Introduction to Therapeutic Apheresis
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Holy Grail of Transfusion Medicine

Manipulate the composition of blood:

With complete control

Without adverse consequences
Transfusion Medicine

Transfusion of “products”:  
RBC, Plt, WBC, PBSC, FFP

Infusion of recombinant proteins:  
FVIII, FVIIa, ATIII

Prescription of “drugs”:  
Epo, G-CSF, GM-CSF

Removal of “evil humors” (provide “good humors”):  
Apheresis of cells and solutes

Hemapheresis

Removal of “evil humors” or cells:  
(e.g. pathogenic autoantibodies, leukemic cells)

Provide “good humors” or cells:  
(e.g. beneficial plasma proteins, Hgb AA RBC)

“Apheresis” not “pheresis”

Plasmapheresis, leukapheresis, plateletpheresis,  
erthrocytapheresis, etc.

Plasmapheresis vs. plasma exchange

Plasmapheresis is not dialysis
**Ideal Solute**

- Completely intravascular
- Completely extracellular (if soluble and non-cellular)
- Accessible to phlebotomy
- No flux between intravascular and extravascular spaces
- No synthesis within the time frame of the procedure
- No catabolism within the time frame of the procedure
- No clearance within the time frame of the procedure

**Ideal Solute**

Discontinuous exchange
Ideal Solute

\[ [\text{solute}]_{\text{final}} = [\text{solute}]_{\text{initial}} \times \frac{1}{e^{(\text{plasma volume removed})}} \]

1 plasma volume → ~37% remaining
2 plasma volumes → ~14% remaining
3 plasma volumes → ~5% remaining

Ideal Solute
Examples

IV infused dextrans
IgM
Fibrinogen
IgG is not an ideal solute
\(2/3\) is extravascular and can re-equilibrate every other day treatments
RBC
WBC (e.g. leukemic cells) are not ideal solutes
Apheresis
Methods

Access: two 16 gauge steel needles

Separation: centrifuge (membrane, column)

Anticoagulation:
Sodium citrate:
  safe
  rapidly metabolized (one pass; hepatic)
  normal physiological constituent

Not heparin
Not EDTA

Apheresis
Complications

Fatalities: ~1/3000 procedures

Unrelated to procedure:
  Coincidental: MI, stroke, etc.
  We treat complex patients

Related to underlying disease:
  Seizure in patient with TTP
Apheresis
Complications
Procedure Related

Air bubbles:
  Tubing problems
  Rare

Hemolysis:
  Kinked tubing
  Rare

Hypovolemia:
  Inappropriate extracorporeal volume
  Children, small adults

Central lines:
  Problem: two 16g steel needles
  Femoral vs. IJ vs. subclavian
  Hemorrhage (placement, anticoagulation)
  Pneumothorax
  Thrombosis and embolism
  Sepsis
Apheresis
Complications
Procedure Related

Chills:
Afferent tubing, efferent tubing, centrifuge: RT
Can use blood warmers
Anything that can go wrong, will go wrong
Blankets
Disease relevance:
Cold-type autoimmune hemolytic anemia
Cryoglobulinemia

Apheresis
Complications
Procedure Related

Citrate toxicity:
Pathophysiology: chelation, hypocalcemia
Symptoms: circumoral paresthesias, tetany
Treatment:
Slow down the procedure
Oral calcium carbonate ("Tums")
IV calcium gluconate
Clear symptoms
Low ionized Ca\(^{+2}\)
Attending approval
Apheresis
Complications
Procedure Related

Other metabolic changes:
Fibrinogen
Drugs:
IVlg
Dilantin: no problem
Antimicrobials
No information for most

Apheresis
Complications
Procedure Related

Plasma exchange with FFP (e.g. TTP):
RBC exchange (e.g. Hgb SS disease):
   Hemolytic transfusion reactions
   Febrile transfusion reactions
   Allergic transfusion reactions
   Transfusion-transmitted diseases
   etc.
Apheresis
Disease Categories
Plasmapheresis

Committee Report

Therapeutic apheresis: A summary of current indication categories endorsed by the AABB and the American Society for Apheresis

Smith JW, Weinstein R, Hiller KL for the AABB Hemapheresis Committee

Transfusion 43:820-823, 2003

Category I: Standard of care

Category II: Generally accepted in a supportive role

Category III: “Not clearly indicated based on insufficient evidence…. Applications…may represent heroic or last-ditch efforts....”

Category IV: “…demonstrated to have a lack of efficacy. Clinical applications should be undertaken only under an approved research protocol.”
Apheresis
Disease Categories
Plasmapheresis

Randomized clinical trials with no effect:
- Rheumatoid arthritis
- Dermatomyositis/polymyositis

Apheresis
Disease Categories
Plasmapheresis

Randomized clinical trials with positive effect:
- Guillain-Barre syndrome
- Plasmapheresis
- IVIg
- Plasmapheresis vs. IVIG
Apheresis
Disease Categories
Plasmapheresis

Guillain-Barre syndrome:
  Acute ascending paralysis
  Areflexia
  Variable clinical presentation
  CSF: increased protein
  EMG: demyelination
  IgG autoantibodies recognizing glycolipids
  Antibody titers correlate with disease activity
  Immune complexes deposited on surface of myelin sheaths
  Animal model by immunizing with myelin components

Apheresis
Disease Categories
Plasmapheresis

Guillain-Barre syndrome:
  Treatment:
    Plasmapheresis vs. IVIG
    Plasmapheresis: 250 ml/kg, alternate days
    Slow improvement (weeks to months)
Apheresis
Disease Categories
Plasmapheresis

Randomized clinical trials with unknown effect:
- Goodpasture syndrome
  - IgG autoantibody: anti-GBM
  - α3 globular domain on collagen IV
  - Pulmonary (hemorrhage) and/or renal (RPGN) presentation
- Plasmapheresis: 1-2 PV on alternate days
  - Include FFP?
  - When stop?

Apheresis
Disease Categories
Plasmapheresis

No randomized clinical trials:
- Waldenstrom’s macroglobulinemia
  - IgM
  - Hyperviscosity syndrome
  - Ideal solute
  - 1-2 PV and follow serum viscosity
**Apheresis**

**Disease Categories**

**Plasmapheresis**

No randomized clinical trials:
- TTP
  - Most important
  - Medical emergency
  - High mortality
  - Significant treatment morbidity
  - Plasmapheresis is curative

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**TTP**

Thrombotic microangiopathies (TMA):
- Familial TTP
- Sporadic, primary TTP
- Adult HUS
- Secondary TTP/HUS
  - Drugs (e.g. FK506)
  - Cancer (e.g. mitomycin C)
  - BMT
  - HIV
- Pregnancy associated
  - HELLP
- Childhood HUS
  - Diarrhea-associated
Deficiency of ADAMTS13 function:
Genetic mutation ("familial, relapsing")
Inhibitors (IgG; "sporadic")


TTP

Pathophysiology

TTP

ADAMTS13

A disintegrin and metalloprotease with thrombospondin type 1 motifs


TTP

Cleavage of UL-VWF multimers by ADAMTS13

Clinical presentation:
Microangiopathic hemolytic anemia
Thrombocytopenia
Not DIC

Fever
Neurological symptoms
Renal dysfunction

Other manifestations of TMA

Lab tests:
CBC (i.e. platelets, Hct)
Smear: schistocytes
LDH
ADAMTS13: not ready for prime time

TTP

Treatment:
*Plasma exchange*
1-2 PV per day
Daily treatments; no skipping
Plt >150K; LDH normal; “no” schistocytes
Additional 2-3 days; then taper (?)

Supportive therapy
Dialysis, etc.
Anti-platelet agents

Treatment failure
How define?
What to do?
Vincristine, IVIg, rituxan, splenectomy,
cryopoor supernatant, etc. etc. etc.

NO PLATELET TRANSFUSIONS
Apheresis
Disease Categories
Plasmapheresis

No randomized clinical trials (no data whatsoever!):
  Good story
  Any case reports?
  Risk < benefit
  Objective endpoint of clinical response
    Huge placebo effect

Preparation for, and treatment after, HLA- and ABO-incompatible renal transplantation (e.g. “humoral rejection”)

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Apheresis
Issues regarding humoral rejection

When do we start? What constitutes a definitive diagnosis?

Removing IgG alloantibodies: alternate day treatment

Need excellent venous access; central line

Careful timing re: IVlg infusions and dialysis

When do we stop? Objective endpoint
Apheresis
Disease Categories
Cytapheresis

RBC exchange (for Hgb SS disease)
Leukapheresis for hyperleukocytic leukemia
Plateletpheresis for essential thrombocytosis
Stem cell collection for PBSCT

Hyperleukocytic Leukemia
WBC contribute more to viscosity than RBC on a cell-to-cell basis

Hyperleukocytic Leukemia

Myeloblasts contribute more to viscosity than other WBC on a cell-to-cell basis

![Graph showing the contribution of different WBC types to blood viscosity.](image)

Hyperleukocytic Leukemia

WBC, RBC, (and plasma proteins) contribute to total blood viscosity

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<thead>
<tr>
<th>MINIMUM APPARENT VISCOSITY (Centipoise)</th>
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<td>Observed Leukocrit (%)</td>
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Gathering data:
  History
  Targeted physical
  Political/logistical (e.g. pt being transferred from OSH, Hgb SS pt with multiple allos)
  Published information about clinical situation
Part of the clinical process:
  Get to know pt, family, clinical team
  Follow pt on a daily basis
  Prevent problems (e.g. ordering PT/PTT immediately after procedure, infuse IVlg before treatment)
Protect the patient
Protect the nurse
True clinical consultation
Rewarding