Introduction to Therapeutic Apheresis
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Manipulate the composition of blood:

- With complete control
- Without adverse consequences

Holy Grail of Transfusion Medicine

Transfusion Medicine

- Transfusion of “products”: RBC, Plt, WBC, PBSC, FFP
- Infusion of recombinant proteins: FVIII, FVila, 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, erythrocytapheresis, 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

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

**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

**Apheresis Complications Procedure Related**

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

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

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

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.

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.”
**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

**Treatment:**
- Plasmapheresis vs. IVIG
- Plasmapheresis: 250 ml/kg, alternate days
- Slow improvement (weeks to months)
No randomized clinical trials:
TTP
Most important
Medical emergency
High mortality
Significant treatment morbidity
Plasmapheresis is curative

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”)

ADAMTS13
- A disintegrin and metalloprotease with thrombospondin type 1 motifs

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

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

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: IVIg infusions and dialysis
- When do we stop? Objective endpoint

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

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”)

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

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

Therapeutic Apheresis Service
Transfusion Medicine Physician Role

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 IVIG before treatment)
- Protect the patient
- Protect the nurse
- True clinical consultation
- Rewarding