

**Introduction to Therapeutic Apheresis**  
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**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

**Holy Grail of Transfusion Medicine**

Manipulate the composition of blood:

With complete control

Without adverse consequences

**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

**Transfusion Medicine**

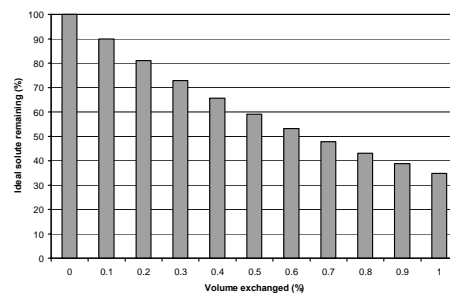
Transfusion of “products”:  
RBC, Plt, WBC, PBSC, FFP

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**  
Discontinuous exchange



## Ideal Solute

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

1 plasma volume → ~37% remaining

2 plasma volumes → ~14% remaining

3 plasma volumes → ~5% remaining

## 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

## 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 Complications Procedure Related

Air bubbles:

Tubing problems  
Rare

Hemolysis:

Kinked tubing  
Rare

Hypovolemia:

Inappropriate extracorporeal volume  
Children, small adults

## 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 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**

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  
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<sup>+2</sup>  
Attending approval

**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

**Apheresis  
Complications  
Procedure Related**

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

**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:  
Rheumatoid arthritis  
Dermatomyositis/polymyositis

**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 positive effect:  
Guillain-Barre syndrome  
Plasmapheresis  
IVIg  
Plasmapheresis vs. IVIG

**Apheresis**  
Disease Categories  
Plasmapheresis

Randomized clinical trials with unknown effect:  
Goodpasture syndrome  
IgG autoantibody: anti-GBM  
 $\alpha 3$  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

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

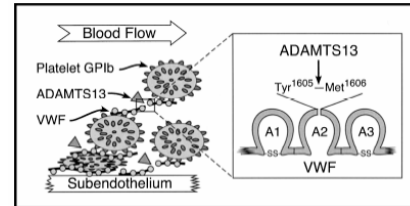
No randomized clinical trials:  
Waldenstrom's macroglobulinemia  
IgM  
Hyperviscosity syndrome  
Ideal solute  
1-2 PV and follow serum viscosity

**Apheresis**  
**Disease Categories**  
**Plasmapheresis**

No randomized clinical trials:  
**TTP**

**Most important**  
**Medical emergency**  
**High mortality**  
**Significant treatment morbidity**  
**Plasmapheresis is curative**

**TTP**  
**Pathophysiology**



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

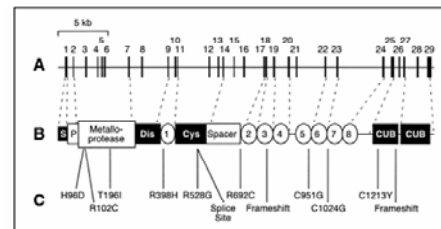
**TTP**

**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**

**ADAMTS13**

**A disintegrin and metalloprotease with thrombospondin type 1 motifs**



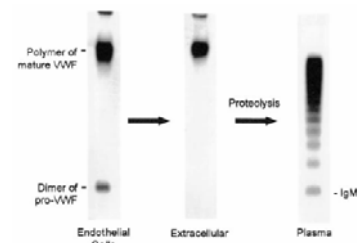
Zheng et al. ADAMTS13 and TTP. Current Opinion in Hematology 9:389-394, 2002.

**TTP**

**Deficiency of ADAMTS13 function:**  
**Genetic mutation ("familial, relapsing")**  
**Inhibitors (IgG; "sporadic")**

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

## 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

## 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 Cytapheresis

RBC exchange (for Hgb SS disease)

Leukapheresis for hyperleukocytic leukemia

Plateletpheresis for essential thrombocytosis

Stem cell collection for PBSC

## Apheresis

### Disease Categories Plasmapheresis

No randomized clinical trials (no data whatsoever!):

Good story

Any case reports?

Risk < benefit

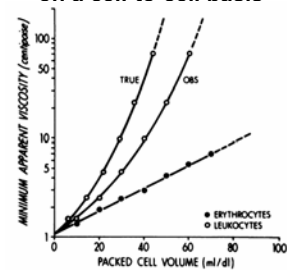
Objective endpoint of clinical response

Huge placebo effect

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

## Hyperleukocytic Leukemia

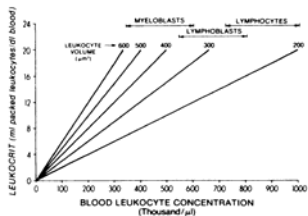
WBC contribute more to viscosity than RBC  
on a cell-to-cell basis



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