APHERESIS: INSIDE THE BLACK BOX

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Learning Objectives

- Re: apheresis, discuss
  - General principles
  - Instruments
  - Vascular access
  - Replacement fluids
  - Types of procedures
  - Adverse events
- Review evidence-based indications for plasma exchange in neurology
- Review current trends in apheresis utilization in Canada
Disclosures

- I have no relevant conflicts of interest
- Other disclosures
  - Advisory board participation: Alexion, Shire, Ablynx
  - Honoraria for speaking: Alexion, Novartis, Shire
  - Clinical trials: Ablynx, CSL Behring, Octapharma
  - Research funding: CSL Behring
Apheresis

- Derived from Greek *apairesos* or Roman *aphairesis* meaning to take away by force
- Medical technology in which the blood of a person is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation
- Other names
  - Therapeutic plasma exchange, plasmapheresis

https://en.wikipedia.org/wiki/Apheresis
Apheresis as a Therapeutic Modality: Key Considerations

- Disease is caused by a pathogenic substance in blood
- Pathogenic substance can be efficiently removed
- Removal will lead to either a resolution of pathogenic state or decrease in morbidity
  - Examples: auto or allo antibodies, antigen-antibody complexes, paraproteins, etc.
Apheresis as a Therapeutic Modality: Effectiveness

- Effectiveness depends on:
  - Volume of plasma removed relative to total plasma volume (more)
  - Distribution of substance to be removed (low volume of distribution, mainly intravascular)
  - Speed at which the substance re-equilibrates between compartments (instantaneous)
  - Rate at which substance is synthesized (slow)
  - Molecular size of substance (>15,000D)
Relationships between internal compartmental and external distribution of target molecules during apheresis
Apheresis as a Therapeutic Modality: Examples of Treatment Regimens

<table>
<thead>
<tr>
<th>Disease</th>
<th>Distribution and half-life of substance</th>
<th>Post-TPE rebound</th>
<th>Number of TPE required</th>
<th>Frequency of TPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperviscosity due to LPL IgM</td>
<td>90% intravascular 5-6 days</td>
<td>Little</td>
<td>1-2</td>
<td>Daily</td>
</tr>
<tr>
<td>Neuromyelitis optica NMO IgG</td>
<td>45% intravascular 21 days</td>
<td>Slow (over 2 days) but substantial</td>
<td>5-6</td>
<td>Alternating days</td>
</tr>
</tbody>
</table>

Williams and Balogun CJASN 2014
Apheresis Prescription: For IgG Mediated Disease

- 1 PV exchange removes about 65% of intravascular IgG (30% of total body IgG)

- To achieve 70-85% reduction in IgG
  - Theoretically need four 1PV exchanges
  - Practically need 5-6 1PV exchanges over 14 days combined with immunosuppression

- Reductions beyond 70-85% are difficult to achieve due to diminishing efficiency of removal
Target Molecule Kinetics During Apheresis

A

B
Apheresis Prescription: Number of Procedures for IgG Mediated Disease

Fig. 3. Theoretical reduction of IgG following plasma exchange of 1, 1.25, and 1.5 plasma volumes and following re-equilibration of total body IgG. The solid line indicates a 85% reduction and the dashed line a 70% reduction. The absolute reduction in IgG is reduced with each subsequent exchange. Calculations assume no degradation or synthesis of IgG, and re-equilibration of IgG at 2 days.
Apheresis Prescription: Frequency of Treatments

- Frequency – Daily vs. Alternating days

Need to remove quickly pathogenic substance to reduce disease effects

Need time for substance to re-equilibrate into the vascular space

Need to minimize risk of bleeding
Common Prescriptions for Neurological Conditions

- GBS, MG
  - 1 PV exchange x 5 over 10 days

- CIDP
  - 1 PV exchange twice weekly for 3 weeks or 10 treatments over 4 weeks; maintenance q1-3 weeks may be required

- NMO, MS
  - 1 PV exchange x 5-7 over 14 days

Raphael et al 2012; Barth et al 2011; Mehndiratta et al 2015; Weinshenker et al 1999
Apheresis Instruments

- Separation by centrifugation
  - Uses centripetal force to separate components according to their density
  - Can be used for plasma exchange and to remove/exchange cellular components (ex. RBC)
Apheresis Instruments

- Separation by **filtration**
  - Uses membranes that are permeable to HMW proteins but not cells (ultra-filtration)
  - Limited to plasma exchange procedures; usually not used to treat TTP
Apheresis Instruments

**Centrifugal TPE**
- Citrate (usually)
- Lower blood flow rate
- Peripheral veins or central line
- Process ~1.5 x blood volume
- Plasma extraction ~80%

**Membrane TPE**
- Heparin (usually)
- Higher blood flow rate
- Central venous line
- Process ~3 x blood volume
- Plasma extraction ~30%

**Plasma replacement**
- FFP for TTP
- 5% albumin for other indications

**Plasma regeneration**
- Adsorption column
- Cascade filtration
Centrifugal vs. Membrane Filtration Apheresis

Mark E. Williams, and Rasheed A. Balogun CJASN 2014;9:181-190
©2014 by American Society of Nephrology
Centrifugal Apheresis

- Plasma: SG 1.025-1.029
- Platelets: SG 1.040
- Mononuclear cells: SG 1.070 (monocytes → lymphocytes)
- Polymorphonuclear cells: SG 1.087-1.092
- Erythrocytes: SG 1.093-1.096

“Buffy Coat”
Membrane Filtration Apheresis

<table>
<thead>
<tr>
<th>BUN</th>
<th>Creatinine</th>
<th>VitB12</th>
<th>β2-microglobulin</th>
<th>K Light Chain</th>
<th>λ Light Chain</th>
<th>Albumin</th>
<th>IgG</th>
<th>IgM</th>
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</thead>
<tbody>
<tr>
<td>0.06</td>
<td>0.113</td>
<td>1.355</td>
<td>11.8</td>
<td>25</td>
<td>50</td>
<td>66</td>
<td>160</td>
<td>950</td>
</tr>
</tbody>
</table>

Hemodialysis: Diffusion Clearance

Hemofiltration: Convective Clearance

Small Molecules

Middle Molecules

Large Molecules

Therapeutic Plasma Exchange
Types of Apheresis Procedures

- Therapeutic plasma exchange (TPE)
- Cytapheresis
  - Red blood cell exchange
  - Plateletapheresis
  - Leukapheresis
- Photopheresis
TPE: Replacement Fluids

- Plasma (FFP, FP, CSP, SDP)
  - Used mainly for treatment of TTP or aHUS
  - May be added to albumin for other indications if patient has coagulopathy, is actively bleeding or peri-invasive procedure

- 5% human albumin solution
TPE: Vascular Access

- Vascular catheter – double lumen, large bore (temporary vs. permanent/tunneled)
  - Tunneled catheters for prolonged (>2 wks) course of TPE
- 2 peripheral veins
  - Limited to conscious, cooperative, able patient, with good venous access
  - Access line must 14 gauge and return line at least 18 gauge
  - Safer (80% less risk of infection) but multiple uses can lead to vein sclerosis and/or thrombosis
- AV fistula
- Vortex double port
TPE: Indications in Neurology

- Diseases with the best data on apheresis efficacy:
  - CIDP
  - GBS
  - MG both moderate–severe and prethymectomy
  - paraproteinemic polyneuropathies (IgG/IgA)
  - MS (acute relapses)
  - LEMS
Categories

(I) TPE is accepted as first line as primary treatment or in conjunction with other treatments

(II) TPE is accepted as a second line treatment, either alone or in conjunction with other treatments

(III) Role of TPE has not been established.

(IV) TPE is ineffective or harmful
### TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

<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>

*Journal of Clinical Apheresis DOI 10.1002/jca*
Thrombotic thrombocytopenic purpura
- Thrombotic microangiopathy – due to anti-CFH, ticlopidine
- Acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Paraproteinemic demyelinating polyneuropathy (IgG/IgA, IgM)
- Myasthenia gravis
- Antiglomerular basement membrane disease (Goodpasture syndrome)
- ANCA-associated rapidly progressive glomerulonephritis
- Recurrent focal segmental glomerulosclerosis in transplanted kidney
- Hyperviscosity syndrome
- Desensitization or antibody mediated rejection for renal transplantation
- NMDA antibody encephalitis
- Progressive multifocal leukoencephalopathy post natalizumab
- Wilson’s disease (fulminant)
American Academy of Neurology (AAN) Evidence-Based Guidelines 2011

- Based on a structured literature review from 1995 to 2009

- TPE is established as effective and should be offered in severe acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome (GBS) and in the short-term management of chronic inflammatory demyelinating polyneuropathy (Class I studies, Level A).
TPE is **probably effective** and should be considered for mild AIDP/GBS, as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS, and for neuropathy associated with IgA or IgG gammopathy, based on at least one Class I or 2 Class II studies (Class I, Level B).

- TPE is probably not effective and should not be considered for neuropathy associated with IgM gammopathy (Class I, Level B).
TPE is **possibly effective** and may be considered for **acute fulminant demyelinating CNS disease** (Class II, Level C).

There is **insufficient evidence** to support or refute the use of TPE for **myasthenia gravis**, pediatric autoimmune neuropsychiatric disorders associated with streptococcus infection, and Sydenham chorea (Class III evidence, Level U).

TPE is established as **ineffective** and should not be offered for **chronic or secondary progressive multiple sclerosis (MS)** (Class I studies, Level A).
TPE: Complications

**Common adverse events (<10%)**
- Citrate toxicity
- Hypotension
- Febrile reactions
- Minor allergic reactions

**Rare adverse events (<1.5%)**
- Arrhythmia
- Thrombosis
- Pulmonary edema
- Seizures
- Major allergic reaction
- Bleeding

**Frequency of AE by severity:**
- Grade 1: 1.5%
- Grade 2: 2.8%
- Grade 3 and 4: 0.8%

Norda 2003
TPE: Complications

- **Procedure-related**
  - Citrate toxicity
    - replace Ca\(^{2+}\)
  - Hypotension (vasovagal, anemia, hypovolemia, bradykinin-mediated hypotension, etc)
    - transfuse RBC if Hb<70g/L, encourage fluid intake or give IVF, hold BP medications esp. ACEI prior to treatment
- Edema
- Cellular losses – anemia, thrombocytopenia
- Removal of drugs - high protein binding (>=75%) and small volume of distribution (<0.3L/kg) – ex. antibiotics
  - Give once daily meds after TPE
  - Wait at least 24 hrs post MAb administration
TPE: Complications

- **Access-related**
  - Vascular catheter-related:
    - Bleeding, infection, thrombosis
  - Peripheral veins
    - Bruising, scarring of veins
TPE: Complications

- **Replacement fluid related**
  - 5% human albumin solution
    - Immunosuppression
      - Treat every other day, add plasma, consider immune replacement dose of IVIG
  - Coagulopathy
    - Post TPE, PT up by 30%, aPTT up by 100%
    - Most factors replenished within 48 hrs, fibrinogen within 72 hrs
      - Treat every other day, add plasma, avoid invasive procedures
- Febrile reactions
- Transfusion transmitted infections
Apheresis Landscape in Canada

- Population 36.3 million
- Approximately 40 centres provide therapeutic apheresis
- 13,000 procedures were performed on 1,087 patients in 2016
- >60% of procedures were performed by 5 centres

Data from CAG annual meeting 2017
Evolution of Apheresis Practice in Canada

1985

5,345 procedures
40 indications
Most common: Hematology (TTP)

2016

13,000 procedures
128 indications
Most common: Neurology (Myasthenia Gravis)
CAG 2017: Procedures by Specialty

- Neurology CNS: 36%
- Renal: 15%
- Transplant: 10%
- Collagen Vascular Rheumatology: 2%
- Neurology CNS: 12%
- Metabolic: 4%
- Miscellaneous: 1%
- Hematology: 20%
- Dermatology: 0%

c/o Canadian Apheresis Group
Canada 2016: Top Indications for TPE by Diagnosis

CAG 2016 data
Neurology Apheresis Indications in Canada

1990
2,870 procedures for 5 diseases
Top 3:
- Acute GBS
- Chronic GBS
- Myasthenia gravis

2017
5,939 procedures for 23 diseases
Top 3:
- Myasthenia gravis
- CIDP
- Transverse Myelitis

Canadian Apheresis Group
TPE for Neurological Conditions in Canada

CAG data

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>333</td>
<td>3423</td>
</tr>
<tr>
<td>2008</td>
<td>389</td>
<td>3573</td>
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<td>2011</td>
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<td>2012</td>
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<td>3848</td>
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<td>2013</td>
<td>360</td>
<td>3877</td>
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<tr>
<td>2014</td>
<td>434</td>
<td>4827</td>
</tr>
<tr>
<td>2015</td>
<td>440</td>
<td>5190</td>
</tr>
<tr>
<td>2016</td>
<td>500</td>
<td>5975</td>
</tr>
</tbody>
</table>

CAG data
Canada 2016: Top 5 Neurological Indications for TPE

- MG
- CIDP
- TM
- NMO
- MS

CAG data
IVIG or PLEX: That is the question

- Efficacy, cost and safety are likely similar; choice depends on availability, acceptability of side effect profile and convenience
  - GBS, CIDP, MG crisis
- Efficacy likely higher for PLEX in
  - MuSK +ve MG
- PLEX is the preferred choice in
  - NMO, MS

Gwathmey et al 2014
Trends in Apheresis vs. IVIG

Mean rate of growth = 1.1%

Mean rate of growth = +7.3%
The top clinical trial opportunities in therapeutic apheresis and neurology


The National Heart, Lung, and Blood Institute convened the 2012 State-of-the-Science Symposium in Therapeutic Apheresis (TA) to identify and prioritize future research proposals:

- 6 subcommittees formed based on organ system, pathophysiology, and technology/special considerations
- Members included clinical subject matter experts and basic scientists
- Each subcommittee developed concept proposals which were then presented, evaluated, and prioritized based on scientific importance, clinical significance, and feasibility by the attendees

Neurology subcommittee developed eight concept proposals:

- TA in neuromyelitis optica;
- TA vs. IVIG in anti-muscle specific kinase associated myasthenia gravis, severe ADEM, and anti-NMDA encephalitis
- Extracorporeal photopheresis in relapsing remitting multiple sclerosis, polymyositis
- Fibrinogen/low-density lipoprotein apheresis in idiopathic sudden sensorineural hearing loss
- Creation of a rare neurologic disease registry and biorepository
Apheresis in Neurology: Current Trials

- Alzheimer’s
- GBS
- MS
- NMO
- MG
- Natalizumab removal in MS
- Autoimmune encephalitis
- Amyotrophic lateral sclerosis
- Acute/severe inflammatory demyelinating diseases
Questions?