Introduction to Therapeutic Apheresis

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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

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

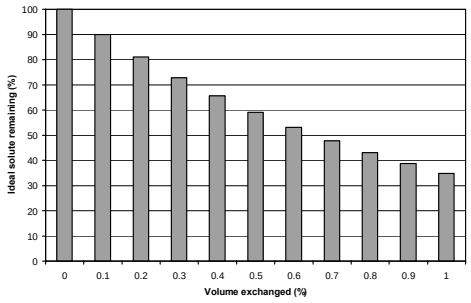
No flux between intravascular and extravascular spaces

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

Ideal Solute
Discontinous exchange



Ideal Solute

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

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**

Apheresis
Complications
Procedure Related

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:**
  - **IVIg**
  - **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 endoresed 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."

Apheresis
Disease Categories
Plasmapheresis

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

Apheresis
Disease Categories
Plasmapheresis

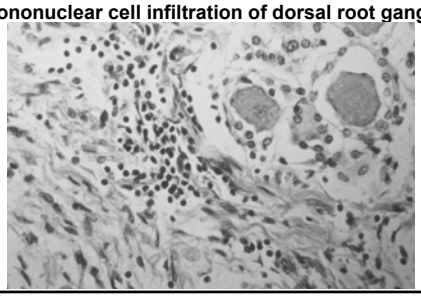
Randomized clinical trials with positive effect:
- **Guillain-Barre syndrome**
  - **Plasmapheresis**
  - **IVIg**
  - **Plasmapheresis vs. IVIG**

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:
Mononuclear cell infiltration of dorsal root ganglion



Dr. A. Hays

Apheresis
Disease Categories
Plasmapheresis

Guillain-Barre syndrome:
Segmental demyelination and remyelination

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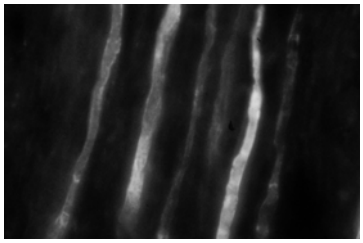
Apheresis
Disease Categories
Plasmapheresis

Guillain-Barre syndrome:
Complement component C3 on myelin sheaths



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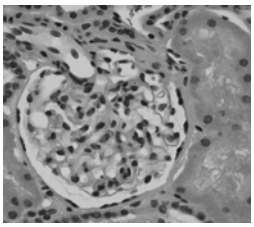
Apheresis
Disease Categories
Plasmapheresis

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

Apheresis
Disease Categories
Plasmapheresis

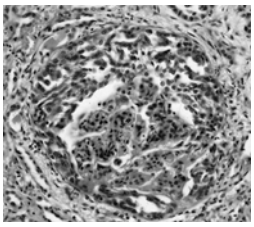
Randomized clinical trials with unknown effect:
- **Goodpasture syndrome**
  - **IgG autoantibody: anti-GBM**
    - **α3 globular domain on collagen IV**
  - **Pulmonary (hemorrahge) and/or renal (RPGN) presentation**
  - **Plasmapheresis: 1-2 PV on alternate days**
    - **Include FFP?**
  - **When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

Goodpasture's Syndrome



Normal glomerulus

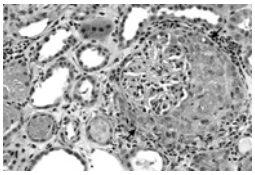
Patrice Spitalnik



Crescentic glomerulonephritis

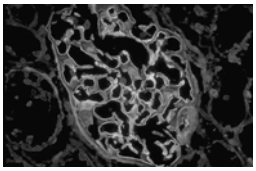
Univ of North Dakota

Goodpasture's Syndrome



Crescentic glomerulonephritis

UCSF (Martha Warnock)



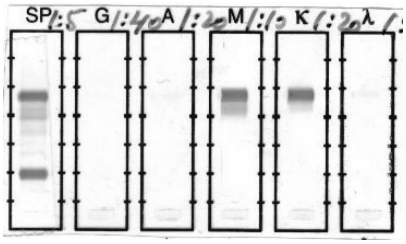
Linear immunofluorescence

Univ of Utah

Apheresis
Disease Categories
Plasmapheresis

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**

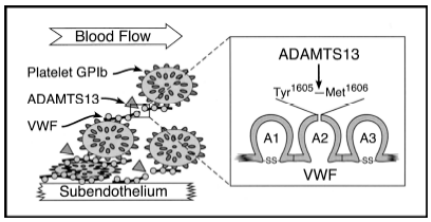
TTP

Deficiency of ADAMTS13 function:

- **Genetic mutation ("familial, relapsing")**
- **Inhibitors (IgG; "sporadic")**

TTP

Pathophysiology

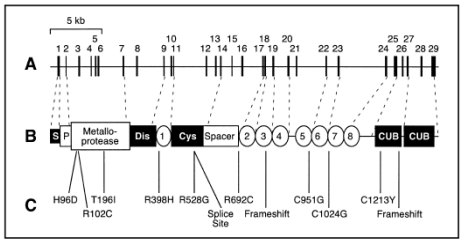


Zheng et al. ADAMTS13 and TTP. Current Opinion in Hematology 9:389–394, 2002.

TTP

ADAMTS13

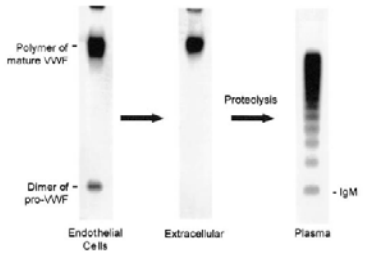
***A d*isintegrin *a*nd *m*etalloprotease with *t*hrombo*s*pondin type 1 motifs**



Zheng et al. ADAMTS13 and TTP. Current Opinion in Hematology 9:389–394, 2002.

TTP

Cleavage of UL-VWF multimers by ADAMTS13



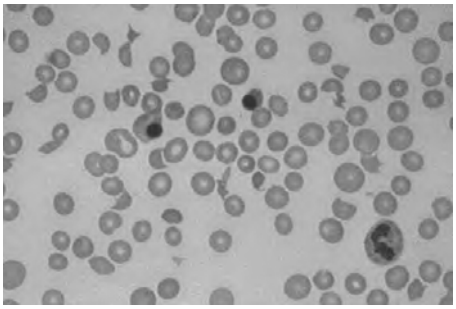
Tsai HM. Advances in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura. J Am Soc Nephrol 14: 1072–1081, 2003.

TTP

- 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

TTP

- Clinical presentation:
  - Microangiopathic hemolytic anemia



TTP

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

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

Apheresis
Disease Categories
Cytapheresis

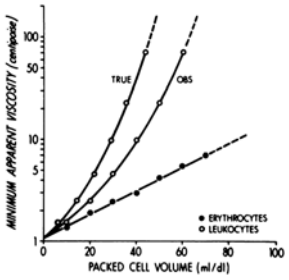
RBC exchange (for Hgb SS disease)

Leukapheresis for hyperleukocytic leukemia

Plateletpheresis for essential thrombocytosis

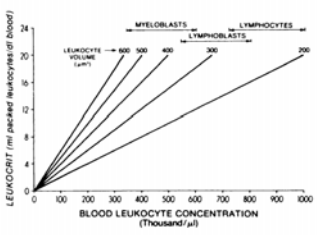
Stem cell collection for PBSCT

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



Lichtman MA, Rowe JM. Hyperleukocytic Leukemias: Rheological, Clinical, and Therapeutic Considerations. Blood 60:279-283, 1982.

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

MINIMUM APPARENT VISCOSITY (Centipoise)

Erythrocrit (%) \ Observed Leukocrit (%)	5	10	15	20	25	30	35	40
40	4.4	4.5	4.8	5.3	6.0	7.0	8.8	13.3
35	4.1	4.2	4.5	5.0	5.7	6.7	8.5	12.0
30	3.8	3.9	4.2	4.7	5.4	6.4	8.2	11.7
25	3.4	3.7	4.0	4.5	5.2	6.2	8.0	11.5
20	3.2	3.5	3.8	4.3	5.0	6.0	7.8	11.3
15	3.0	3.1	3.4	3.9	4.6	5.6	7.4	10.9
10	2.7	2.9	3.2	3.7	4.4	5.4	7.2	10.7

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