<td>17 (430)</td>
<td>19</td>
<td></td>
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</table>

*At presentation, defined as Cr > 6 mg/dL. DAH = diffuse alveolar hemorrhage
Anti-GBM

• In 1985: RCT of 17 patients → disappearance of Ab and serum Cr improved by half in TPE group, though % crescents on biopsy was less in TPE group

• In 2001: → 77 patients followed up long term: severe renal failure (not on dialysis) responded to therapy almost as well as pts with moderate renal impairment; those that needed immediate dialysis rarely recovered renal function (5%)

• “The presence of lung hemorrhage, which resolved in 90% of our patients, provides a separate indication for intensive treatment, regardless of the severity of renal disease”

  • Pusey Kl: 64:1535, 2003

• In 2007: retrospective look at 28 cases that had DAH “Pts with normal initial renal function did not receive TPE but did well, in agreement with previous data suggesting that patients with predominantly pulmonary involvement and preserved renal function do well with or without plasma exchange.”
Anti-GBM – Take home messages

- Start therapy quickly
- Use FFP if risks of bleeding/DAH
- TPE if DAH?
- If dialysis *usually* no TPE – *unless young*
- DFPP, immunoadsorption used in some institutions worldwide
ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (GRANULOMATOSIS WITH POLYANGIITIS; WEGENER’S GRANULOMATOSIS)

<table>
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<th>Incidence: 8.5/1,000,000/yr</th>
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<th>Procedure</th>
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<tbody>
<tr>
<td></td>
<td>Dialysis dependence&lt;sup&gt;+&lt;/sup&gt;</td>
<td>TPE</td>
<td>Grade 1A</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>DAH</td>
<td>TPE</td>
<td>Grade 1C</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Dialysis independence&lt;sup&gt;+&lt;/sup&gt;</td>
<td>TPE</td>
<td>Grade 2C</td>
<td>III</td>
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# of reported patients*: >300

<table>
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<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (296)</td>
<td>1 (26)</td>
<td>22 (347)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* At presentation, defined as Cr>6 mg/dL. DAH = diffuse alveolar hemorrhage.
ANCA Associated GN

- 2007 MEPEX trial: 7 TPE over 2 weeks, 70 patients
  - 3 months – renal recovery in 49% (steroid) vs 69% (PLEX)
  - 12 month follow up: TPE associated with 24% reduction in ESRD
  - Cr >~5.8 or need for dialysis benefited from TPE

- 2013: Walsh, et al Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear, Kidney International (2013) 84,397-402

- PEXIVAS – 704 patients enrolled, GFR <50, & 7 TPE over 2 weeks
  - Prelim results:
  - Endpoint (death, ESRD) in 28% of TPE group c/w 31% in no TPE (p = 0.27).
  - ESRD/death in 28% in reduced steroids vs. 26% standard (non-inferiority).
# CRYOGLOBULINEMIA

**Incidence:** About 50% of patients with chronic HCV

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Indication</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>Severe/symptomatic</td>
<td>Grade 2A</td>
<td>II</td>
</tr>
<tr>
<td>IA</td>
<td>Severe/symptomatic</td>
<td>Grade 2B</td>
<td>II</td>
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**No. of reported patients:** >300

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Condition</th>
<th>Recommendation</th>
<th>Category</th>
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<tbody>
<tr>
<td>RCT</td>
<td></td>
<td>CS</td>
<td>CR</td>
</tr>
<tr>
<td>TPE</td>
<td>1(57)</td>
<td>24(302)</td>
<td>NA</td>
</tr>
<tr>
<td>IA</td>
<td>1(17)</td>
<td>1(4)</td>
<td>0</td>
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</table>

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**Incidence:** About 50% of patients with chronic hepatitis C

<table>
<thead>
<tr>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe/symptomatic</td>
<td>TPE</td>
<td>Grade 2A</td>
<td>I</td>
</tr>
<tr>
<td>Severe/symptomatic</td>
<td>IA</td>
<td>Grade 2B</td>
<td>II</td>
</tr>
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</table>

**# of reported patients:** 100–300

<table>
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<th>Procedure</th>
<th>Condition</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td></td>
<td>CS</td>
<td>CR</td>
</tr>
<tr>
<td>TPE</td>
<td>1(57)</td>
<td>20(270)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>IA</td>
<td>1(17)</td>
<td>1(4)</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Incidence:** 1-2% of patients with chronic hepatitis C, approximately 80% of patients with cryoglobulinemia have hepatitis C

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>Grade 1B</td>
<td>I (severe/symptomatic)</td>
</tr>
<tr>
<td>IA</td>
<td>Grade 2B</td>
<td>II (secondary to hepatitis C)</td>
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**# of reported patients:** 100–300

<table>
<thead>
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<th>Procedure</th>
<th>Condition</th>
<th>Type of evidence</th>
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<tr>
<td>TPE</td>
<td>0</td>
<td>Type II-3</td>
</tr>
<tr>
<td>IA</td>
<td>1 (17)</td>
<td>Type I</td>
</tr>
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</table>
Cryoglobulinemia

• TPE as an adjunctive therapy in severe disease, remove circulating cryoglobulins
• Data has been difficult to compile into a meaningful meta-analysis as outcomes not well defined, follow up data vague
• HCV treatment and rituximab use have changed practice
• Warm room, draw and return lines, and replacement solutions to avoid precipitation of cryos
• Acute symptoms: treat daily to q3days x 3-8 procedures then re-eval, can be a bridge to other therapy
• Other modalities of cryo removal reported/done: DFPP, cryofiltration, and cryogel removal techniques
Immune complex disease with Hepatitis C

**Concentration in Plasma**
- **Antigenemia** (Hep C virus)
- **Circulating immune complexes** (mixed cryoglobulinemia)
- **Antiviral antibody**

**Vasculitis & Glomerulonephritis**

**Antigen excess** = small C.I.C.
**Equivalence** = large C.I.C.
**Antibody excess** = small C.I.C.

**Antiviral antibody** + Rheumatoid Factor (IgM)

**Plasmapheresis** removes both

**Immunosuppressants** reduce antibody
**Antivirals** reduce antigen

**Zone of Deposition**

_dmward@ucsd.edu_
## MYELOMA CAST NEPHROPATHY

<table>
<thead>
<tr>
<th>Incidence: 1/100,000/yr</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPE</td>
<td>Grade 2B</td>
<td>II</td>
</tr>
<tr>
<td>No. of reported patients: 100–300</td>
<td>RCT</td>
<td>CT</td>
<td>CS</td>
</tr>
<tr>
<td></td>
<td>5(182)</td>
<td>0</td>
<td>8(102)</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td></td>
<td>7(10)</td>
</tr>
</tbody>
</table>
TPE for Multiple Myeloma = Controversial

- Many things can cause AKI in MM (cast nephropathy, hypercalcemia, ATN, LCDD, amyloid etc)
- Cast nephropathy present in about 1/3rd of biopsies, biopsies not consistently done in the TPE literature nor are free light chains (FLC) measured, and TPE regimens vary significantly
- It can take days to weeks to reduce FLC with chemo, which are directly toxic to the tubules + renal failure increases their ½ life
TPE for Multiple Myeloma

- Meta-analysis in 2015 of the 3 RCT to eval 6-mo survival & dialysis dependence rate
  - 84 chemo + TPE; 63 chemo only
- 6 month survival: no significant difference between the two groups
- Dialysis dependence rate: much lower in TPE group (p = 0.04)
  - 15.6% vs 37.2%, risk ratio: 2.02
- Conclusion: TPE + chemo beneficial in the dialysis dependent
- Problems: small number of patients, differences in clinical presentations & chemo regimens, limited number of renal biopsies, different end points chosen, 3 trials were done prior to having FLC assay to monitor response, publication bias may occur if negative studies are not published.
TPE in Multiple Myeloma

• 78% with biopsy-proven cast nephropathy resolved renal disease when FLCs were reduced >50% following TPE & chemo (Leung, KI 2008)

• Similar results seen in a pilot study of high-cut off dialyzers in patients with cast nephropathy
  • 60% sustained reduction in FLCs by day 21 a/w renal recovery rate in 80%

• Burnette et al in NEJM 2011: retrospective study of 14 patients with biopsy proven cast nephropathy tx w TPE & bortezomib had renal recovery of 86%, associated with a mean reduction in FLC of 74.6%

• 2018 retrospective review also concluded role of TPE with AKI (better GFR at 3 mos)
My Conclusions in 2019

• Study designs have been small and treatment regimens have varied

• **Get a kidney biopsy**
  • High serum FLC does not necessarily mean cast nephropathy on biopsy
  • Only cast nephropathy responds to TPE

• Consider TPE with concurrent chemo ***if***: cast nephropathy, dialysis dependent, and a 50% reduction in FLC can be achieved
  • May need to do a lot of TPE initially to keep up with production rate (ie daily)
  • **MUST MONITOR serum FLC to guide TPE**
  • If unable to bring down FLC sufficiently, abandon therapy

• Newer agents are being used for MM and may be able to bring down FLCs faster and more sustained
  • Consider TPE as a bridge if chemo is being delayed
Thrombocytopenia in the ICU

- Many causes: TTP, atypical and “typical” HUS, HIT, ITP, sepsis, consumptive/bleeding, liver disease, autoimmune (lupus etc)
- TTP: rapid fall in platelets, profoundly low at presentation, anemia from MAHA, high LDH, schistocytes on smear
  - Get ADAMTS13 activity level and inhibitor assay prior to initiation of TPE. If TTP is suspected, do not wait for confirmatory tests
- TTP usually does NOT present with renal failure, but aHUS almost always has some
- ADAMTS13 will be low in other diseases, including sepsis and pregnancy, but not as low as with TTP (<5%)
<table>
<thead>
<tr>
<th>Familial Relapsing TTP</th>
<th>Acute Sporadic TTP</th>
<th>Ticlopidine TTP/HUS</th>
<th>CSA Tacrolimus TTP/HUS</th>
<th>Atypical HUS (aHUS)</th>
<th>Typical HUS (D+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary ADAMTS13 deficiency</td>
<td>Auto-antibody to ADAMTS13</td>
<td>Auto-antibody to ADAMTS13</td>
<td>Variable lab findings</td>
<td>ADAMTS13 normal. Abnormal CFH, etc.</td>
<td>ADAMTS13 normal. Positive Shiga toxin</td>
</tr>
<tr>
<td>TPE is not needed. Give FFP</td>
<td>TPE is 1ST- line treatment</td>
<td>TPE is 1ST- line treatment</td>
<td>TPE sometimes used (Cat III)</td>
<td>TPE may help (Factor H ab – Cat I)</td>
<td>TPE/FFP usually ineffective</td>
</tr>
</tbody>
</table>

In these diseases, TPE replacement volume should all be FFP

In autoantibody-type TTP, plasmapheresis removes autoantibody and replenishes ADAMTS13

Modified from dmward@ucsd.edu
AIDP (Guillain-Barré Syndrome)

- Spontaneous recovery occurs, if ambulatory: supportive care
- Severely affected patients often need ICU, mechanical ventilation, & rehab that can take months to years
- Steroids alone ineffective
- Plasmapheresis and IVIG have been shown to impact disease favorably
Plasmapheresis vs. Intravenous Immunoglobulin (IVIG) vs Both

RANDOMIZED TRIAL (379 patients)
- Comparing three treatment plans:
  1. TPE (5 exchanges over 2 weeks)
  2. IVIG (0.4 gm/Kg/day x 5 days)
  3. Both (TPE + IVIG)

RESULTS:
- TPE and IVIG have equivalent efficacy
- Combination not significantly better than either treatment alone.

DISCUSSION:
“IVIG may be preferable to TPE... equal benefit, greater convenience, similar overall cost... provided there are no contraindications to IVIG.”

Slide modified from dmward@ucsd.edu
Direct inpatient costs:

- 5 infusions of IVIG (each 0.4 g/Kg) (IVIG plus infusion center cost) versus
- 5 TPE treatments (each 1.2 plasma volumes) (including central venous access, albumin replacement fluid, equipment amortization, and personnel time).
Myasthenia Gravis

• Well characterized & understood autoimmune d/o

• Motor nerves release acetylcholine in NMJ → binds AChR → muscle contraction

• Abs to AChR and other targets
  • However Ab levels do not necessarily correlate with disease activity
  • Often associated with thymomas/thymic hyperplasia

Modified from dmward@ucsd.edu
Myasthenia Gravis

• Fluctuating weakness in ocular (ptosis, diplopia), bulbar (mastication/swallowing/speaking), respiratory & limb muscles
  • Usually improves with rest
  • Most prevalent in 20-40yo women

• Myasthenia crisis ➔ Life threatening
  • Can occur spontaneous or be triggered by a stress (infection, surgery, etc)
  • Respiratory failure requiring intubation
  • Bulbar weakness ➔ dysphagia and high risk for aspiration

https://mmcneuro.wordpress.com/2013/01/
Myasthenia Gravis: Approach to Treatment

- Thymectomy (anti-AchR >> anti-MUSK)
- Acetylcholinesterase inhibitors (pyridostigmine)
- Steroids
- Other immunosuppression (AZA, Cellcept, CSA/FK etc)
- TPE or IVIG
  - Plasmapheresis removes circulating antibody
  - Usually performed daily to every other day in crisis
  - Some patients require long term TPE

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### MYASTHENIA GRAVIS

<table>
<thead>
<tr>
<th>Incidence: 1/100,000</th>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate–severe</td>
<td>TPE</td>
<td>Grade 1B</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Pre-thymectomy</td>
<td>TPE</td>
<td>Grade 1C</td>
<td>I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of reported patients: &gt; 300</th>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate–severe</td>
<td>RCT</td>
<td>CT</td>
<td>CS</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>8(279)</td>
<td>8(2837)</td>
<td>30(556)$^a$</td>
<td>NA</td>
</tr>
<tr>
<td>Pre-thymectomy</td>
<td>0</td>
<td>5(342)</td>
<td>2(51)$^a$</td>
<td>NA</td>
</tr>
</tbody>
</table>

$^a$6 (405) CS contained both groups of patients; CS added anti-MuSK 110, with rippling muscle disease 2 (10).
Plasma exchange and MG

- ~2/3rds of MG patients will respond
  - Equal to IVIG
  - Response typically transient (~8 weeks)
- Good treatment choice for:
  - MG crisis (ventilator)
  - MG exacerbations
  - Pre-thymectomy patients
  - MuSK myasthenics
  - Chronic, recurrent plasma exchange is sometimes necessary
Autoimmune Encephalitis

- Presentation: seizures, psychiatric symptoms, cognitive decline, movement disorder and autonomic symptoms
- Various antibodies have been detected
- Immunotherapy potentially curable if started early
  - No consensus guidelines exist
  - 1st line: pulse IV high dose corticosteroids f/b IVIG and/or TPE
    - Typical TPE course: 5-7 treatments, alternate days
    - 2nd line: rituximab, cyclophosphamide, AZA, MMF, MTX
- More frequently being asked to perform TPE in the inpatient setting after failed trial of steroids etc & awaiting antibody panel

Anti-NMDA-R Encephalitis

- Autoantibodies to the NMDA receptor
  - First described in a case series in 2007, now MCC autoimmune encephalitis
  - Women > men (4:1)
- Often associated with ovarian teratoma
- Often psychiatric symptoms initially
- Males>females initially present with seizures
- Memory loss, catatonia, dyskinesia
- EEG: ‘extreme delta brush’ pattern

Wright & Vincent, Neurology (2016) Vol 29
Treatment of Anti-NMDA-R Encephalitis

- Diagnosis can be delayed, which affects outcome
- Screen for tumors
- First line: steroids, IVIG, plasmapheresis
- Second line: rituximab, cyclophosphamide, tumor removal
- Reported that 79% have good outcome within 12-24 months of diagnosis (if diagnosed early)

<table>
<thead>
<tr>
<th></th>
<th>One or no treatment categories</th>
<th>At least two treatment categories</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete recovery within approximately one year</td>
<td>19</td>
<td>44</td>
<td>63</td>
</tr>
<tr>
<td>Complete recovery beyond one year</td>
<td>19</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>56</td>
<td>94</td>
</tr>
<tr>
<td>Efficacy rate</td>
<td>0.5,</td>
<td>0.786</td>
<td>0.67</td>
</tr>
<tr>
<td>95% CI of efficacy rate</td>
<td>(0.34, 0.66)</td>
<td>(0.68, 0.89)</td>
<td>(0.57, 0.77)</td>
</tr>
</tbody>
</table>

Other apheresis procedures in the ICU

• Blast crisis / symptomatic hyperleukocytosis—leukapheresis (Cat II)
• Acute chest syndrome (Cat II) and acute stroke—RBC exchange (Cat I)
• Acute liver failure – high volume plasmapheresis (Cat I)
• Chronic lung transplant rejection / BOS – ECP (Cat II)
• Catastrophic antiphospholipid syndrome – TPE (Cat II)
• Severe cryoglobulinemia – life, limb or organ threatening (Cat II)
• HIT— presurgical for emergent cardiopulm bypass (Cat III)
• Symptomatic thrombocytosis – thrombocytapheresis (Cat II)
Combined Circuits

• In patients undergoing IHD, TPE is typically performed before the HD treatment
  • Correct alkalosis, electrolyte abnormalities and volume status

• CRRT and therapeutic plasmapheresis can be run simultaneously
  • In series or in parallel
  • Performed in critically ill patients when TPE needed but dialysis cannot be interrupted

• CRRT can also be run in combination with secondary plasma purification
  • Selective columns available worldwide, often used in sepsis
Combined Circuits

- Advantages of combining circuits
  - Same access can be used
  - CRRT does not have to be interrupted
    - Volume issues / high O2 requirement
    - Severe acidosis
    - Hyperkalemia
  - Pediatric (small kg): less blood exposure, as multiple procedures = multiple blood primes

- Extracorporeal blood volume in combined CRRT/TPE circuit ~355ml
  - TPE Optia circuit 185ml and CVVHD 170 ml

- Use of citrate, heparin, or a combination of the two has been reported in the literature

Combined Circuits

• Alternative: disconnect from CRRT to run TPE, then reconnect
  • Circuit can be recirculated for a certain period: “Bypass mode”
  • Cost could increase if multiple circuits required
  • More potential hemodynamic instability with starting of each procedure
  • Less clearance if dialysis interrupted
Combined Circuit: In Parallel

Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

200 ml/min

100 ml/min

Citrate

Blood return

100 ml/min

Prefilter Dilution

Hemofilter

Ca++ free Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

CENTRIFUGAL PLASMAPHERESIS

replacement: Albumin/FFP

CONTINUOUS HEMODIAFILTRATION

Image courtesy of David M. Ward, MD
Combined Circuit: In Series

Lower total blood flow - lower anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

Use the apheresis machine’s citrate pump. (Switch to CRRT citrate pump when apheresis is stopped and by-pass line is in use.)

Image courtesy of David M. Ward, MD
• 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.
• https://cme.ucsd.edu/apheresis/

Contact: lbarron@ucsd.edu
Thank you!

- Apheresis can be another “tool”
- ASFA guidelines
- a6sanchez@ucsd.edu