Uncomplicating the Complicated: Management of Transfusion Medicine Emergencies

Melissa L. Petras, MD, MPH
Department of Pathology
Clinical Assistant Professor University at Buffalo
UB Pathology, Transfusion Medicine
Kaleida Health Utilization Management Advisor

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Conflict of Interest

I have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this presentation.

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Learning Objectives

1. Define **apheresis**/apheresis emergencies and consider what medications may be helpful/harmful to the patient
2. Consider medications that may interact ***in vivo*** to cause transfusion related issues
3. Consider medications that may interact ***in vitro*** to cause transfusion related issues
4. Understand when medications are indicated to prevent or treat **transfusion reactions**

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Apheresis

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Apheresis

- From the Greek *apairesos* or Roman *aphairesis* meaning “to take away”
- Whole blood is separated extracorporeally, separating the portion desired from the remaining blood
- Desired portion (e.g. plasma) is removed and/or manipulated and the remainder returned to the patient

Assumptions:

1. The disease state is causally related to the presence of the substance in the blood
2. The pathogenic substance can be removed efficiently enough to permit resolution of illness or decrease morbidity

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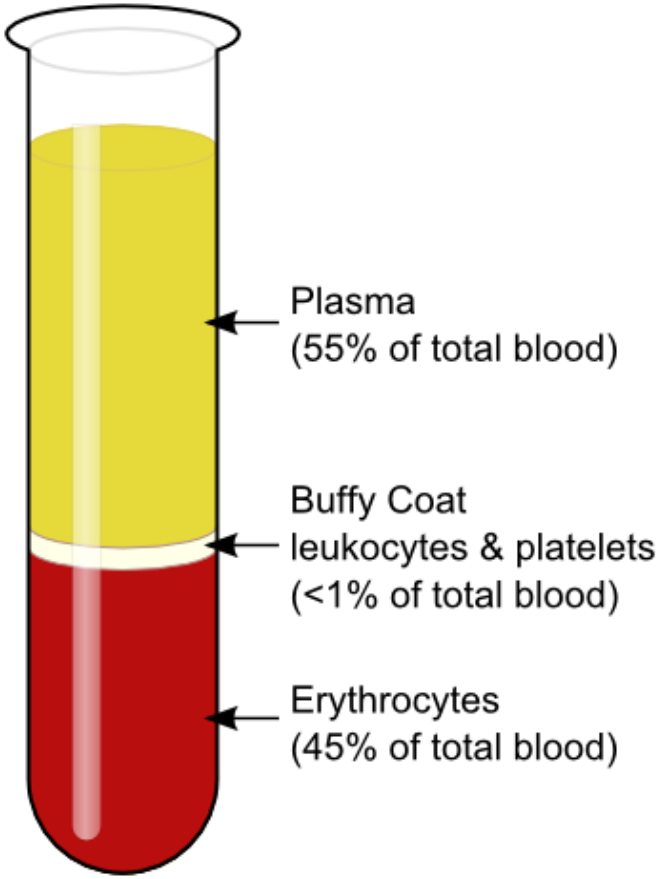
Centrifugal Separation



- Large-bore intravenous catheter
- Whole blood is drawn from the patient into the spinning centrifuge bowl
- Continuous separation of blood elements according to density
  - simultaneously remove and reinfuse
- More dense elements (RBC) settle to the bottom, less dense elements (WBC, platelets, then plasma) at the top

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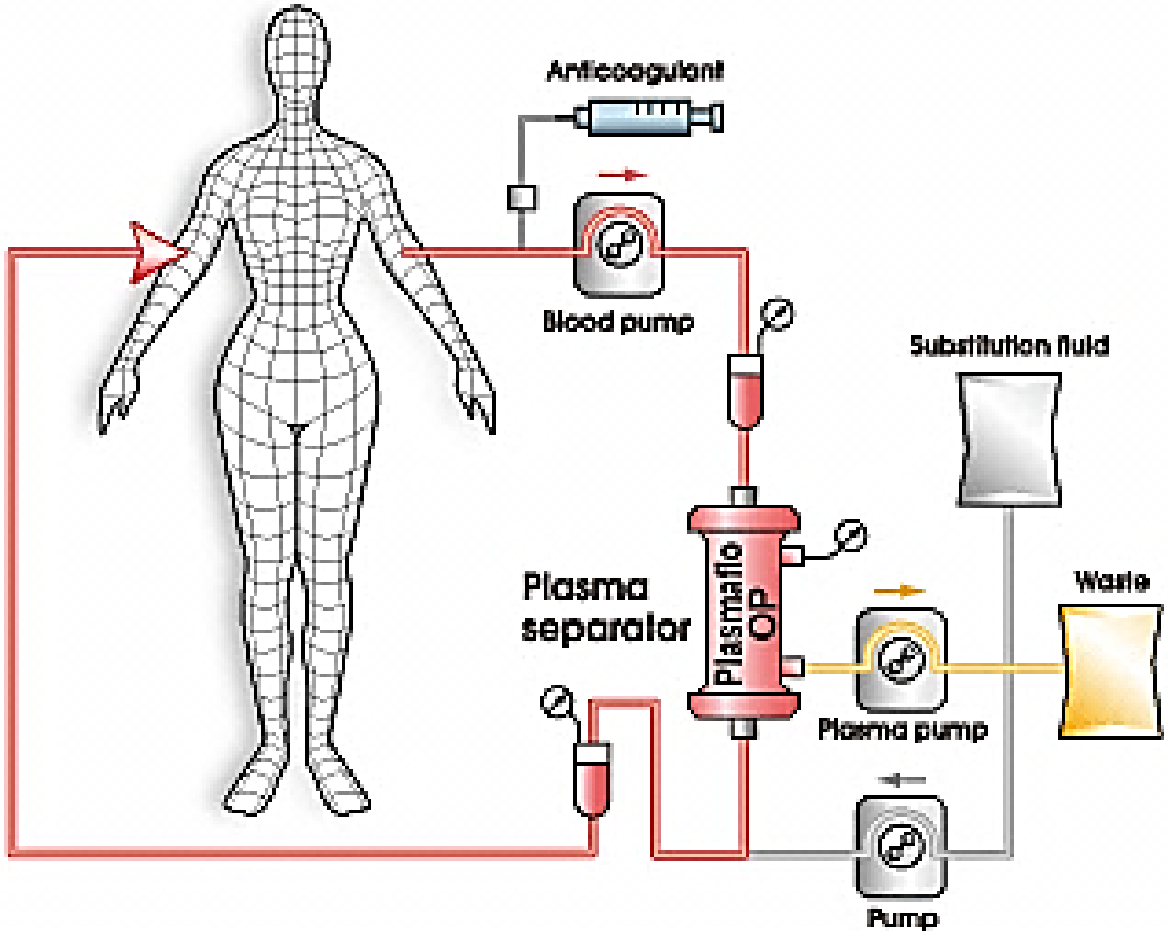
Plasma Exchange Treatment



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Removal Kinetics of Apheresis

1. Distribution between intravascular and extravascular compartments
2. Synthetic and catabolic rates
3. Equilibration rate

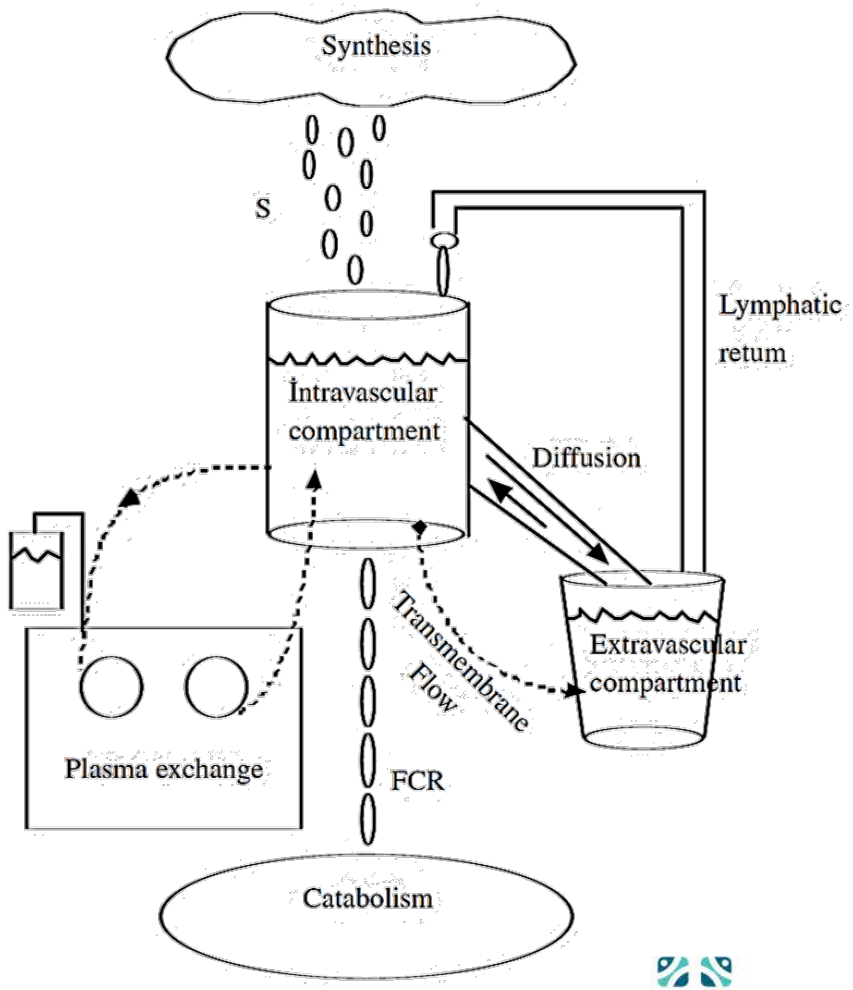

Figure 1. Single compartment model for TPE (Adapted from Weinstein E, Basic Principles of Therapeutic Blood Exchange. In: McLeod B, Price TH, Drew MJ, et al, (eds). Apheresis: Principles and Practice. 1st ed. Maryland: AABB Press, 1997, p.264).

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Apheresis Uses

Therapy

- Removal of undesirable substances like autoantibodies, paraproteins, lipids, toxins or drugs bound to albumin, etc.
- Automated exchange of sickled red cells
- Removal of WBC/platelets in myeloproliferative disorders

Collection

- Red cells, plasma, platelets, hematopoietic progenitor cells

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ASFA Guidelines

- Evidence-based assessment of the therapeutic apheresis literature
- Categorization of indications
  I. Apheresis is accepted as **first-line therapy**, either as a primary standalone treatment or in conjunction with other modes of treatment

  II. Second-line therapy

  III. Optimum role of apheresis therapy is **not established**

  IV. Apheresis to be **ineffective or harmful**

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ASFA Examples*

- **Category I**
  - Guillain-Barré, Anti-GBM (Goodpasture), TTP, MG, CIDP, acute stroke in SCD (RBC exchange)
- **Category II**
  - MS with acute CNS disease, NMO, ACS in SCD (RBC exchange)
- **Category III**
  - Guillain-Barré ***after*** IVIg, HIT/T, Thrombotic Microangiopathy
- **Category IV**
  - Psoriasis, SLE nephritis, diarrhea associated HUS

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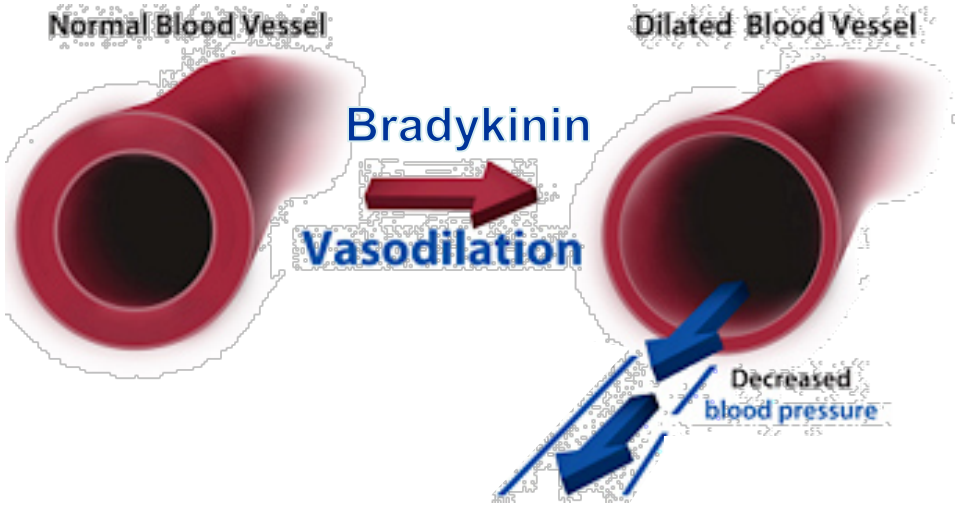
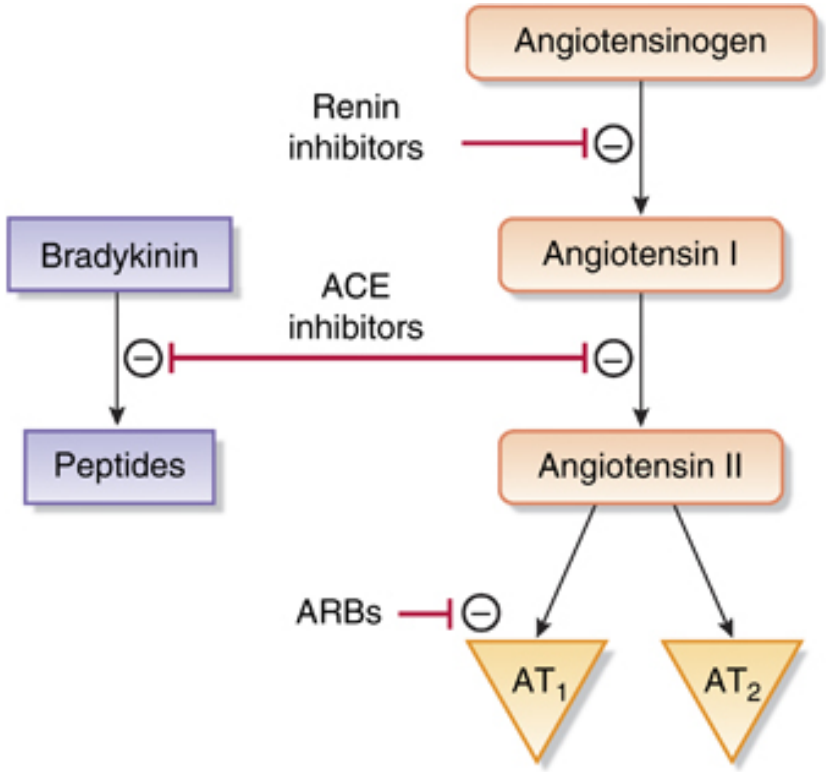
*2016 ASFA Guidelines

Medications

- Is the patient on medications that can be removed by the procedure?
  - Antibiotics and anticoagulants
  - Hold and give after the procedure
- Acid Citrate Dextrose Solution A (ACD-A)
  - 10,665 mg citrate/500 mL
  - Citrate toxicity
- Angiotensin-converting enzyme (ACE) inhibitors

ACE Inhibitors





Graphic: http://www.nature.com/ki/journal/v81/n7/fig_tab/ki2011460f1.html

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Replacement Fluids

- Must be FDA approved to use with blood products
  - Mixed with RBC before return phase

- Crystalloids
  - Normal saline, 0.9%
- Colloids
  - 5% Albumin
  - Human plasma

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Complications

- Hypocalcemia (Citrate toxicity) – 3%
  - Perioral tingling, paresthesia, chills, vibrations
  - Inform them of signs and symptoms of hypocalcemia during informed consent
  - Monitor patient closely
  - Parenteral calcium supplementation
  - Decrease blood flow rate
  - If severe, stop procedure and give calcium

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Apheresis Emergencies

- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome
- Guillain-Barré
  - IVIg
  - TPE after IVIG
- Multiple Sclerosis
- Myasthenia Gravis

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TTP

- Widespread platelet-fibrin thrombi deposition in the small arteries and arterioles and capillaries
- Pathogenesis TTP and HUS may differ
- Acquired or congenital deficiency in ADAMTS13
  - Enzyme that cleaves vWF into small multimers
  - Ultra large multimers bind platelets causing microthrombi

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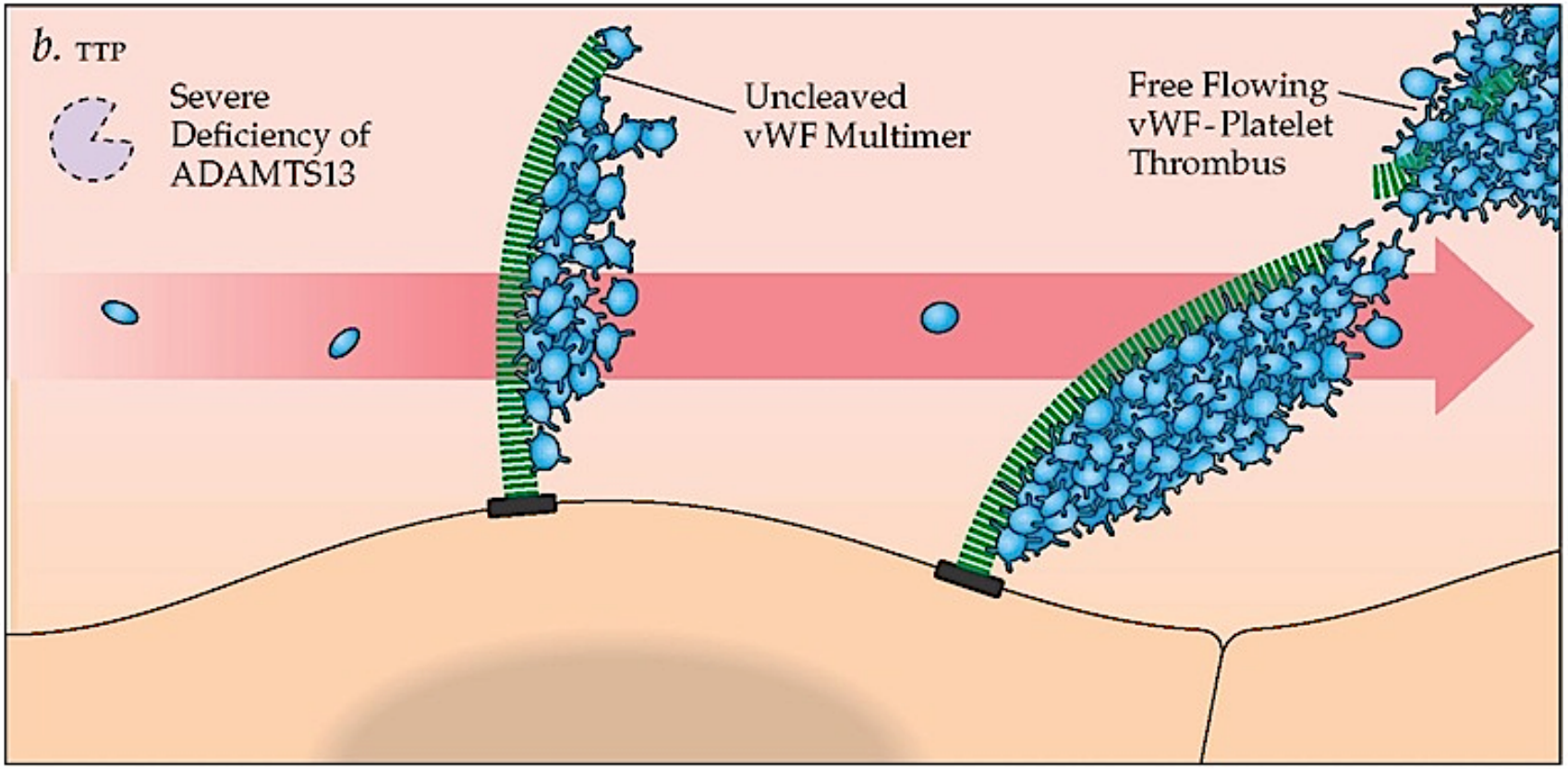
ADAMTS13



http://what-when-how.com/acp-medicine/platelet-and-vascular-disorders-part-2/

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Testing for ADAMTS13

- Results may take a long time to come back
  - Severe deficiency predicts an increased risk of relapse
- Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP

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The TTP Pentad

1. **Microangiopathic hemolytic anemia**
2. **Thrombocytopenia, often with purpura but not usually severe bleeding**
3. Acute renal insufficiency that may be associated with anuria and may require acute dialysis
4. Neurologic abnormalities, usually fluctuating
5. Fever

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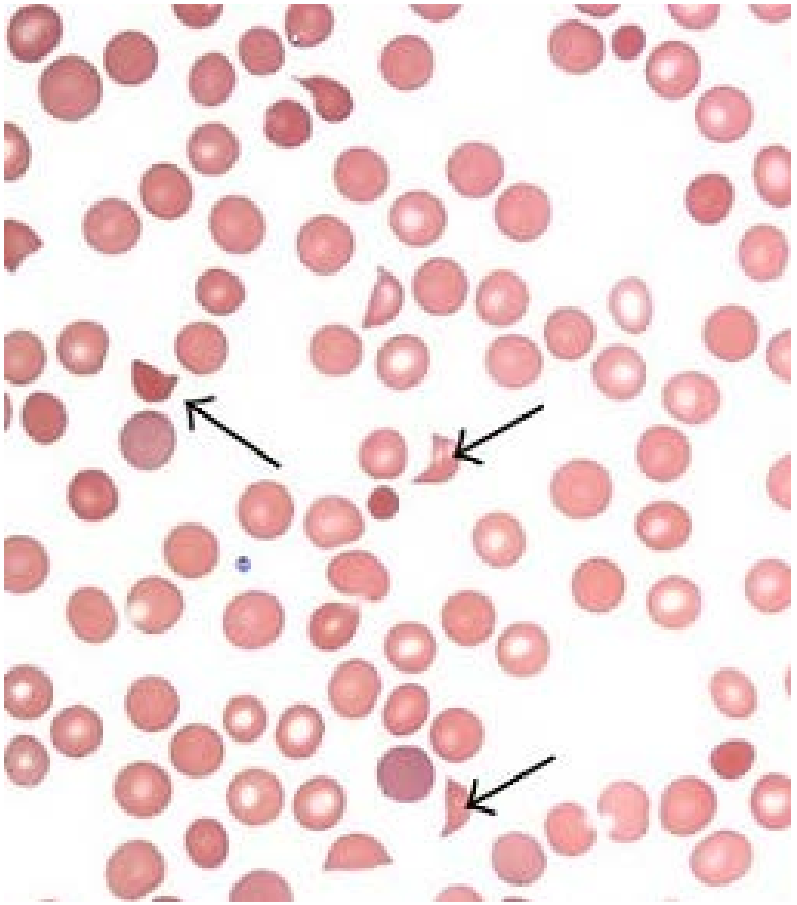
Pathology

Microangiopathic hemolysis

- Fragmented red cells (schistocytes)
- Polychromatophilic red cells (reticulocytes)
- Lack of platelets



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Epidemiology

- Suspected TTP-HUS
  - 11 cases/million population per year
- Idiopathic TTP-HUS
  - 4.5 cases/million per year
- Severe ADAMTS13 deficiency
  - 1.7 cases/million per year
- Incidence rates are higher for women, African Americans and obese patients

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Causes

- Idiopathic — 37 percent
- Drug-associated — 13 percent
- Autoimmune disease — 13 percent
- Infection — 9 percent
- Pregnancy/postpartum — 7 percent
- Bloody diarrhea prodrome — 6 percent
- Hematopoietic cell transplantation — 4 percent

Drugs associated with TTP

- Anti-neoplastics
  - Mitomycin C
- Antibiotics
- Immunosuppressive Agents
  - Cyclosporine
- Platelet Aggregation Inhibitors
  - Ticlopidine; Clopidogrel
- Oral Contraceptives
- Quinine

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Treatment

- Plasma infusions
- Plasma exchange with FFP
  - Decreased mortality from fatal to <10%
  - Platelet count ≥ 150 x 10^9/L
  - LDH in normal range
- Immunosuppressive therapies
  - Corticosteroids
  - Rituximab
  - Cyclosporine
  - Cyclophosphamide
  - Vincristine
- Platelets should only be transfused for significant clinical indications such as potential life-threatening bleeding

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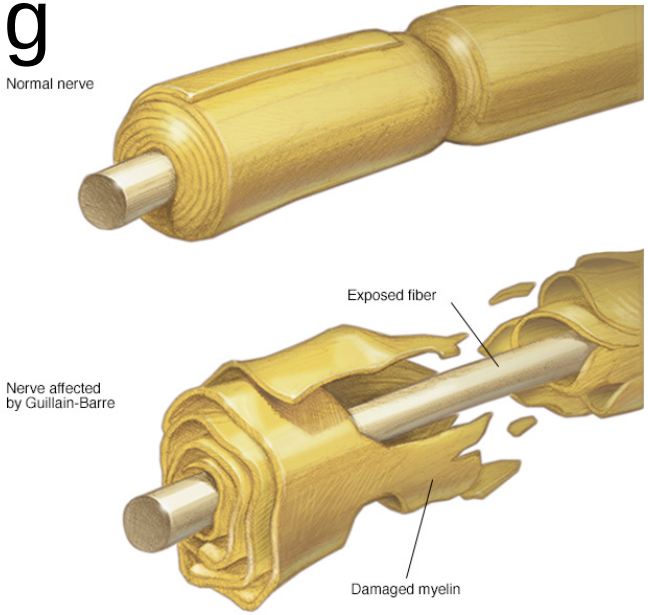
Guillain-Barré

- Immune system attacks peripheral nervous system
- Weakness or tingling sensations in the legs, spread to the arms and upper body
- When severe, life threatening
  - Respiration
  - Blood pressure
  - Heart rate
- Most individuals recover



Guillain-Barré & TPE

- Autoimmune antibody-mediated damage to peripheral nerve myelin
- TPE can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones
- TPE is most effective when initiated within 7 days of disease onset
- ASFA Category I, Grade 1A *before IVIg*
- ASFA Category III, Grade 2C *after IVIg*

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In Vitro Issues

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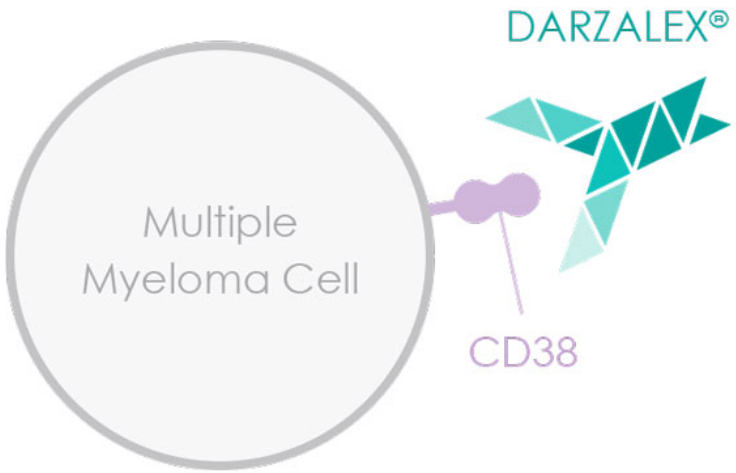
DARZALEX® (daratumumab)

- Multiple myeloma:
  - In combination with lenalidomide/dexamethasone or bortezomib/dexamethasone
  - Alone in patients who received at least three prior medicines to treat MM



Monoclonal antibody attaches to multiple myeloma cells

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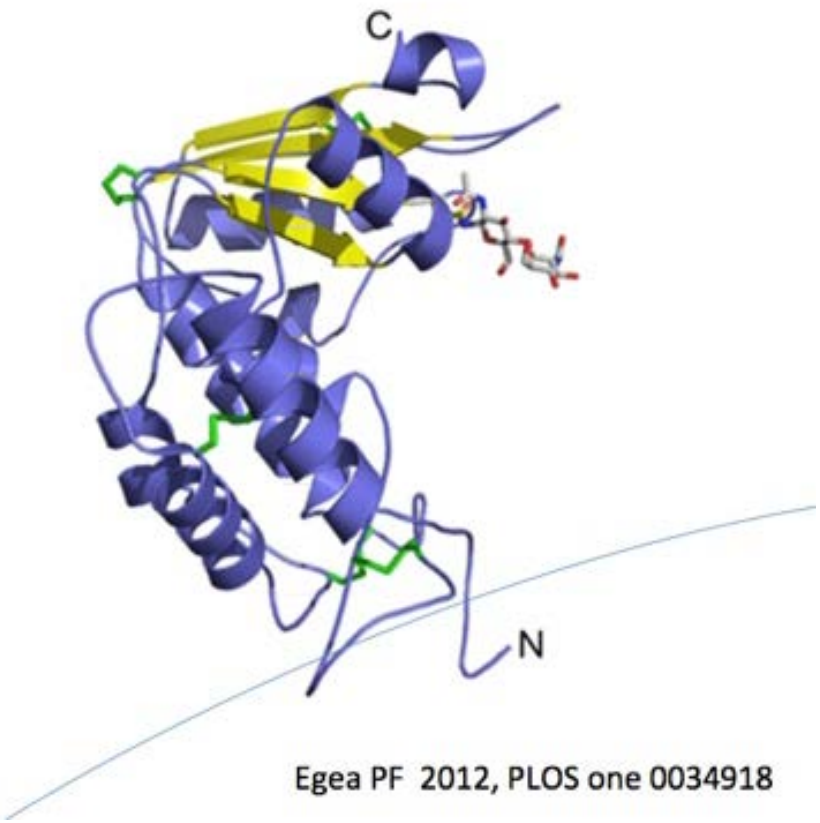
CD-38

Tissue Distribution

- Myeloid cells
- Lymphoid cells
- RBC
- Other tissues



Egea PF 2012, PLOS one 0034918

Dr. Rick Kaufman http://www.bbguy.org/2016/05/31/010/

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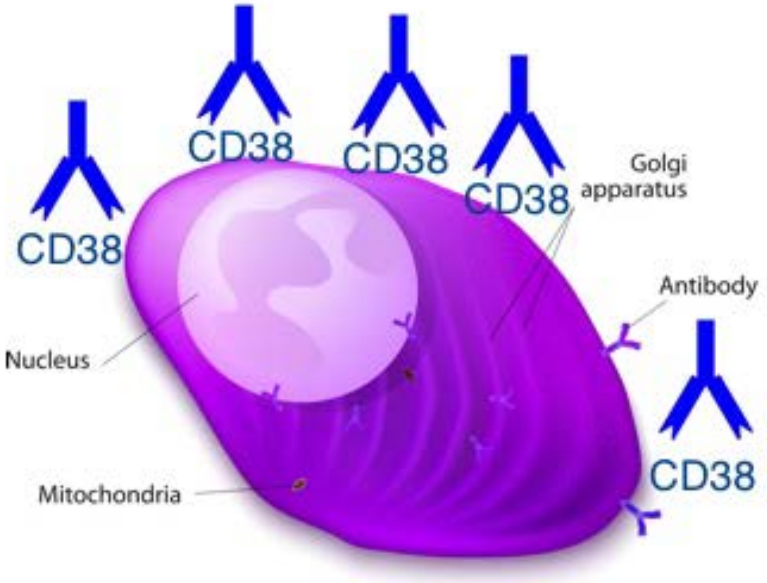
Daratumumab Effect



Plasma cell

Red cell

Y = DARA

Dr. Rick Kaufman http://www.bbguy.org/2016/05/31/010/

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In Vitro

- Anti-CD38 potently interferes with blood compatibility tests
  - Positive antibody screen
  - RBC panels: panreactivity
  - Positive crossmatches with all units
  - Unable to absorb away
  - Up to 6 months after final dose
- Type and screen patients prior to starting daratumamab

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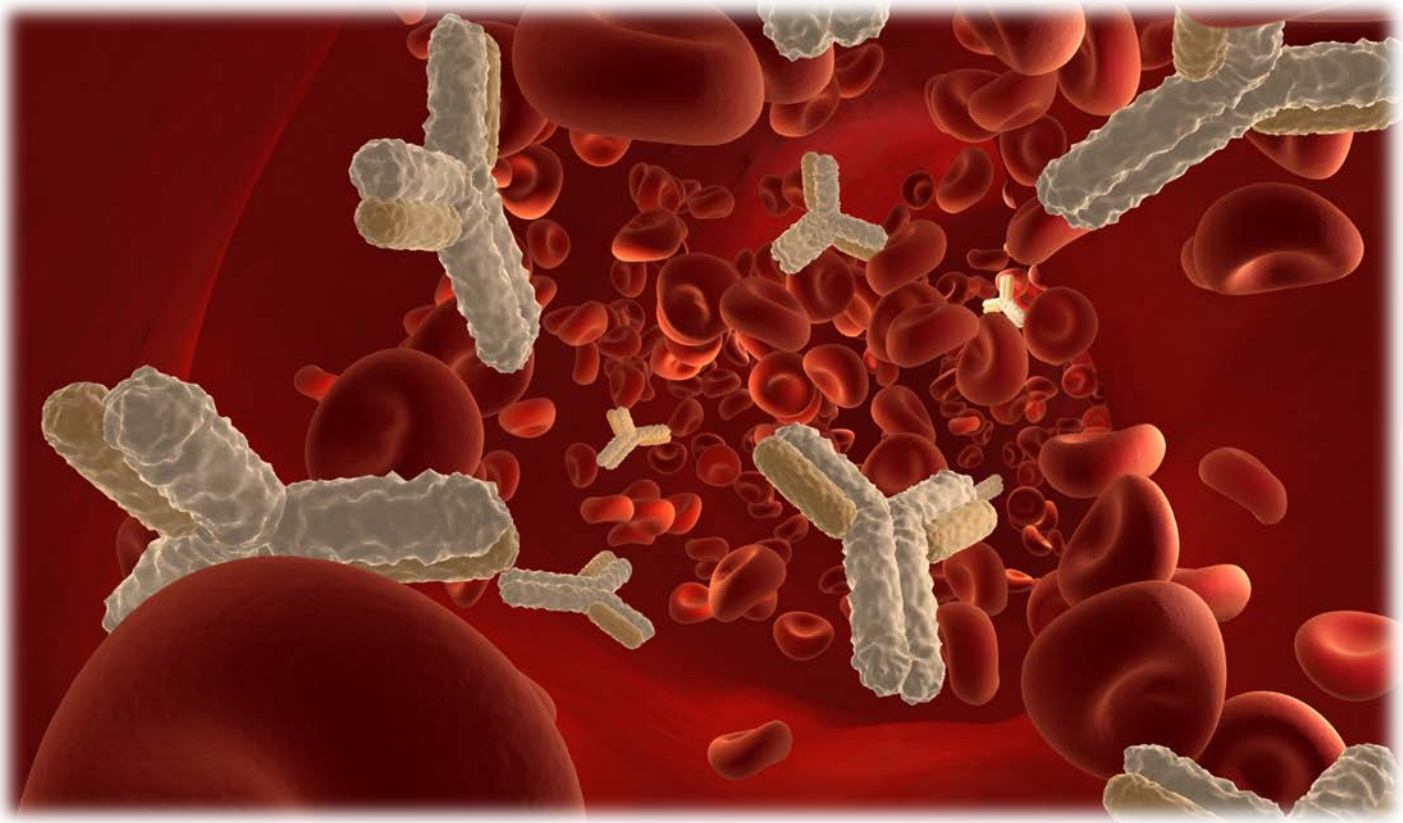
In Vivo Issues



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In Vivo

Hemolytic anemia

Platelet destruction

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Drug-Induced Hemolytic Anemia

- **Cephalosporins**
- **Penicillin and its derivatives**
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Dapsone
- Levodopa
- Levofloxacin
- Methyldopa
- Nitrofurantoin
- Phenazopyridine (pyridium)
- Quinidine

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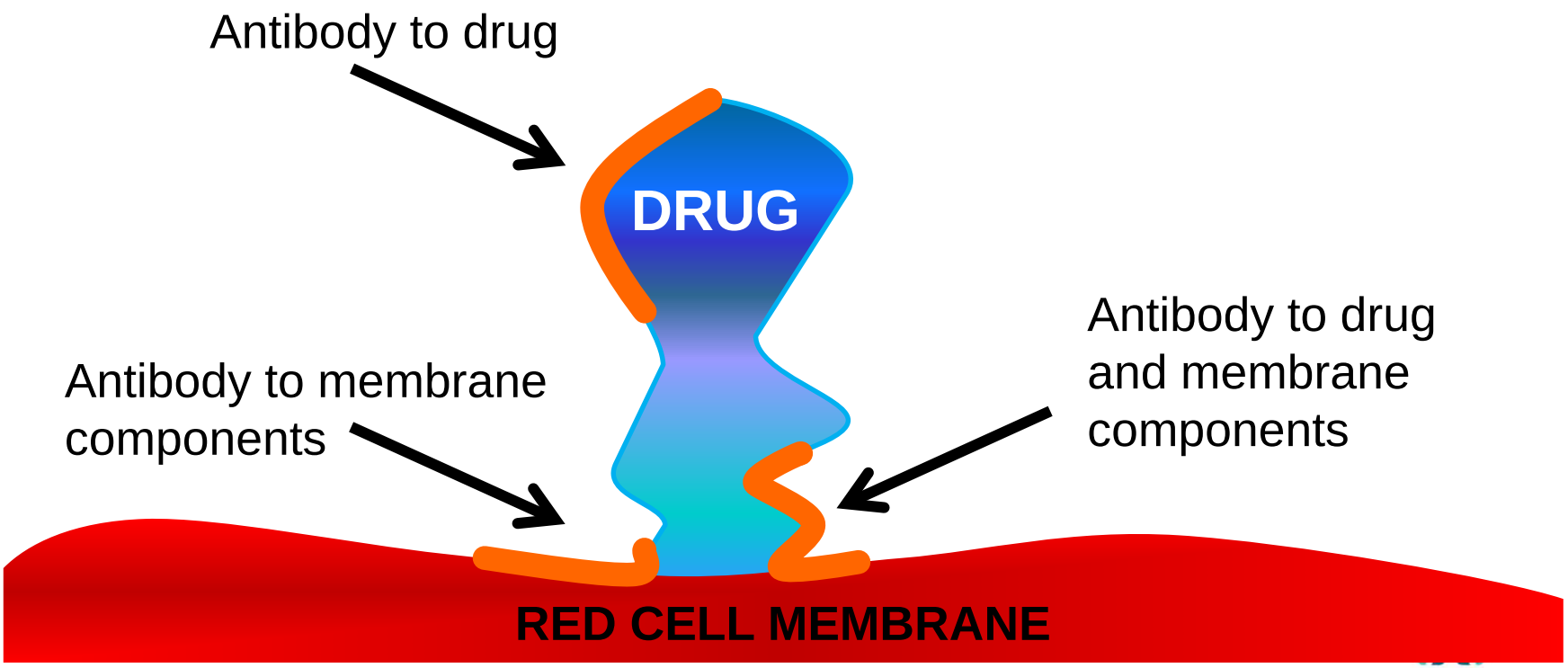
Drug-Dependent Antibodies



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Work-Up

1. Indicators of hemolysis
   - Hemoglobin ↓
   - Reticulocytes ↑
   - Indirect bilirubin ↑
   - Haptoglobin ↓
   - LDH ↑
   - Hemoglobinuria?
2. DAT: positive
3. What drugs is the patient taking?
4. Temporal relationship

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Drug-Induced Thrombocytopenia

- ACE-Inhibitors
- Abciximab (ReoProTM)
- Carbamazepine
- Ceftazidime
- Ceftizoxime
- Ceftriaxone
- **Colloidal gold**
- Eptifibatide (IntegrelinTM)
- Fentanyl
- **Heparin**
- Ibuprofen
- Loracarbef
- Naproxen
- Orbofiban
- Phenytoin
- Propoxyphene
- **Quinidine**
- **Quinine**
- Ranitidine
- Rifampin
- **Sulfamethoxazole**
- **Sulfisoxazole**
- Suramin
- Tirofiban (AggrastatTM)
- Trimethoprim
- Vancomycin
- Xemilofiban

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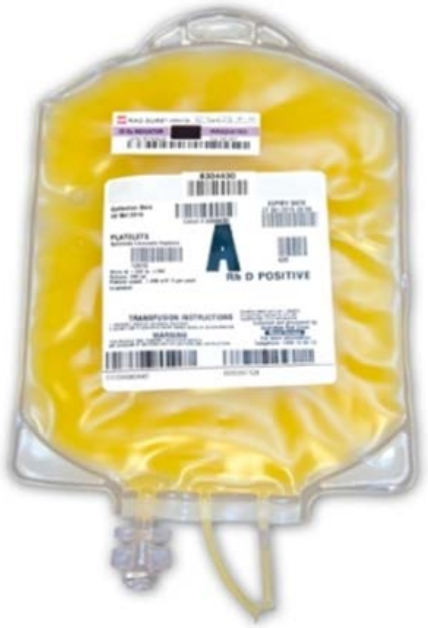
Spotlight on…

Indications

- Thrombocytopenia
  - Prophylactic threshold:
    - 5-10 K if stable
    - 20 K if risk factors: fever, sepsis, bleeding
    - 50 K if about to have major surgery
  - Therapeutic threshold:
    - 50 K if bleeding
    - 100 K if intracranial or pulmonary hemorrhage
- Thrombocytopathy
  - Congenital defects with bleeding
  - Drugs, sepsis, tissue trauma, OB complications
  - External agents
    - Cardiac bypass
    - ECMO
- Contraindications: TTP, HIT, ITP



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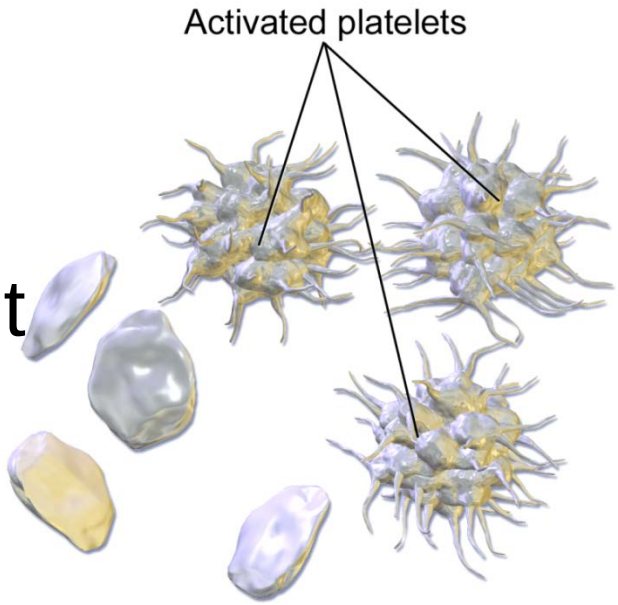
Apheresis Platelets

- What's in the bag?
  - 3 x 1011 platelets/apheresis unit
  - Plasma, PAS
  - Red blood cells, leukocytes and cytokines
- Storage
  - 20-24 °C for 5 days
  - Constant, gentle agitation
- One unit usually raises platelet count by 30-50,000/mL
- 1-hour post platelet count



Clinical Connection

- A 55 yo woman presented with bleeding from her nose and mouth and gums
- PMH: DM, HTN, DJD
- Medications: Glucotrol, Glucophage, HCTZ, quinine for leg cramps
- Physical Exam: petechiae over limbs and torso, blood blisters in mouth, epistaxis
- Platelet count **2K**

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Clinical Connection

- Pt admitted to hospital, quinine stopped, patient treated with platelet transfusions and IVIg
- Platelet count rose to normal over the next 5-6 days
- Eight months later, thrombocytopenia recurred, and patient admitted to taking quinine again for recurrent leg cramps

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Drug Antibodies

- If serological studies show that a patient has an antibody to a drug, that patient should be warned to not receive that drug again

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Transfusion Reactions

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Types of Transfusion Reactions

- Allergic
- Febrile Non-hemolytic
- Transfusion Associated Circulatory Overload (TACO)
- Acute Hemolytic
- Transfusion Associated Acute Lung Injury (TRALI)
- Transfusion Transmitted Infection (TTI)
- Transfusion-Associated Graft vs. Host
- Transfusion Associate Dyspnea
- Hypotensive
- Delayed Hemolytic
- Delayed Serologic
- Post Transfusion Purpura

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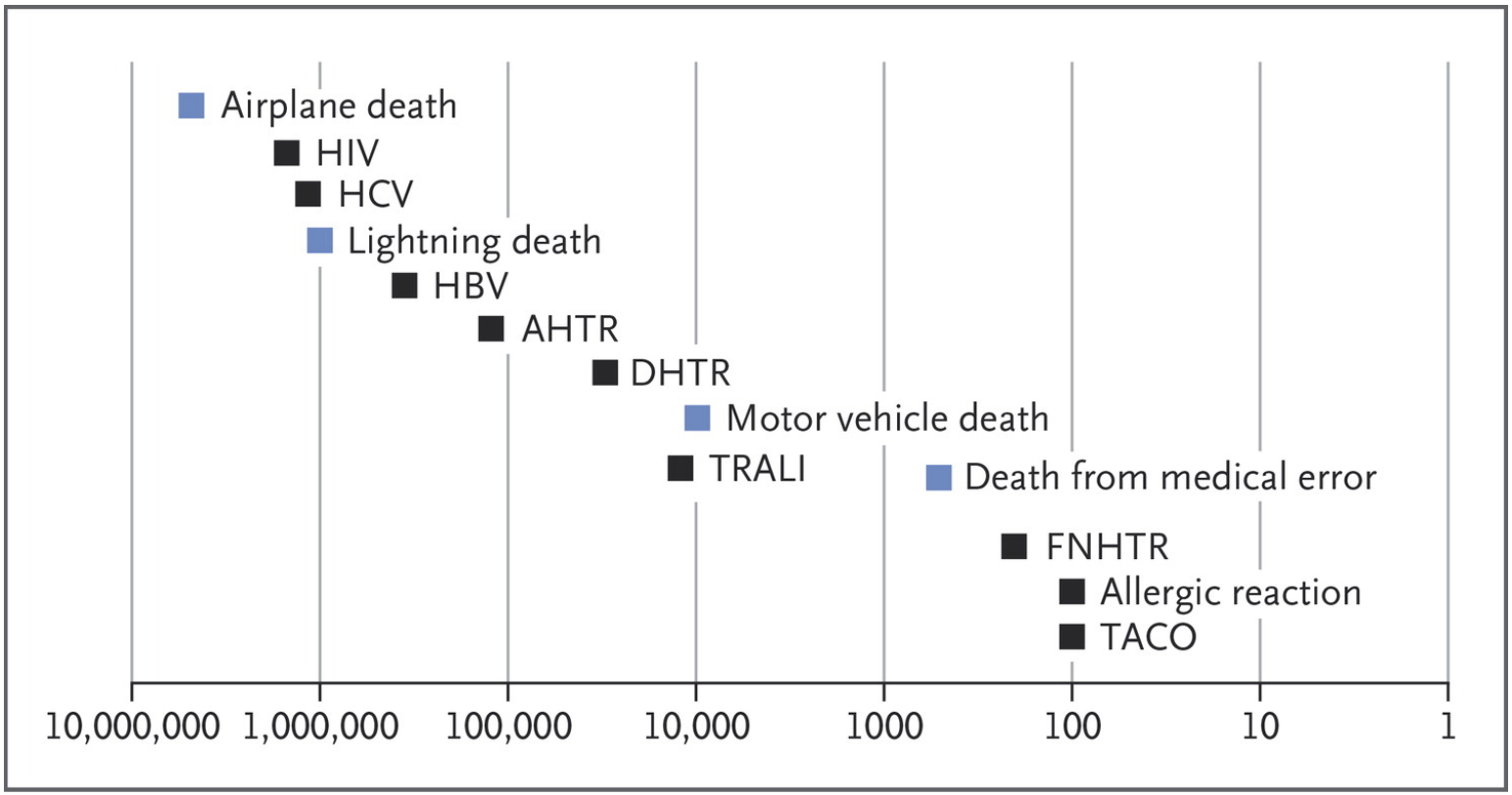
Frequency of Transfusion Reactions



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Jeffrey L. Carson, M.D., Darrell J. Triulzi, M.D., and Paul M. Ness, M.D. N Engl J Med 2017; 377:1261-1272

Transfusion Reactions

- Signs/symptoms
  - Conjunctival edema
  - Edema of lips/tongue
  - Erythema
  - Flushing
  - Hypotension
  - Maculopapular rash
  - Puritis
  - Urticaria
  - Respiratory distress
  - Fever (≥ 38°C or change of ≥ 1°C)
  - Chills/rigors
  - Back/flank pain
  - Epistaxis
  - Hematuria
  - Elevated BNP, CVP
  - Radiographic evidence of pulmonary edema/infiltrates

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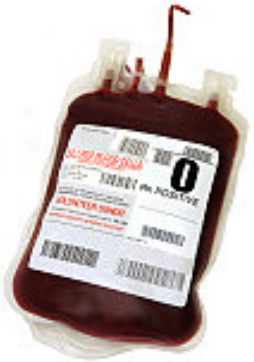
Febrile Reactions



- Underlying
- Febrile No
- Acute Her
- Transfusion
- TRALI

8°C or 100.4°F
change of
/1.8°F

n

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Transfusion Reactions

- Signs/symptoms
- STOP the transfusion immediately

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Allergic Reactions

- 1-3% of transfusions
- Most are mild
  - Puritis, urticaria, flushing
- History of allergies
- Prophylactic premedication with diphenhydramine does not decrease rate of reactions*
- Diphenhydramine can be used to treat a cutaneous transfusion reaction
- Do not restart if rash is extensive

*Kennedy et al. Transfusion. 2008 Nov;48(11):2285-91.

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Premedication

- Acetaminophen, Diphenhydramine, Solumedrol
- 50% to 80% of transfusions in the US and Canada
- Strongest predictor of who would receive premedication was whether the patient had been premedicated for a previous transfusion
- Data suggest premedication not effective in diminishing the incidence of febrile or allergic reactions
- No difference in reaction rates with premedication use, even when patients had a history of 2 or more reactions

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Premedication

- Acetaminophen: hepatotoxicity with acute overdose, hepatic injury after repeated doses in the mildly supratherapeutic range
- Diphenhydramine: effects on memory, psychomotor performance, and mood
- Routine premedication may result in substantial cumulative costs diphenhydramine
  - 800 hours of pharmacist time and 700 hours of nursing annually
  - $15,000 for drug acquisition per year

*Transfus Med Rev. 2007 Jan; 21(1): 1–12.

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Learning Objectives

- ✓ Define apheresis/apheresis emergencies and consider what medications may be helpful/harmful to the patient
- ✓ Consider medications that may interact ***in vivo*** to cause transfusion related issues
- ✓ Consider medications that may interact ***in vitro*** to cause transfusion related issues
- ✓ Understand when medications are indicated to prevent or treat **transfusion reactions**

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Questions?

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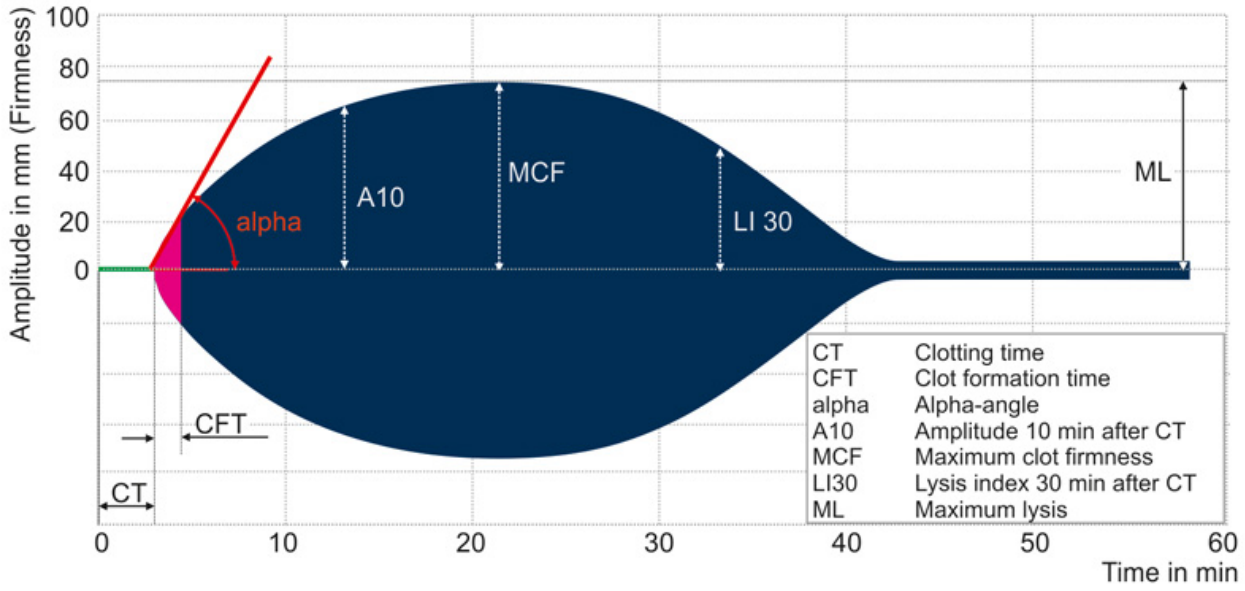
ROTEM®



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“Point of Care”

- Hyperfibrinolysis
- Dilutional coagulopathies
- Substitution of fibrinogen
- Factors or platelets
- The control of heparin or protamine dosage

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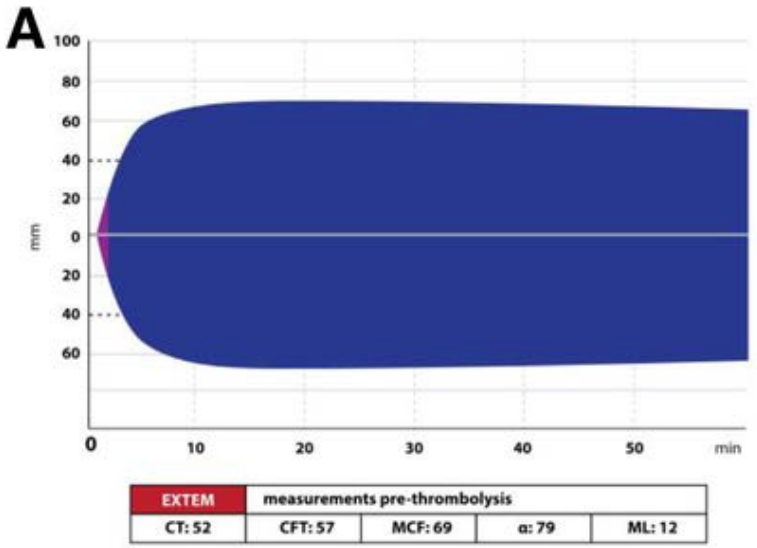
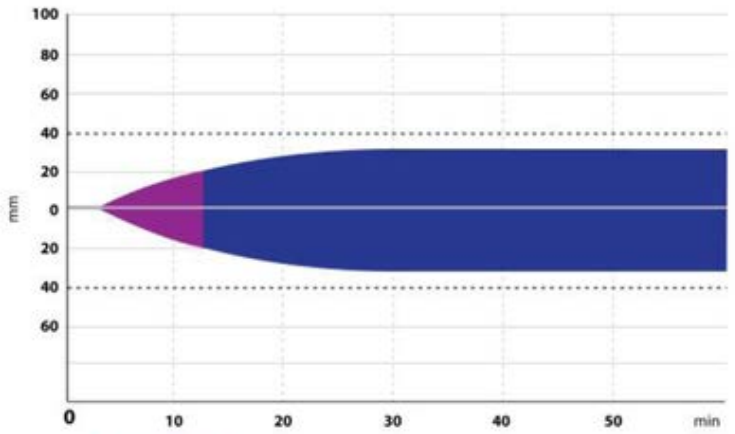
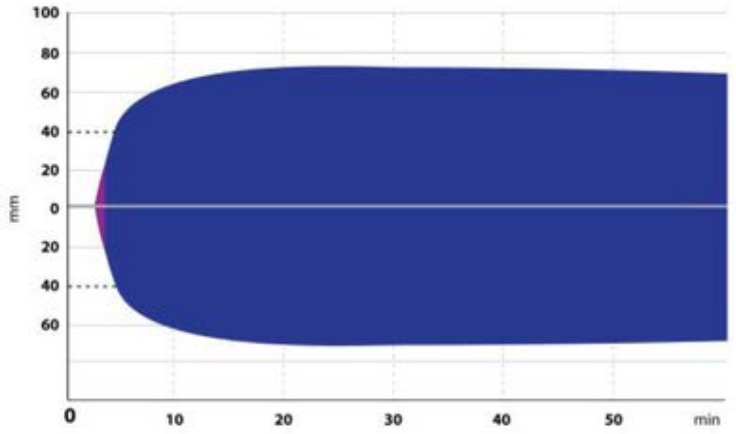


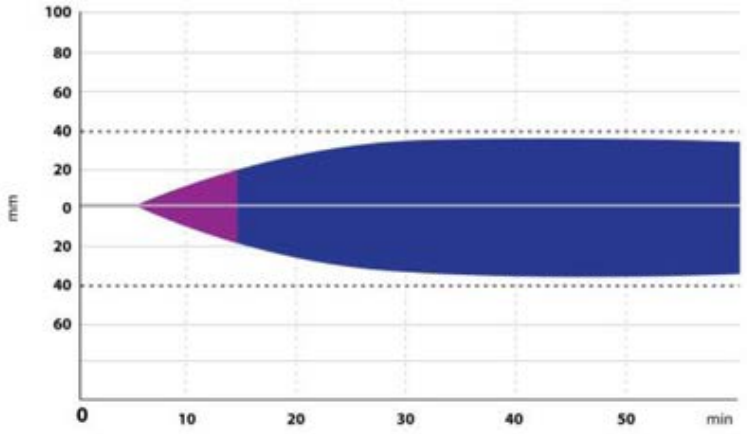
EXTEM	measurements pre-thrombolysis			
CT: 52	CFT: 57	MCF: 69	α: 79	ML: 12



EXTEM	measurements 2 hours post-thrombolysis			
CT: 182	CFT: 563	MCF: 33	α: 28	ML: 33



INTEM	measurements pre-thrombolysis			
CT: 156	CFT: 47	MCF: 72	α: 80	ML: 8



INTEM	measurements 2 hours post-thrombolysis			
CT: 335	CFT: 540	MCF: 36	α: 28	ML: 14

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ROTEM® *connect*

- Real-time, patient specific results to any authorized remote user via the browser-based ROTEM® live module

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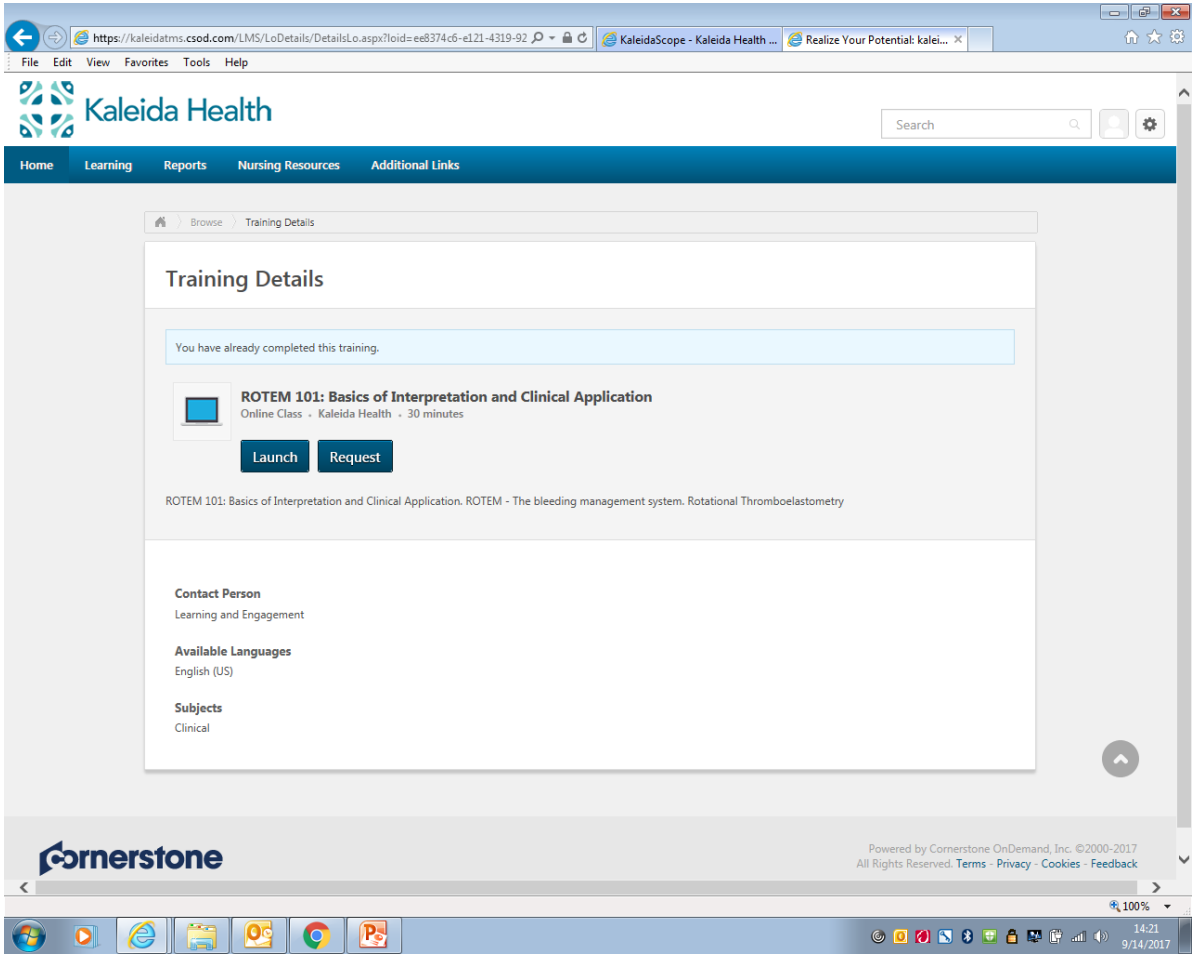
Talent Management



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Clinical Connection

- A 65 yo male smoker in ER with unstable angina
- PMH: peripheral vascular disease
- Admitted to the hospital
  - Platelet count on admission was **450K**
- Cardiac catheterization: severe 3-vessel coronary disease
- CABG on hospital day #7
  - Pre-op platelet count was **200K**; Post-op platelet count was **90K**

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Clinical Connection

- Hospital day #12: acute left leg swelling; DVT was diagnosed by ultrasound
  - Platelet count was **150K**
  - IV heparin
- Hospital day #13: pulseless left leg
  - platelet count of **30K**
  - In vascular radiology, he developed acute chest pain and suffered a cardiac arrest and subsequently died
- Autopsy showed occlusion of all of his bypass grafts

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HIT/T

- Seen in 1-3% of patients treated with heparin
- Usually, 7-10 d after heparin started, platelets fall by at least 1/3 to 1/2.
  - Patients do not have to be thrombocytopenic.
  - Can occur earlier in patients who have been previously exposed to heparin, even as SQ injections.
- Caused by antibodies against the complex of heparin and PF4. These antibodies activate platelets.
- Can lead, paradoxically, to THROMBOSIS, in up to half of patients.
- More common in patients with vascular disease

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Alternate Presentations of HIT/T

- Small drop in platelet count (especially with skin necrosis)
- Earlier onset thrombocytopenia with heparin re-exposure
- Delayed-onset thrombocytopenia/ thrombosis after stopping heparin
- Thrombosis after heparin exposure

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