Apheresis

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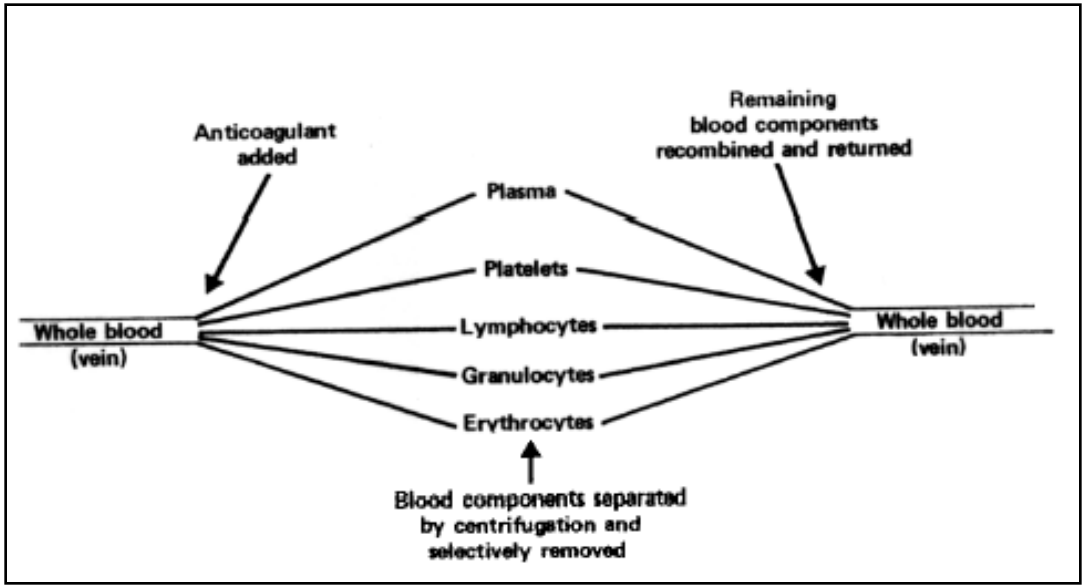
Outline

- Basics
- Operations
- Reactions
- Indications
- TTP
- Sickle Cell Disease
- Special Considerations

Basics of Apheresis

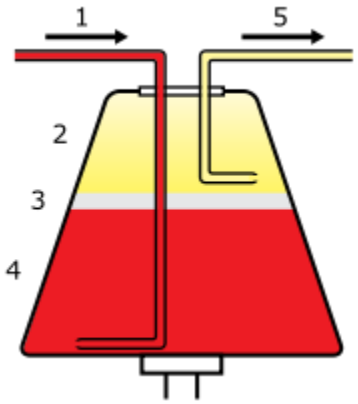
- Real time separation of whole blood into components with selective removal of one component (with/without replacement) and return of remaining blood products.



Basics of Apheresis

- Most equipment operates on continuous flow centrifugation
- Detection of interface
- Collection of desired component
- Return of remaining blood components
  - + replacement fluid in many cases

- Modification of filtration systems to separate cells from plasma



Basics of Aphereis

- Component Apheresis
  - Plasma, Platelets, RBCs
  - Granulocytes, Stem Cells
- Therapeutic Apheresis
  - Plasmapheresis, Plasma Exchange, RBC Exchange
  - Leukopheresis, Plateletpheresis, Erythrocytapheresis
  - Extracorporeal Photophoresis/Immunoadsorption/ Rheopheresis

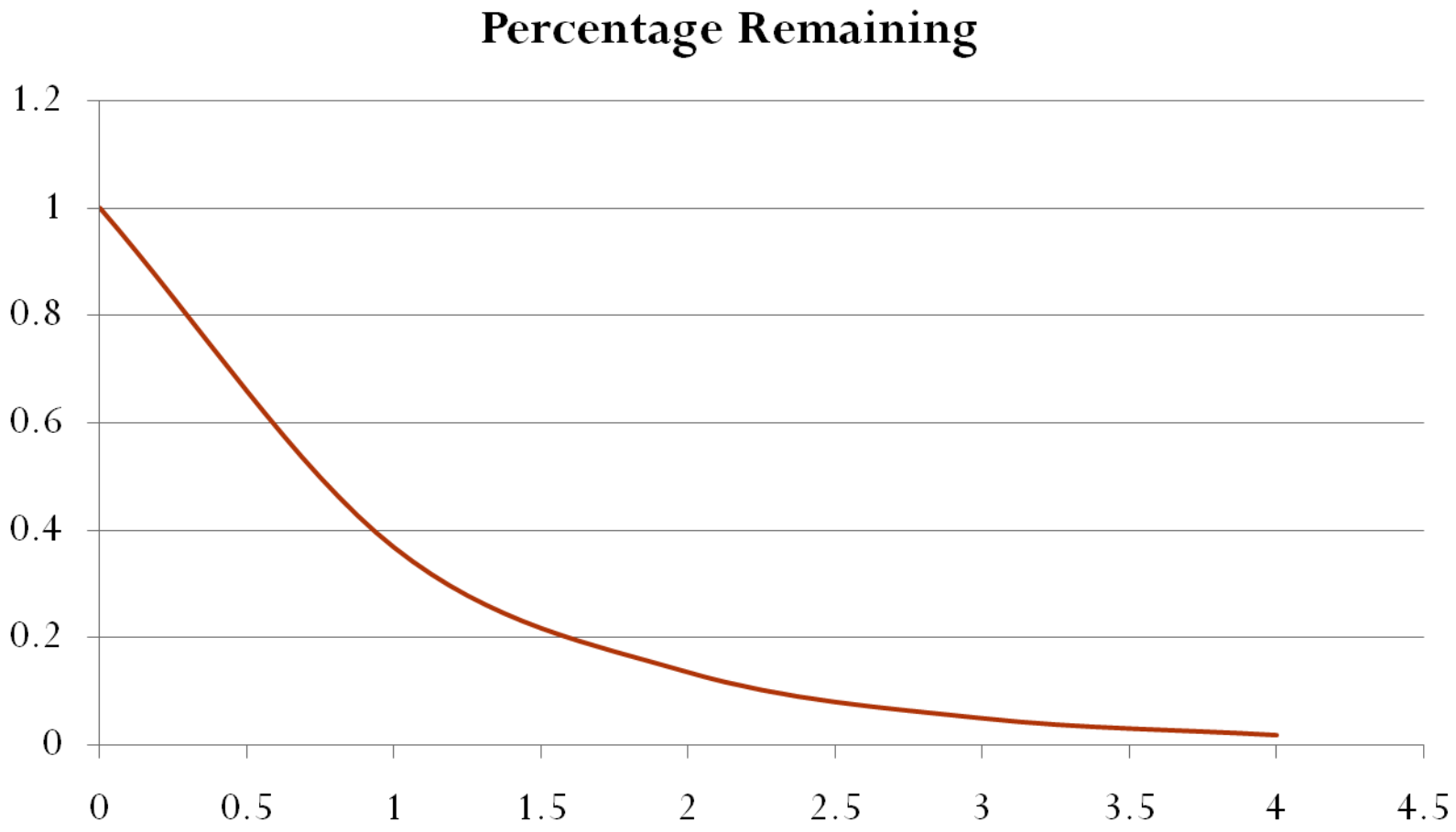
Basics of Donor Apheresis

- All apheresis donors are screened the same as a typical blood donor
  - Ensures safe product
- All component collected via apheresis are pre-storage leukocyte reduced.
  - No need for bedside filter.
- Significantly better collection for plasma-containing products
  - 5.5 x 10^10 vs 3.0 x 10^11 for 90% collections
  - Most platelets and some plasma

Apheresis Equipment

- ACD-A anticoagulant for anti-coagulation and preservation of cellular components
- Saline
- Replacement fluid
- Large collection bag
- Blood warmer
- Vascular Access
  - Two rigid IV catheters for collection
  - Central venous access for procedures

Basics of Apheresis



Alteration In Blood Constituents By a Single Plasma Volume Exchange

CONSTITUENT	% DECREASE FROM BASELINE	% RECOVERY 48 HRS AFTER TPE
CLOTTING FACTORS	25-50	80-100
FIBRINOGEN	63	65
IMMUNOGLOBULINS	63	~45
PARAPROTEINS	30-60	VARIABLE
LIVER ENZYMES	55-60	100
BILIRUBIN	45	100
C3	63	60-100
PLATELETS	25-30	75-100

Apheresis Operations

- Qualified staff operating the machine
  - Majority are RN's
  - MLS/MLT's with structured training in apheresis
- Qualified medical supervision
  - Documented training and observation requirements
    - 10 procedures, 5 patients, each procedure done "regularly"

Apheresis Operations

- Completion of pre-printed orders with valid signature
- In-house accessibility in case of adverse reaction
- Review and signature of the nurses' note
- Short procedure note outlining:
  - 1. The physician reviewed and evaluated the pertinent clinical and laboratory data relevant to the treatment of the patient that day.
  - 2. The physician has made the decision to perform the therapeutic procedure on the day in question.
  - 3. The physician saw and evaluated the patient for the procedure.
  - 4. The physician remained available to respond in person to emergencies or other situations requiring his/her presence throughout the duration of the procedure.

Reactions

- Citrate hypocalcemia
  - Ionized calcium levels with replacement
- Hyper/Hypovolemia
  - Screen out those who would not tolerate procedure
  - Blood Prime possible
- Site Bleeding
  - Apheresis requires large volume vascular access with assoc. higher bleeding risk
- Vasovagal Responses
- Allergic/Anaphylactic

Indications

- American Society for Apheresis publishes guidelines for therapeutic apheresis (latest 2023)
- Indications (first-line I, second-line II, unknown benefit III, ineffective/harmful IV)
- Strength of evidence (RCT Type I, well-designed non-random control trials Type II-1, cohort/case control Type II-2, dramatic non-controlled/multiple longitudinal studies Type II-3, expert opinion Type III)

TABLE 1 Category and grade recommendations for therapeutic apheresis.

Disease/condition	Indication	Procedure	Category	Grade	Page
Acute disseminated encephalomyelitis	Steroid refractory	TPE	II	2C	95
Acute inflammatory demyelinating polyradiculoneuropathy	Primary treatment	TPE	I	1A	97
		IA	I	1B	
Acute liver failure	Acute liver failure	TPE-HV	I	1A	99
		TPE	III	2B	
	Acute fatty liver of pregnancy[a]	TPE	III	2B	
Acute toxins, venoms and poisons	Mushroom poisoning	TPE	II	2C	101
	Envenomation	TPE	III	2C	
	Other[a]	TPE/RBC exchange	III	2C	
Age related macular degeneration	Dry, high risk	DFPP	III	2B	103
Alzheimer's disease[a]	Mild or moderate	TPE	III	2A	105
Amyloidosis, systemic, dialysis related		$ß_2$-microglobulin adsorption	II	2B	107
Anti-glomerular basement membrane disease	Diffuse alveolar hemorrhage	TPE	I	1C	109
	Dialysis-independence	TPE	I	1B	
	Dialysis-dependence, no diffuse alveolar hemorrhage	TPE	III	2B	
Atopic dermatitis, recalcitrant		ECP/IA/TPE/DFPP	III	2B	111
Autoimmune dysautonomia[a]		TPE	III	2C	113
Autoimmune hemolytic anemia, severe	Severe cold agglutinin disease	TPE	II	2C	115
	Severe warm autoimmune hemolytic anemia	TPE	III	2C	

Level I Indications

- Plasma exchange
  - Thrombotic thrombocytopenia purpura, Guillain-Barre, Goodpasture's syndrome (dialysis independent or with DAH), chronic inflammatory demyelinating polyneuropathy, hyperviscosity syndrome due to hypergammaglobulinemia, relapsing FSGS in transplant kidney, thrombotic vasculopathy due to factor H autoantibody, myasthenia gravis (severe/pre-operative), ABO incompatible living kidney/liver donor desensitization, humoral mediated renal allograft rejection, Wilson's disease with fulminant hepatic failure, thrombotic microangiopathy after Ticlopidine, catastrophic anti-phospholipid syndrome, NMDA receptor-Ab encephalitis

Thrombotic Thrombocytopenic Purpura (TTP)

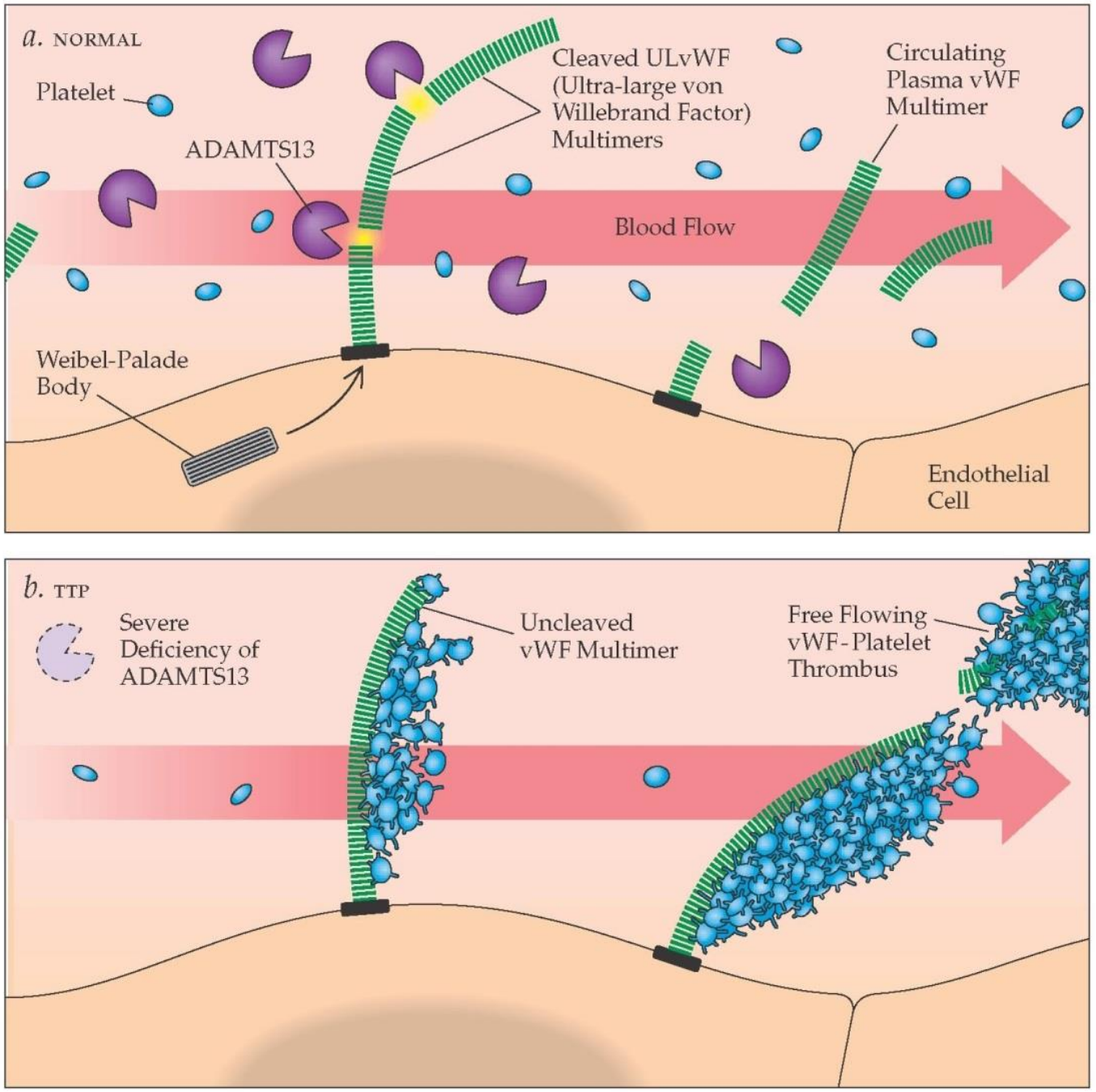
- Neurologic syndrome with non-specific signs and symptoms and frequently fatal before apheresis
- Microangiopathic hemolytic anemia (MAHA)
  - Schistocytes
  - Thrombocytopenia
  - High LDH/Low Haptoglobin
  - Classic test of coagulation are variable

TTP

- vWF is a large multimeric glycoprotein produced in endothelium, megakaryocytes, platelets and subendothelial connective tissue.
- It binds platelets at the glycoprotein Ib/IX/V complex.
- It binds to coagulation factor VIII in circulation and collagen in the subendothelium after vascular damage
- It relies on a metalloprotease, ADAMTS13, for cleavage

TTP

- If ADAMTS13 is functionally deficient, ultra-large multimers of vWF can bind long strings of platelets together.
- Leads to thrombosis in the microvasculature and microscopic necrosis
  - Brain>Kidney as compared to HUS – Kidney>Brain
- Shear stress on RBCs results in the classic schistocyte


a. NORMAL
Platelet
ADAMTS13
Cleaved ULvWF (Ultra-large von Willebrand Factor) Multimers
Circulating Plasma vWF Multimer
Blood Flow
Weibel-Palade Body
Endothelial Cell
b. TTP
Severe Deficiency of ADAMTS13
Uncleaved vWF Multimer
Free Flowing vWF-Platelet Thrombus

TTP

- Prior to plasma exchange, mortality was nearly 90%
- With prompt initiation of plasma exchange, mortality is less than 10% at six months
- Replacement fluid must contain ADAMTS13
  - Plasma
  - Cryo-poor plasma
- High tendency to relapse
  - Rituximab has decreased relapse significantly
- PLASMIC score
  - Exclude underlying conditions

TTP

- Recalcitrant
  - Platelets rising back to normal
  - LDH decreasing
  - No schistocytes
- Consider "taper regimen"
  - Daily to goal + 5, then 5 over 2 weeks, then weekly for 2 months

For several days

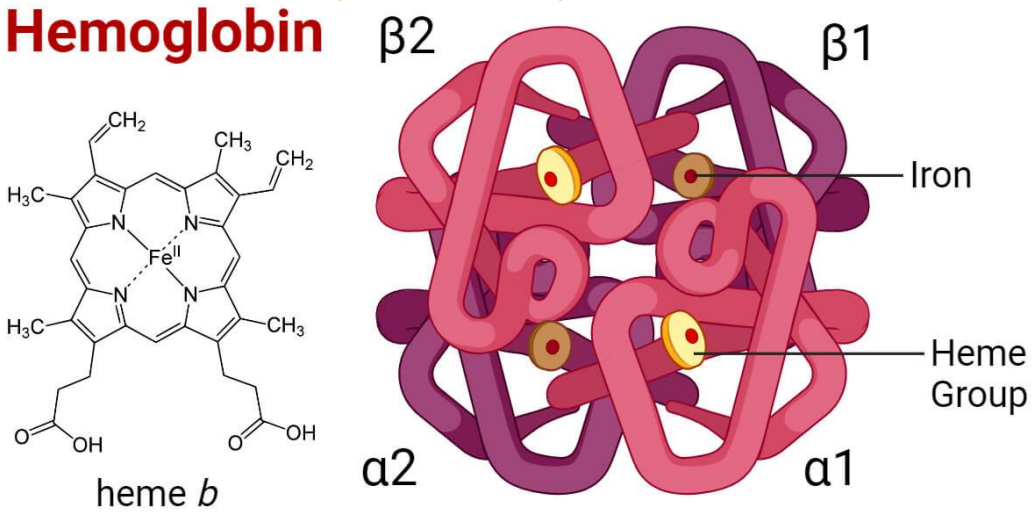
Level I indications

- RBC exchange
  - Sickle cell disease with acute stroke/subsequent prophylaxis
    - Other crises are level II, but typically should be approved anyway
- Erythrocytophoresis
  - Polycythemia Vera as new level I
    - Survival benefit of Hct <45%
- WBC depletion/Platelet depletion
  - Only level II indications

HgbSS (Sickle Cell) Disease

- Hemoglobin formed by two α chains and two β chains in connection with iron-bearing heme molecule
- Inherit two α genes and one β gene from each parent
  - Asymptomatic carrier state possible

Hemoglobin: Structure, Types, Functions, Diseases (microbenotes.com)



HgbSS Disease

- HgbS is formed by a single point mutation in the β chain
- "Sticky" point which allows hemoglobin to polymerize into long multimers in low oxygen states
- Distorts the shape of RBCs resulting in non-laminar flow and mechanical obstruction in a variety of small vessels
- Stroke, priapism, autosplenectomy, acute pain crises
- Mortality 1 death/200 person-years
- Other beta chain mutations with HgbS can result in similar clinical disease

HgbSS Disease

- Estimated lifelong prevalence of stroke in untreated HgbSS disease is 30-40% - only 10% overt.
- Recurrence rate of 46 to 90%
- Recurrence after RBC exchange vs simple transfusion as primary treatment was 21% vs 57%
- Progressive neurologic deficits with recurrent stroke

Hulbert ML, Scothorn DJ, Panepinto JA, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr. 2006;149: 710-712.

HgbSS Disease

- Multiple transfusions increases risk of anti-RBC antibodies
  - Phenotypic matched RBC with delay in availability
    - Most scheduled outpatients – can plan days ahead for procedure
    - Newly acquired RBC genotyping – used to phenotype match in BB
  - Scheduled procedures and BB orders
- Simple transfusion as temporizing measure
  - Hct <30%
  - Aggressive fluid resuscitation
  - O2
  - Pain control

Other Important Level II Indications

- Life threatening cold agglutinin disease
  - Warm autoimmune hemolytic anemia has large volume of distribution
- Severe systemic lupus erythematosus
- Refsum's disease (phytanic acid storage disease)
- Pediatric autoimmune neuropsychiatric disorders
- Multiple Sclerosis acute demyelination syndrome unresponsive to steroids/NMO (Devic's disease)
- Established multiple sclerosis with acute relapse
- Idiopathic dilated cardiomyopathy with poor function
- Myeloma cast nephropathy
- Acute disseminated encephalomyelitis – steroid refractory

Other Important Level II Indications

- Anti-RBC antibodies with evidence of severe fetal anemia as temporizing measure prior to intrauterine transfusion
- Pre-ABO mismatch HPC transplant
- Desensitization prior to cardiac transplant
- Mushroom poisoning

Column Electrophoresis (Immunoadsorption [IA])

- Specific binders to collect excess cells/substances
  - Rheumatoid arthritis
    - Absorbs large WBCs (granulocytes/monocytes)
  - Hyperlipidemia
- Highly expensive!!

Extracorporeal Photopheresis (ECP)

- Expose a leukophoresis collection(s) to psoralen and UV light inducing DNA damage
- Downregulation of cytotoxic T cells
- Level I
  - Cutaneous T cell lymphoma
  - Prophylactic for heart rejection
- Level II
  - Dermal acute/chronic GVHD
    - Level III for non-skin manifestations

Rheopheresis - DFPP

- Selective removal of high molecular weight serum proteins
- Level III indication for Age-Related Macular Degeneration
- Platform not approved by FDA – available in Europe, Canada and Asia

Special Considerations

- RBC exchanges
  - Machine can adjust mix of replacement fluids, donor blood and patient blood to target end Hct%
    - Optimum viscosity/anemia in peds is 27-33% - tend to use 30%
- Multiple plasma exchanges
  - High frequency of acquired allergic transfusion reactions
    - Clinical liaison to start antihistamine/steroid therapy
    - Patient counseling/informed consent
- Futility of care
  - Procedure should have a defined endpoint rather than continue until status changes

Use of plasma

- TTP/Thrombotic Microangiopathy
- Coagulation factors "critically low"
  - Healthy individuals are OK at 15-20% of normal
  - Fibrinogen around 100
- Fulminant hepatic failure

- Otherwise, typically use 5% albumin +/- saline
- Can perform saline procedure with caution
- Can perform hetastarch procedure (only at Iowa)

Frequency of Procedures

- Predominantly intravascular
  - Daily procedures
- High volume of distribution
  - Daily – QOD initially, then transition to QOD
- Relapsing Disease
  - Maintenance therapy to effect

Granulocytes

- Expert opinion
  - Profound neutropenia without anticipated recovery within 10 days
  - Documented infection requiring neutrophils (bacterial/fungal)
- Donors stimulated with G-CSF/dexamethasone
  - Platelet donors
- RING study 2014 – no mortality benefit
  - Possible low dosage as complicating factor

Review

- Basics
- Operations
- Indications
- Reactions/Responses
- Special Considerations

Questions??