Introduction to Therapeutic Apheresis
October 17, 2006
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Learning Objectives
1. Define the characteristics of an ideal solute
2. Provide 1-2 examples of an endogenous constituent that behaves like an ideal solute
3. Explain the current understanding of the pathophysiology of TTP and the role that plasma exchange plays in its treatment

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

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

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

Discontinuous exchange

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

1 plasma volume $\rightarrow$ $\sim$37% remaining
2 plasma volumes $\rightarrow$ $\sim$14% remaining
3 plasma volumes $\rightarrow$ $\sim$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: $\sim$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.

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
Apheresis
Disease Categories
Plasmapheresis

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.”

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

Randomized clinical trials with positive effect:
Guillain-Barre syndrome
Plasmapheresis
IVIG
Plasmapheresis vs. IVIG

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

Guillain-Barre syndrome:
Mononuclear cell infiltration of dorsal root ganglion

Guillain-Barre syndrome:
Segmental demyelination and remyelination
Guillain-Barre syndrome:
Complement component C3 on myelin sheaths

Treatment:
Plasmapheresis vs. IVIG
Plasmapheresis: 250 ml/kg, alternate days
Slow improvement (weeks to months)

Goodpasture’s Syndrome

Randomized clinical trials with unknown effect:
Goodpasture syndrome
IgG autoantibody: anti-GBM
Ω3 globular domain on collagen IV
Pulmonary (hemorrhage) and/or renal (RPGN) presentation
Plasmapheresis: 1-2 PV on alternate days
Include FFP?
When stop?

Goodpasture’s Syndrome

Crescentic glomerulonephritis
UCSF (Martha Warnock)

Linear immunofluorescence
Univ of Utah

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

Apheresis
Disease Categories
Plasmapheresis

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

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

TTP
Pathophysiology

ADAMTS13
A disintegrin and metalloprotease with thrombospondin type 1 motifs


**Clinical presentation:**
- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Not DIC
- Fever
- Neurological symptoms
- Renal dysfunction
- Other manifestations of TMA

**Lab tests:**
- CBC (decreased platelets, Hct)
- Smear: schistocytes
- LDH: elevated
- ADAMTS13: not ready for prime time

**Treatment:**
- Plasma exchange (FFP)
  - Remove evil humors (autoantibody)
  - Provide good humors (fresh ADAMTS13)
  - 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”)
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

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