Indications of therapeutic apheresis in internal medicine

Anna Tremmel MD, Eszter Horváth MD,
Semmelweis University
1st. Department of Internal Medicine, Apheresis Unit

2014.11.07. English Lecture
Outline

• Components of blood
• Apheresis definition
• Types of apheresis /therapeutic apheresis
• Aim of treatment - (Therapeutic, Donation)
• Methods – ECP and TPE
• Therapeutic Plasma Exchange
  – Mechanism of plasma removal
  – Anticoagulation
  – Replacement fluids
  – Required conditions for patient
  – Complications
• Indication - American Society for Apheresis (ASFA) guideline
Components of blood

1. Plasma 55%

2. Cellular elements 45%
   - Buffy coat < 1%
   - White Blood Cells
   - Platelets
   - Red Blood Cells ~45%
Apheresis is derived from a Greek word (ἀφαίρεσις aphairesis), which means „to separate”, „to take away from”, or „to remove”
Apheresis definition

**Apheresis** - a medical technology in which the blood of a patient or donor is passed through a medical device that first separates the components of blood then returns the remainder with or without extracorporeal treatment or replaces the separated components.
Types of apheresis

• Donation
  – collect component(s) of blood from a healthy donor (fresh frozen plasma (FFP), stem cell harvesting etc.)

• Therapeutic apheresis (TA)
  – separates components of blood to treat a disease.
  – general term which includes all apheresis-based procedures used therapeutically.
Types of therapeutic apheresis (TA)

**Therapeutic plasma exchange (TPE)**
- separates out plasma from other components of blood
- the plasma is removed and replaced with a replacement solution such as colloid solution or a combination of crystalloid/colloid solution.

**Extracorporeal photopheresis (ECP)**
- separates buffy coat from patient's blood
- treats it extracorporeally with a photoactive compound (8-methoxysprolalen - UVADEX) and exposes it to ultraviolet A light and subsequently reinfuses to patient.

**Cytapheresis/Hemapheresis**
- Leucocytapheresis (LCP): separates out white blood cells (lymphomononuclear, CD34+, leukemic blasts or granulocytes)
- Thrombocytapheresis (TP): separates out and removes the platelets

**Immunoadsorption (IA)**
- separated plasma is passed through a medical device which has a capacity to remove immunoglobulin by specifically binding them to the active component (e.g., Staphylococcal protein A) of the device.

**LDL Apheresis (DALI):**
- selective removal of low-density lipoproteins from the blood
- a variety of instruments are available which remove LDL cholesterol based upon charge (dextran sulfate and polyacrylate, size (double-membrane filtration), precipitation at low PH (HELP), or immunoadsorption with anti-Apo B-100 antibodies.

**MARS (Molecular Absorbent Recirculating System)/ Prometheus (Fractional Plasmapheresis and Adsorption, FPSA with high flux dialysis)**
- selective removal of toxins, which are binding with protein (albumin) from the blood and this apheresis is combined with dialysis. “Supportive liver replacement therapy”
Aim of treatment

• To remove

I. Plasma (therapeutic plasma exchange)

Therapeutic

• Auto-antibodies
  • Wegener-granulomatosis - c-ANCA
  • Microscopic polyangiitis - p-ANCA
  • Goodpasture-syndrome - anti-GBM
  • Neurological diseases – Guillain-Barrè-syndrome, Myasthenia-gravis (antibodies against acetylcholine receptors (AChR)), Chronicus Inflammatory demyelinating polyneuropathy (CIDP)

• Toxins – drug intoxication, poisoning

• Cytokines – SIRS (IL2, TNF-alfa)

• Immune complexes – Cryoglobulinemia

• Lipids – Low Density Lipoprotein (LDL)- Familiar hypercholesterinaemia

• Paraproteins (immunglobulin) – Multiple myeloma (MM)

Donation

• Fresh Frozen Plasma (FFP)
Aim of treatment

II. Cells (cytapheresis)

• Therapeutic
  
  • *White blood cells (Leucocytapheresis)*
    • Acut lymphoblastic leukemia (ALL),
    • Acut myeloid leukemia (AML)
    • Chronic lymphoid leukaemia (CLL)
  
  • *Platelets (Thrombocythapheresis)*
    • Essentialis thrombocythaemia (ET),
    • Acut myeloid leukaemia FAB-AML M7
  
  • *(Red blood cells – sickle cell anemia dis.)*

• Donation
  
  • *Stem cells collection* – for transplantation (autolog, allogen)
Aim of treatments

• Remove → treat → give back

I. Extracorporeal photopheresis (ECP)

- Collect buffy coat - WBC (Leucocytapheresis)
  - Treat: 8-methoxypsoralen + UVA
  - Treat: cause apoptosis of activated or abnormal T cells
- Give back to circulation
  - modify the immune response,
  - rebalance of skewed immune system

• Indication:
  - Cutan T cells lymphoma – Sézary-syndrome, Mycosis fungoides
  - Graft versus host disease (GVHD)
  - Progressive systemic sclerosis (PSS)
  - Severe atopic dermatitis
  - Nephrogenic systemic sclerosis
  - Kidney/ liver transplant rejection
  - Crohn disease
Methods- Extracorporael photopheresis
Methods - Therapeutic plasma exchange

2 types of device:

• One that separates the plasma from the cellular components based on size (Filtration-based apheresis), and

• One that separates components based on density (Centrifugation-based apheresis)
Mechanism of plasma removal I.

The predominant method for TPE is centrifugation.

Separates the blood components into layers based upon their density:

1. the most dense elements are the RBCs and the least dense portion is the plasma.
2. Intermediate layers (buffy coat)
Mechanism of plasma removal II.
How many millilitres of plasma is exchanged by TPE?

- **Volume of removed plasma**
  - based on:
    - estimated plasma volume (EPV) in patient’s blood
    - the body weight (kg) and hematocrit

  \[ \text{Removed plasma volume} = (0.065 \times \text{body weight}) \times (1 - \text{Hct}) \]

  - Normal: 40 ml/kg (large: 60 ml/kg)

- this is equal to 1-1.5 plasma volume
- time: 1.5-2 hours per one complete plasma exchange
Mechanism of plasma removal III.

• Effect:
  
  – **Macromolecule of blood:**
    • 1x plasma volume exchange: 60% of macro molecules is removed,
    • 1,5x plasma volume exchange: 75% of macro molecules is removed.
  
  – **Immunglobulins:**
    • 90% of Igs are removed in ten days with 5 TPEs
    • IgM – 75% intravascular, one or two TPE rapidly reduce level
    • IgG – 45% intravascular, need more procedures to reduced level
    • level of Igs is resolved in 48-72 hours after one TPE,
  
  – **Complement factors**
    • perfect restitution is 48 hours,
  
  – **Enzyme function and coagulation factors**
    • are resolved in 24-48 hours.
Anticoagulation

ACD-A (Anticoagulant Citrat Dextrose Solution A)

• Benefit of ACD-A:
  – The *hemostasis* is less disturbed
  – *Influence* is short.

• Disadvantage of ACD-A:
  – binds *Ca (citrat toxicity)* → replaces *Ca*
Replacement fluid I.

I. Saline

II. 5% human albumin (HA)

III. Fresh Frozen Plasma (FFP)

- Use albumin and saline in combination
  - Colloid should not be less than 50% of total
  - Replacement fluid consists of 60 to 80% colloid and 20 to 40% saline
  - Does not contain all of the removed plasma components (coagulation factors)

- FFP
  - Contains normal protein that has been removed
  - Complication more common (urticaria, anaphylactoid reaction)
Required conditions of TPE (for patient) I.

I. Laboratory:
• Normal level of ions (Na, K, Ca, Mg),
• Minimum Htc, 0.20 (20%),
• Minimum Hgb, 80 g/l,
• Minimum PLT, 20 G/l

II. Physiology:
• Blood pressure, 90-160/70-100 Hg/mm,
• Pulse, 60-140/s.
Required conditions of TPE (for patient) II.

II. *Physiology*:

- TPE requires reliable vascular access
  - two large, durable periferal veins (one in left and one in right arm)
  - or
  - use double-lumen central venous catheter (CVC)
- TPE is a double line, so the extracorporeal blood volume is low, blood removal and return is continuous.
- Optimal blood flow is 40-60 ml/s.
Complications of TPE

- Paresthesias (*ACD-A* binds Ca from blood, hypocalcaemia),
- Hypotension, (*hypovolemia*),
- Nausea, vomiting (*high flow*),
- Urticaria, anaphylactoid reaction (*FFP*),
- Bleeding/ haematoma (*peripheral puncture, clotting factors, anticoagulation solutions*).
# Indications for Therapeutic Apheresis

(ASFA — American Society for Apheresis-2013)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Disorders for which <strong>apheresis is accepted as first-line therapy</strong>, either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II.</td>
<td>Disorders for which <strong>apheresis is accepted as second-line therapy</strong>, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III.</td>
<td>Optimum role of <strong>apheresis therapy is not established</strong>. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV.</td>
<td>Disorders in which published evidence demonstrates or suggests <strong>apheresis to be ineffective or harmful</strong>.</td>
</tr>
</tbody>
</table>
## Indication

### Nephrology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of TA</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA- associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; Wegener’s Granulomatosis)- Dialysis dependence</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis – recurrent in transplanted kidney</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Immune complex rapidly progressive glomerulonephriti</td>
<td>TPE</td>
<td>III</td>
</tr>
<tr>
<td>Immunoglobulin A nephropathy- crescentic/chr. Progressive</td>
<td>TPE</td>
<td>III</td>
</tr>
<tr>
<td>Myeloma cast nephropathy</td>
<td>TPE</td>
<td>II</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>TPE</td>
<td>III</td>
</tr>
</tbody>
</table>
## Indication

### Haematology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of TA</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia-severe cold agglutinin disease</td>
<td>TPE</td>
<td>II</td>
</tr>
<tr>
<td>Hyperleukocytosis – leukostasis</td>
<td>Leukocytapheresis</td>
<td>I</td>
</tr>
<tr>
<td>Hyperviscosity in monoclonal gammopathies - symptomatic</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>TPE</td>
<td>IV</td>
</tr>
<tr>
<td>Thrombocytosis- symptomatic</td>
<td>Thrombocytapheresis</td>
<td>II</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Heparin induced thrombocytopenia</td>
<td>TPE</td>
<td>III</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome,infection-associated – Shiga toxin/S. pneumoniae</td>
<td>TPE</td>
<td>IV/III 23</td>
</tr>
</tbody>
</table>
## Indication

### Immunology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of TA</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Cryoglobulinemia – severe/symptomatic</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome- erythrodermic</td>
<td>ECP</td>
<td>I</td>
</tr>
<tr>
<td>Scleroderma (Progressive systemic sclerosis)</td>
<td>ECP</td>
<td>III</td>
</tr>
<tr>
<td>Systemic lupus erythematosus – severe/nephritis</td>
<td>TPE</td>
<td>II/IV</td>
</tr>
<tr>
<td>Guillian-Barré-syndrome</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>TPE</td>
<td>I</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>ECP</td>
<td>II</td>
</tr>
</tbody>
</table>
Conclusion

• Think about these methods:
  – when you meet patients with an abnormally high number of cells (haematology)
  – when you meet a rare disease (immunology, neurology) are caused removable blood component
• Pay attention to required conditions of patients
• Use the ASFA guideline to indicate the treatment
Thank you for your attention!