Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence Based Approach from the Writing Committee of the American Society for Apheresis: The 7th Special Issue

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Introduction

• Therapeutic Apheresis using automated blood processing rich and varied field.

• ASFA special issue. Appeal practitioners of apheresis medicine.

• Link specific ASFA categories with analysis based on quality of evidence.
Evidence Based Approach

• Provide uniformity to ASFA category assignment * disease discussion
  ✓ Minimizing personal bias

• Provide strength of recommendation

• Provide comprehensive, condensed information
ASFA Fact Sheet

• Introduction of comprehensive ASFA Fact sheet.

• Format designed summarize and condense available medical literature pertaining diseases treated Apheresis

• Sheets used educational tool
ASFA Fact Sheet

• Compilation of all fact sheets
  I, II, III, IV

• Fact sheets categorized and graded

• “Level of Evidence” recommendations not included in fact sheets
Therapeutic Apheresis Procedures

- Adsorptive cytapheresis
- Therapeutic plasma exchange (TPE)
- Erythrocytapheresis
- Red blood cell (RBC) exchange
- Thrombocytapheresis
- Leukocytapheresis
- Filtration-based selective apheresis
- Extracorporeal photo-apheresis (ECP)
- Immunoabsorption (IA)
- LDL apheresis, adsorptive cytapheresis
- B2 microglobulin column
- High-volume plasma exchange (HVP)
- Rheopheresis.
ASFA Fact Sheet

- General disease description and treatment
- Rationale for Apheresis
- Apheresis regimen
- Parameters for discontinuation
ASFA Fact Sheet

• Disease incidence
• Description
• Management
• Rationale
• Technical Notes

• Volume Treated
• Replacement fluids used
• Treatment frequency
• Optimal duration of therapeutic apheresis
• References
<table>
<thead>
<tr>
<th></th>
<th>New Diseases Included in the JCA Special issue 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atopic (neuro-) dermatitis (atopic eczema), recalcitrant</td>
</tr>
<tr>
<td>2.</td>
<td>Cardiac neonatal lupus</td>
</tr>
<tr>
<td>3.</td>
<td>Complex regional pain syndrome</td>
</tr>
<tr>
<td>4.</td>
<td>Erythropoietic porphyria, liver disease</td>
</tr>
<tr>
<td>5.</td>
<td>Hashimoto’s encephalopathy: Steroid-responsive encephalopathy associated with autoimmune thyroiditis</td>
</tr>
<tr>
<td>6.</td>
<td>HELLP syndrome</td>
</tr>
<tr>
<td>7.</td>
<td>Hematopoietic stem cell transplantation, HLA desensitization</td>
</tr>
<tr>
<td>8.</td>
<td>Hemophagocytic lymphohistiocytosis; Hemophagocytic syndrome; Macrophage activating syndrome</td>
</tr>
<tr>
<td>9.</td>
<td>N-methyl D-aspartate receptor antibody encephalitis</td>
</tr>
<tr>
<td>10.</td>
<td>Prevention of RhD alloimmunization after RBC exposure</td>
</tr>
<tr>
<td>11.</td>
<td>Progressive multifocal leukoencephalopathy associated with nataluziamab</td>
</tr>
<tr>
<td>12.</td>
<td>Pruritus due to hepatobiliary diseases</td>
</tr>
<tr>
<td>13.</td>
<td>Thrombotic microangiopathy, coagulation mediated</td>
</tr>
<tr>
<td>14.</td>
<td>Vasculitis</td>
</tr>
</tbody>
</table>
ASFA Fact Sheet

• Previously published fact sheets have been renamed

• Treating each medical condition as a separate entity within the same disease

• Assigning separate recommendation grade & category

• Separate fact sheets e.g lung & liver transplantation
ASFA Fact Sheet

The total number of diseases and indications addressed in the Seventh Edition are 87 and 179.
Methodology

Evidence Based Approach

• JCA Special Issue 2007 (4th) incorporated EBM into well-defined & widely accepted ASFA Categories and quality of the evidence.

• JCA Special Issue 2010, this system was modified to revise category definitions, maintain quality of the evidence, and add strength of the recommendation
Methodology

Evidence Based Approach

- JCA Special Issue 2013 (6th), this was further refined to provide information on categorization, and strength of recommendation based on the GRADE system.

- The current edition follows the format used in the Sixth Edition.
## ASFA Categories

(Unchanged in 7th, 2016)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disorders for which apheresis is accepted as first-line therapy, either as a primary stand alone 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. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.</td>
</tr>
</tbody>
</table>
## GRADE of Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Strong recommendation, moderate quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Weak recommendation, high quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
GRADE of Recommendation

• Grade can be used in support or against the use of the therapeutic intervention.

• Previously designated weak recommendations for diseases, such as Grade 2C, are more likely to be affected by additional evidence of higher quality than diseases that already have strong recommendations.
DESIGN OF THE FACT SHEET
RESOURCES

DRAFT I

ASSIGN 7-10 ENTITIES TO EACH COMMITTEE MEMBER

DRAFT II

COMMENTS FROM TWO REVIEWERS

DRAFT II WG

REVIEW BY THE COMMITTEE

DRAFT III

REVIEW BY INDEPENDENT REVIEWERS FOR SELECT FACT SHEETS

CATEGORY AND RECOMMENDATION GRADE ASSIGNMENT AT FACE TO FACE MEETING OR CONFERENCE CALL

FINAL VERSION

FINAL FACT SHEETS

MANUSCRIPT COMPILED

5th EDITION OF ASFA SPECIAL ISSUE 2010

REVIEW OF PREVIOUS ASFA INDICATIONS (ADDITIONS/DELETIONS AS INDICATED)

PUBMED FACT SHEET TEMPLATE
# Modified McLeod’s Criteria for Evaluation of Efficacy of Therapeutic Apheresis

<table>
<thead>
<tr>
<th>Evidence grade</th>
<th>McLeod’s criteria</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>“Plausible pathogenesis”</td>
<td>The current understanding of the disease process supports a clear rationale for the use of therapeutic apheresis modality.</td>
</tr>
<tr>
<td>Correction</td>
<td>“Better Blood”</td>
<td>The abnormality, which makes therapeutic apheresis plausible, can be meaningfully corrected by its use.</td>
</tr>
<tr>
<td>Clinical effect</td>
<td>“Perkier patients”</td>
<td>There is a strong evidence that therapeutic apheresis confers benefit that is clinically worthwhile, and not just statistically significant.</td>
</tr>
</tbody>
</table>
Practical Consideration of Planning a Therapeutic Apheresis

- Therapeutic Apheresis – whole blood removed in instrument, separates components centrifugation

- Selectively remove a substantial proportion of one or more components causing diseases ⇔ returning remaining with or without replacement
# General Issues to be Considered When Evaluating a New Patient for Therapeutic Initiation

<table>
<thead>
<tr>
<th>General</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale</strong></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>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>The effect of the therapeutic apheresis on comorbidities and medications (and vice versa) should be considered.</td>
</tr>
<tr>
<td><strong>Technical Issues</strong></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>
</tr>
<tr>
<td><strong>Therapeutic Plan</strong></td>
<td>Total number and/or frequency of therapeutic apheresis procedures should be addressed.</td>
</tr>
<tr>
<td><strong>Clinical and/or laboratory end-points</strong></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>
</tr>
<tr>
<td><strong>Timing and location</strong></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 also be 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>
</tr>
</tbody>
</table>
Timing of Procedures

- Emergency (within hours)
- Urgent (within a day)
- Routine

- Every patient clinical condition and situation considered when deciding timing of treatment
Potential Concerns

• Replacement fluid

• Daily TPE. Plasma maybe indicated

• Fibrinogen > 100 mg/dl

• Plasma at the end.
Risks and Benefits

• Low incidence of complications (5 – 12 %)

• Most adverse events Grade I: Mild
  (no intervention required 1.5%)

• Grade II: Moderate
  (intervention required but treatment completed, 2.5%)
  ✓ Most commonly reported urticaria or rigors (0.7-12%)
  ✓ Hypocalcemia symptoms (1.5 – 9 %)
  ✓ Hypovolemia symptoms (0.3 – 5%)
Risks and Benefits

• Grade III: Severe (procedure interrupted or abandoned, 0.8%)

• Grade IV: Fatal (0.5%)
  ✓ Cardiovascular Events
  ✓ Pulmonary Edema & Embolism
  ✓ Respiratory Arrest
Choice of Replacement Fluid

5% Albumin

✓ iso-oncotic

✓ lower frequency of adverse reactions

✓ Lack of coagulation factors & plasma proteins which are depleted during TPE dilutional coagulopathy

✓ Most plasma proteins return normal 24 hr

✓ Fibrinogen levels rebound more slowly
• **Plasma**

  ✓ Iso – Oncotic

  ✓ Contains Coagulation factors & other plasma proteins

  ✓ Requires ABO blood group compatibility

  ✓ Higher risk of hypocalcemic reactions and infectious and noninfectious complications

  ✓ Should be avoided if possible

  ✓ Except TTP
• **Calcium Levels**

  ✓ Citrate anti-coagulant

  ✓ Hypoalemia occurs 1.5-5% of Procedures

  ✓ Increased with donor plasma as replacement fluid, large volume apheresis procedures, pts. hepatic cirrhosis

  ✓ \( \text{Ca}^{+2} \) levels drop within first 15 minutes of the procedure

  ✓ ↑PTH

  ✓ Continuous IV infusion of 10% calcium gluconate
• **Magnesium Levels**

- Blood levels of ionized Mg drop 60%
- Symptoms similar to hypocalcemia
- No prophylactic infusions is needed
Medication Effects

• Elimination of medication is a passive process with linear kinetics

• Plasmapheresis removes 40-60 ml plasma/kg

• Medication high rate protein binding most likely removed

• Immunoglobulins, monoclonal antibody therapies

• Immunosuppressant post TPE

• Corticosteroids, cyclosporine & tacrolimus minimally impacted by plasmapheresis
Vascular Access

- Anticubital/peripheral venipuncture
- Femoral catheter
- Subclavian catheter
- Jugular access
- Ports
- Arteriovenous fistula or graft
• Informed Consent

✓ For central line

✓ Blood usage

✓ Plasmapheresis
Therapeutic Apheresis in Pediatric Patients

- Sedation
- Vascular access
- Anti-coagulation
- Maintenance of Constant intravascular volume
- Maintenance of adequate red cell volume in circulation
Thank You