Evidence and Decision Making in Apheresis Medicine

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# 2010 Revised ASFA Indication Categories

*(with examples)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Indications</th>
</tr>
</thead>
</table>
| Category I | First-line therapy: primary stand-alone treatment or in conjunction with other modes of treatment.  
  *Acute Guillain-Barré Syndrome; Myasthenia Gravis* |
| Category II | Second-line therapy: stand-alone treatment or in conjunction with other modes of treatment.  
  *Photopheresis for chronic GVHD after corticosteroid failure* |
| Category III | Optimum role of apheresis therapy not established. Decision making should be individualized.  
  *DCM; Sepsis with Multiorgan Failure* |
| Category IV | Published evidence indicates apheresis to be ineffective or harmful. IRB approval is desirable.  
  *Plasma Exchange for Active Rheumatoid Arthritis* |

*adapted from: Szczepiorkowski ZM et al. J Clin Apheresis 2010;25:83-177*
Fact Sheet: the Sixth ASFA Guidelines

ACUTE INFLAMMATORY DEMYELENATING POLYNEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

<table>
<thead>
<tr>
<th>Incidence: 1-2/100,000/yr</th>
<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>After IVIG*</td>
<td></td>
<td>TPE</td>
<td>Grade 1A</td>
<td>I</td>
</tr>
<tr>
<td>After IVIG*</td>
<td></td>
<td>TPE</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
</tbody>
</table>

# of reported patients*: >300

<table>
<thead>
<tr>
<th>Procedure</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>19 (1770)</td>
<td>0</td>
<td>9 (369)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>After IVIG*</td>
<td>0</td>
<td>0</td>
<td>1 (46)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*completed course of IVIG at 2 g/kg

GRAFT-VERSUS-HOST DISEASE

Incidence: After allogenic HSC transplant: 10-60% Grade II-IV acute GVHD; 6-80% moderate-severe chronic GVHD

<table>
<thead>
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<th>Condition</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (chronic)</td>
<td>ECP</td>
<td>Grade 1B</td>
<td>II</td>
</tr>
<tr>
<td>Skin (acute)</td>
<td>ECP</td>
<td>Grade 1C</td>
<td>II</td>
</tr>
<tr>
<td>Non-skin</td>
<td>ECP</td>
<td>Grade 2B</td>
<td>III</td>
</tr>
</tbody>
</table>

# of reported patients*: >300

<table>
<thead>
<tr>
<th>Condition</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic skin</td>
<td>1 (95)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute/chronic skin and non-skin</td>
<td>0</td>
<td>2 (41)</td>
<td>44 (944)</td>
<td>9 (13)</td>
</tr>
</tbody>
</table>

GVHD = graft-versus-host disease

adapted from Schwartz J et al. J Clin Apher 2013
McLeod’s Criteria for Likelihood of Benefit of Apheresis Therapy

“Plausible Pathogenesis”  A secure understanding of the disease process suggests a clear rationale for apheresis therapy.

“Better Blood”  The abnormality that makes apheresis plausible is meaningfully corrected by apheresis therapy.

“Perkier Patients”  There is strong evidence that apheresis therapy confers clinical benefit that is meaningful (not only statistically significant).

Acute Guillain-Barré Syndrome

- Idiopathic inflammatory demyelinating polyneuropathy
  - Ascending, progressive muscle weakness, areflexia
  - Association with antecedent Campylobacter jejuni infection (60%)
  - Annual incidence: 1 to 4 per 100,000 worldwide

- Clinical course
  - Assisted ventilation: 10-25%
  - Death: 4-15%
  - Persistent mild neurological deficits: 67%
  - Persistent disabling neurological deficits: 5-15%

- Autoimmune disorder
  - Complement fixing IgM anti-peripheral nerve myelin antibodies
  - Anti-GM$_1$ antibodies (severe axonal involvement)
  - Anti-GQ$_{1b}$ antibodies (Fisher’s syndrome: ataxia, ophtalmoplegia, areflexia)
Rapid Response of Acute Guillain-Barré Syndrome to Plasma Exchange

109 TPE vs 111 controls
92% ≥ grade 3

from the French Cooperative Group Trial:
Ann Neurol 1987;22:753-761

<table>
<thead>
<tr>
<th></th>
<th>TPE</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to grade 2 (days*)</td>
<td>70</td>
<td>111</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay (days*)</td>
<td>28</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Full strength by 1 year</td>
<td>71%</td>
<td>52%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*median
### “McLeod’s Criteria” Applied to Conditions Treated by Apheresis

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Better Blood</th>
<th>Perkier Patients</th>
<th>Recommended Regimen</th>
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<tbody>
<tr>
<td>Acute GBS Cat I Grade 1A</td>
<td>Anti-myelin Antibody</td>
<td>Antibody↓ with TPE</td>
<td>Randomized trials</td>
<td>Based on clinical trials</td>
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</table>

adapted from McLeod BC *J Clin Apheresis* 2002;17:124-132
Myasthenia Gravis
An Autoimmune Disorder of the Neuromuscular Junction

• Autoantibody mediated
  – Acetylcholine receptor (AChR) antibodies
  – Anti-muscle-specific receptor tyrosine kinase

• Thymoma in 10-15%, esp. ♂ >40 yrs

• Variable weakness of voluntary muscles
  – Accentuated by repetitive motion
  – Alleviated by rest
  – Bulbar, extremity, trunk muscles

• Treatment
  – Acetylcholinesterase inhibitors
  – Immunosuppression

• Major role of TPE
  – Pre-op preparation for thymectomy
  – Acute exacerbations

## Compilation of Level II Evidence Regarding TPE for Myasthenia Gravis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>patients</th>
<th>Pred</th>
<th>Immunosuppressor</th>
<th>TPE/pt</th>
<th>L exchanged</th>
<th>Effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behan</td>
<td>1979</td>
<td>21</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>16-32</td>
<td>100</td>
</tr>
<tr>
<td>Dau</td>
<td>1981</td>
<td>60</td>
<td>48</td>
<td>48</td>
<td>9-33</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Olarte</td>
<td>1981</td>
<td>21</td>
<td>13</td>
<td>12</td>
<td>2-10</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Perlo</td>
<td>1981</td>
<td>17</td>
<td>?</td>
<td>?</td>
<td>3-5</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Fornasari</td>
<td>1985</td>
<td>33</td>
<td>11</td>
<td>11</td>
<td>4-8</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Antozzi</td>
<td>1991</td>
<td>70</td>
<td>?</td>
<td>?</td>
<td>2</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Chiu</td>
<td>2000</td>
<td>94</td>
<td>?</td>
<td>?</td>
<td>4-5</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>316</td>
<td></td>
<td></td>
<td></td>
<td>76.4</td>
<td></td>
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“No adequate randomised controlled trials have been performed to determine whether plasma exchange improves the short- or long-term outcome for myasthenia gravis. However, many case series studies report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis. Further research is need to compare plasma exchange with alternative short-term treatments for myasthenic crisis and to determine the value of long-term plasma exchange for treating myasthenia gravis.”

## Controlled Trials of TPE in Myasthenia Gravis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Goti P et al. Thorax 1995;50:1080-6. | Non-randomized, baseline to treatment | 9 patients with grade IIb myasthenia | Baseline of treatment with pyridostigmine compared to treatment with TPE | • Pulmonary volumes  
• Inspiratory and expiratory muscle force  
• Respiratory muscle strength, Ventilatory pattern  
  o Inspiratory time  
  o Expiratory time  
  o Total time of respiratory cycle  
  o Tidal volume | Decrease in FRC and RV  
Increase in FEV1, MIP  
Increase in MEP  
TPE vs pyridostigmine (p<0.05). |
32 patients: thymectomy alone. | • Incidence of MG crisis  
• Pharmacologic remission and improvement rate, evaluated by graded scale | TPE vs CONTROL  
• Crisis within 1 year post-op: 5.3% vs 28.1% (p=0.049);  
• Crisis within 30 days post-op: 0 vs 15.6% (p=0.0724).  
• Improvement rate: 100% vs 81.3% (p=0.0466).  
• Complete remission (5-7 yrs): 79% vs 50% (p=0.0427). |

*adapted from Cortese I et al. Neurology 2011;76:294-300*
“McLeod’s Criteria” Applied to Conditions Treated by Apheresis

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<tr>
<td>Myasthenia Gravis Cat I Grade 1B</td>
<td>ACh-receptor Antibody</td>
<td>↓ ACh receptor Antibody</td>
<td>Strong but anecdotal</td>
<td>? optimal regimen</td>
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adapted from McLeod BC J Clin Apheresis 2002;17:124-132
Rasmussen’s Encephalitis  
(Epilepsia Partialis Continua)

- Intractable focal seizures
- Onset usually in childhood
- ?post-viral etiology
- Clinical picture
  - Anticonvulsant-refractory epilepsy
  - Progressive hemiparesis
  - Progressive unilateral cerebral atrophy
  - Progressive cognitive decline
- Treatment
  - Anticonvulsant medication
  - High-dose corticosteroids
  - Subtotal, functionally complete, hemispherectomy
  - IVIG, IFN, ?Rituximab

“A clinicopathologic report is made of three children suffering from a chronic illness, producing focal seizures and gradually producing severe damage to one cerebral hemisphere. The... lesion is a chronic focal encephalitis. The etiology is undetermined...”
Rasmussen T et al. Neurology 1958;8:435-45

adapted from Weinstein R  J Clin Apheresis 2000;15:121-3
Is Rasmussen’s Encephalitis an Autoimmune Disease Treatable with Plasma Exchange?

- Attempt to raise rabbit glutamate receptor antibodies
- Rabbits developed anti-GluR3
  - Recurrent seizures
  - Inflammatory histopathology
  - Localization to cortex
- Anti-GluR3 in patients’ serum
  - 3 of 4 children with RE
  - ? correlated with disease activity
- 1 child treated with TPE
  - Single volume procedures
  - Improvement during 1st 7 weeks
    - Seizures ↓ 80%
    - Cognition, speech
    - Hemiparesis
  - Subsequent relapse

adapted from Rogers SW et al. Science 1994;265:648-51
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<td>Strong but anecdotal</td>
<td>? optimal regimen</td>
</tr>
<tr>
<td>Rasmussen’s Encephalitis Cat III</td>
<td>?autoimmune inflammation</td>
<td>? ↓ GluR3 autoantibodies</td>
<td>Low-quality evidence</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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adapted from McLeod BC  J Clin Apheresis 2002;17:124-132
McLeod’s Criteria for Likelihood of Benefit of Apheresis Therapy

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<td>“Perkier Patients”</td>
<td>There is strong evidence that apheresis therapy confers clinical benefit that is meaningful (not only statistically significant).</td>
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Corollary Considerations
- Is the problem potentially reversible with apheresis therapy?
- Is there a first-line or standard therapy?
  - Has it been tried?
  - Outcome?
- If apheresis to be tried, is the goal of a therapeutic trial defined?
Individualize Apheresis Decision Making for Patients with Rasmussen’s Encephalitis

- 18 y/o ♀ with RE since age 8 yrs
  - Major partial seizures Q 15 min
  - Cognitive decline (7-8 y/o level)
  - Right hemiparesis (wheelchair)
  - Anti-GluR3 negative
- Therapies applied
  - Anticonvulsants – partial control
  - Surgery – transient↓ seizures
  - IVIG – no response
- Plasma exchange (since 5/2/2008)
  - Initially 3 TPE per week
  - Weekly since Sept 2008
  - Ambulatory
  - ↓↓ seizures
  - ↑ cognitive function

Now maintained with intermittent TPE
68 year old ♀ with CMML

Peripheral Blood:
- WBC: 45,000/µL
- HCT: 31.8%
- MCV: 73.7 FL
- PLT: 3,000/µL
- Mono: 3,400/µL

Bone Marrow:
- Cellularity: 95%
- Morphology: dysplastic
- Megakaryocytes: ↓↓↓
- Iron: absent
Platelet Support of Patient PK

- Platelet Pre-Count
- Platelet Post-Count
- CCI

Date of Platelet Transfusion

Platelet Count (x10^-3)

CCI Count (x10^-3)

HLA antibody ↓56% (35-82%)
41 of 274 (15%) products crossmatch compatible

TPE
Clinical Guidelines that are Useful…

- Assist clinicians in their decision making
- Provide guidance when Type I evidence is lacking
- Help to guide decision making for a patient who would have been excluded from existing Type I study
- Transparently take all of the evidence into account
Using Available Tools for Clinical Decision Making in Apheresis Medicine

• Indication Categories – ASFA Fact Sheets
  – Where does apheresis fit into treatment scheme
  – Assessment of strength of published evidence

• McLeod’s Criteria
  – Framework for taking stock of available data
  – Plausibility of achieving benefit with apheresis

• Corollary Considerations
  – Framework for incorporating clinical judgment
  – Formulation of specific therapeutic trial
Apheresis at the Bedside

Evidence x Knowledge ÷ Individualized Judgment = Rational Apheresis Decision Making