Plasmapheresis in Immunological Conditions

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Introduction to plasmapheresis

- Extracorporeal therapy
- Removal of plasma and contained:
  - autoantibodies
  - immune complexes
  - complement components
  - coagulation cascade factors
  - and the replacement with 0.9% saline/5% albumin
- 5% albumin/0.9% saline does dilute coagulation factors and so FFP may be used in patients with increased risk of bleeding

Can you think of another scenario in which FFP would be a better replacement than 5% albumin/0.9% saline?

In TTP replacement fluid is FFP to replace ADAMSTS13 enzyme- avoidance of FFP in most TPE is advisable because of the risk of allergic events with FFP

- Volume of plasmapheresis depends on patient size eg 50-60mL/kg ie 3.5L for 70kg pt; approx 1.2x circulating plasma volume or 60-72% of plasma constituents
- Frequency of treatment depends on disease characteristics eg IgM autoantibodies in Waldenstrom's Macroglobulinemia is more efficiently cleared than IgG as it stays intravascular
- Often used in conjunction with immunosuppressive therapy
- Historically progress has been limited by a lack of well designed clinical trials

Types of plasmapheresis

- Normally performed in a Blood Bank
- No limit in the size of molecule being removed

Immunoadsorption columns can be added to both centrifugal and membrane machines to extract specific proteins eg anti-apolipoprotein B for the treatment of familial hypercholesterolemia
- Secondary processing to purify plasma and allow it to be returned to the patient is being explored but not yet in wide use
Examples of Pathogenic Autoantibodies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantibody To:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia Gravis</td>
<td>ACHR, MuSK</td>
</tr>
<tr>
<td>Guillain-Barre</td>
<td>GM1, GM1b, GQ1b (Miller-Fisher)</td>
</tr>
<tr>
<td>NMO</td>
<td>Aquaporin-4</td>
</tr>
<tr>
<td>stiff person syndrome</td>
<td>GAD65</td>
</tr>
<tr>
<td>Goodpastures Syndrome</td>
<td>Alpha-3 chain of collagen IV</td>
</tr>
<tr>
<td>Wegeners</td>
<td>MPO, PR3, LAMP2</td>
</tr>
<tr>
<td>idiopathic dilated cardiomyopathy</td>
<td>Beta-1R, cardiac myosin</td>
</tr>
</tbody>
</table>

Adverse events in plasmapheresis

Common Adverse Events:

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>Parasthesia</td>
<td>1.5-9</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Muscle Cramps Headache</td>
<td>0.4-5</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>Urticaria</td>
<td>0.7-12</td>
</tr>
</tbody>
</table>

Adverse events in plasmapheresis

Rare Adverse Events:

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Myocardial Ischemia</td>
<td>0.03-1.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Respiratory Arrest PE</td>
<td>0.1-0.3</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombosis/Bleeding</td>
<td>0.2-0.7</td>
</tr>
<tr>
<td>Infectious</td>
<td>Hepatitis</td>
<td>0.3-0.7</td>
</tr>
<tr>
<td>Neurologic</td>
<td>CVA</td>
<td>0.3-0.4</td>
</tr>
<tr>
<td>Pyrogenic</td>
<td>Hyperthermia</td>
<td>0.7-1</td>
</tr>
</tbody>
</table>

What kind of conditions can be treated with plasmapheresis?

Neurological

Renal

Immunological

Indications for plasmapheresis from the American Society for Apheresis

- **Category I**: Disorder for which apheresis is accepted as first-line therapy, alone or in conjunction with other treatment
- **Category II**: Disorder for which apheresis is accepted as a second-line therapy, alone or in conjunction with other treatment
- **Category III**: Optimum role of apheresis is not established
- **Category IV**: Published evidence suggests apheresis is ineffective or harmful

Plasmapheresis in Neurological conditions

**Category I Indications**:
- **Guillain-Barre Syndrome**
  - Autoantibodies cross-react with element of pathogens and those of presynaptic neurons (Campylobacter, CMV, EBV, Mycoplasma and Influenza)
  - First-line treatments include plasmapheresis and IVIG, data suggest both are equally efficacious
  - In a Cochrane review 2001 there was no difference between IVIG and plasmapheresis in the treatment of Guillain-Barre after 4 weeks in terms of mechanical ventilation, death or residual disability
  - Current guidelines suggest plasmapheresis only be considered in the more severe forms of GBS where walking and/or ventilation are compromised
- **CIDP**
  - plasmapheresis shown to be superior to placebo
  - Dyk et al Ann Neurol 1996 studied plasmapheresis vs IVIG in 20 patients with CIDP and found no significant differences between the two groups in the short term 4 weeks
Plasmapheresis in Neurological conditions

- **MS**
  - Category II for steroid resistant relapsing and remitting MS
  - Not to be used in primary or secondary progressive forms
- **Myasthenia Gravis**
  - Autoantibodies against Ach R 90% and 7% to MuSK
  - Historically plasmapheresis has been used pre- and post-thymectomy in severe forms of disease as well as in Myasthenic crisis.
  - However there is a lack of randomized trials to guide consensus
  - Data suggests IVIG and plasmapheresis are equally efficacious but in crisis patients IVIG results in a briefer hospital stay, less complications, less expense and lower mortality.

**Category II indications:**
- Acute disseminated encephalomyelitis, NMO, Chronic focal encephalitis and Lambert-Eaton syndrome

Plasmapheresis in Renal Disease

- **Rapidly Progressive Glomerulonephritis**
  - **Type I: anti-GBM Disease**
    - Characterised by IgG depositions into the BM
    - Category I indications if associated with diffuse pulmonary hemorrhage or dialysis dependence; plasmapheresis combined with immunosuppressive drugs to inhibit de novo Ab synthesis
    - Prior to introduction of plasmapheresis mortality was 90%; now 1 year survival is 70-90%
  - **Type III: ANCA associated RPGN (Wegeners)**
    - Increasing evidence that ANCA are pathogenic
    - Meta-analysis found evidence of plasma exchange compared with standard therapy found benefits in terms of decrease in development of ESKD, and death
    - Category I indication

Plasmapheresis in Hematology

- **Thrombotic microangiopathies**
  - **TTP- Category I recommendation**
    - Thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, fever
    - Deficiency in ADAMTS13 (vWF cleavage) leading to ultra large vWF
    - May be genetic or acquired
    - Micro thrombi are platelet and vWF rich

- **HUS**
  - **Typical HUS:**
    - Thrombocytopenia, microangiopathic hemolytic anemia, renal failure
    - Shiga-toxin producing E.Coli accounts for the majority of typical HUS
    - **Suspicion for plasmapheresis is DON'T GIVE**
  - **Atypical HUS**
    - Includes above triad in the absence of diarrhea but also
    - irritability.
    - May have a genetic basis.
    - Associated with anti-factor H autoantibodies +/- functional abnormalities of ADAMTS13
    - Category I recommendation for plasmapheresis

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Plasmapheresis in Renal Disease

- **Myeloma Kidney**
  - A retrospective study from the Mayo Clinic found plasmapheresis was beneficial in patients with cast nephropathy, high light chain levels and severe renal impairment

Plasmapheresis in TTP

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Plasmapheresis in Hematology

- DIC
  - No specific recommendation for plasmapheresis in DIC
  - Category II recommendation for plasmapheresis in sepsis with multiorgan failure
- Catastrophic antiphospholipid syndrome
  - Acquired hypercoagulable state due to ACL/APL antibodies causing acute microvascular venous and arterial thrombosis and organ failure
  - Category II indication for plasmapheresis

Plasmapheresis in Immunological conditions

- SLE
  - Category II recommendation for severe lupus eg with cerebritis or diffuse alveolar hemorrhage. Not indicated in lupus nephritis
- Cryoglobulinaemia
  - Type I (associated with lymphoma/myeloma) monoclonal Ig can be removed by plasmapheresis reversing the hyperviscosity and cryoprecipitation
  - Type II (associated with HCV/lymphoma) IgM/IgG complexes can be removed by plasmapheresis

Summary

- Plasmapheresis involves the removal of pathogenic proteins in the plasma
- It is generally well tolerated
- Plasmapheresis has been trialed in a large number of medical conditions often in processes that are non-randomized or well-controlled
- In some conditions the pathogenic basis of disease is clearly delineated and in others not
- The best evidence for plasmapheresis is for neurological, hematological, renal and immunological conditions

Thank you