# Hematology

## Transfusion Reactions

### *MINOR*

#### Febrile Non-Hemolytic Transfusion Reaction

- During or up to 4 hours after transfusion
- Incidence: 1:500
- Low grade temp, otherwise asymptomatic
- Cytokine-mediated
- Higher in old blood products and platelets; lower in leukocyte-reduced products
- Treatment: Acetaminophen; hold transfusion for 30 mins (then likely restart)

#### Simple Allergic (Urticarial) Reaction

- During or a few hours after transfusion
- Incidence: 1:3-1:300
- Only transfusion reaction where if mild you can continue transfusion without stopping
- Treatment: Diphenhydramine
- Premedicate if known history of same

### *CRITICAL*

#### Acute Hemolytic Transfusion Reaction

- During transfusion or up to 4 hours after transfusion
- True EMERGENCY: high grade fever, flank pain, hematuria, SICK/SHOCKY
- Diagnosis: pink plasma, positive Coombs test (looks for anti-human antibodies)
- Incidence: 1:38,000-1:70,000
- Mortality: 1:30
- Usually due to ABO incompatibility
- Management: STOP transfusion; recheck patient/blood; notify blood bank; send Coombs, Type and Cross, Chemistry and Hgb
- Can lead to DIC/shock/ARF
- Treatment: supportive, IVF (keep urine output 100-200cc/hr), treat hyperkalemia if present

#### Sepsis

- Usually in first hour
- Very rare
- Management: stop transfusion and notify blood bank; culture blood (recipient and donor)
- Broad spectrum reaction

### Severe Allergic (Anaphylactic) Reaction

- Usually occurs right at the start but can be delayed up to 4 hours
- Incidence: 1:20,000-1:50,000
- Shock, hypotension, angioedema, respiratory distress
- Normal CXR
- Treatment: stop transfusion; supportive; epinephrine

### Transfusion Related Acute Lung Injury (TRALI)

- Occurs during or up to 6 hours after transfusion
- Incidence: unknown but estimated 1:5,000 - 1:150,000
- Cause: unknown; leading theory involves HLA antibodies causing inflammatory response in pulmonary vasculature
    - More common in female donors and reduced incidence in females screened for HLA antibodies
- "Two-Hit" Theory: patients with underlying systemic inflammation more likely
    - SIRS/Sepsis
    - Trauma
    - Massive Transfusion
- Diagnosis: Non-cardiogenic pulmonary edema (tachypnea, tachycardia, hypotension, frothy pink sputum, fever)
    - CXR reveals pulmonary edema
- Treatment: stop transfusion; supportive; NO furosemide

### Transfusion-Associated Circulatory Overload (TACO)

- Occurs during or a few hours after transfusion
- Incidence variable but increased in patients with CHF
- Symptoms similar to TRALI
- Distinguishing Features
    - Hypertension
    - Symptoms of overload: increased jugular venous pressure, increased blood pressure, and increased BNP
- Treatment
    - Stop transfusion, supportive, furosemide

**If a patient receiving a blood transfusion begins having trouble breathing and looks uncomfortable it is due to one of the following: Severe Allergic (Anaphylactic) Reaction, Transfusion Related Acute Lung Injury (TRALI) or Transfusion-Associated Circulatory Overload (TACO).

## *Premedicate?*

- Pros: eliminates minor reactions, patient comfort
- Cons: masks major reactions, delays treatment
- Studies conclude no difference in transfusion reactions

### *Pearls*

- Suspect acute transfusion? Stop the transfusion, check the blood, and call the blood bank. If severe, get labs (especially Coombs).
- ***Symptom based diagnosis is critical!***
- Low-grade fever → Febrile Non-Hemolytic Transfusion Reaction → antipyretics
- Isolated urticaria → Simple Allergic (Urticarial) Reaction → antihistamines
- High Fever/Shock → Acute Hemolytic Transfusion Reaction or Sepsis → antipyretics, vasopressors, fluids, antibiotics.
- Respiratory Distress + Hypertension → TACO → furosemide (like CHF)
- Respiratory Distress + Hypotension → TRALI → pulm edema, support, no furosemide
- Respiratory Distress + Anaphylaxis (clear CXR) → epinephrine, steroids, vasopressors, airway.

# Coagulopathy

## *Coagulation: 3 parts*

1. Vessel constriction
2. Primary hemostasis
    a. Injury to the blood vessel wall → endothelial cell goes away →
    b. Von willebrand factor is exposed on subendothelium and platelets stick to it
    c. Fibrinogen attaches to platelets → more platelets attach to fibrinogen → primary platelet plug
3. Secondary hemostasis (in a nutshell)
    a. Intrinsic and extrinsic pathways
    b. Prothrombin is converted to thrombin
    c. Fibrinogen is converted to fibrin and results in a stable fibrin clot

## *Fibrinolysis (clot breakdown)*

- Key players: Anti-thrombin III, proteins C & S, mainly plasminogen activation, fibrin breakdown
- How it happens: tissue plasminogen activator (tPA) released from endothelial cells → converts plasminogen to plasmin → breaks down fibrin clots → fibrin degradation products (think D-Dimer)

## *Coagulopathy Clues*

- Spontaneous bleeding, Bleeding gums, Bleeding out of proportion to injury Menometrorrhagia, Delayed bleeding/bruising, Umbilical stump bleeding, Post-procedure bleeding, Easy bruising/petechiae, Joint/deep tissue bleeding, Hematuria, Epistaxis, Family History

- Site of Bleeding: Mucocutaneous vs Joints/potential spaces vs Both

# Hemostatic Disorders - Inherited

## *Hemophilias*

### General

- 2 Types
  - Type A: Factor VIII deficiency; 85% of cases
  - Type B: Factor IX deficiency; “Christmas disease”
  - Both types X-linked recessive and clinically indistinguishable
  - Up to 30% will have no family history
- Clinical Presentation
  - Bleeding red flags pain
  - Hallmark symptom: hemarthroses
  - Pain
- What will kill your patient?
  - Life-threatening hematomas: airway, compartment syndrome, retroperitoneal bleeds
  - **CNS bleeds**

### Workup

- Prolonged PTT (may be falsely normal if factor activity is >30%)
- Factor activity levels are definitive test
- Grading based on factor activity level as a % of normal (13:00)
  - Mild: 6-60%
  - Moderate: 1-5%
  - Severe: <1%

### Treatment

- Recombinant factors
- Amount of factor depends on severity of bleed
- *Assume a starting factor level of 0, replace FVIII vs FIX based on type of hemophilia

| Type of Bleed | Factor Level Required | Initial Dose FVIII/FIX (U/kg) |
|---|---|---|
| Minor:<br>Hemarthroses, hematuria | 20-30% | 12.5/25 |
| Moderate:<br>Epistaxis, GI, dental | 50% | 25/50 |
| Severe:<br>CNS, retroperitoneal | 75-100% | 50/100 |

- Rule of Thumb
    - Factor VIII = “V”
        - FVIII raises activity 2% for every U/kg
    - Factor IX = “1”
        - FIX raises activity 1% for every U/kg
- Alternative Treatments (if factor VIII not available)
    - **FFP**: equivalent to 1U of FVIII per 1mL FFP
    - **Cryoprecipitate**: equivalent to 100U of FVIII per bag (also rich in vWF)
    - **DDAVP**: increases FVIII activity 2-3 times; no free FVIII but causes release of extra vWF, which carries FVIII
        - DDAVP dosing: 0.3mcg/kg IV/SQ; 150mcg nasal spray if <50kg; 300mcg nasal spray if >50kg

# *Von Willebrand’s Disease*

## Basics

- Most common inherited bleeding disorder (1% of population)
- Varied heritability → can be autosomal dominant or recessive
- vWF: promotes platelet adhesion to collagen; causes platelet activation; protects factor VIII
    - In primary hemostasis, attaches subendothelium to platelets by glycoprotein Ib receptor
    - In secondary hemostasis, protects FVIII from degradation delivers FVIII to site of injury
- Von Willebrand’s disease can be a quantitative or qualitative defect in vWF and is classified by type

| Type | Occurrence | Defect & Inheritance Pattern |
|---|---|---|
| 1 | 70-80% | Decreased vWF / Autosomal dominant |
| 2 | 10-15% | Non-functional vWF / Autosomal dominant |
| 3 | <10% | Complete Lack of vWF / Autosomal recessive ** ddAVP will not work for this type |

## Clinical

- Platelet Dysfunction
- Epistaxis, prolonged bleeding from lacs, gingival bleeding, hematomas/hemarthrosis (type 3), easy bruising, heavy menses

## Laboratory Evaluation

- Platelet count: Normal (deficiency in platelet function NOT number)

- Bleeding time: Prolonged
- PT: Normal
- PTT: Normal/Elevated
- vWF level: Normal/Decreased (depending on type)
- vWF activity: Decreased
-

### Treatment

- DDAVP (desmopressin acetate) causes release of more vWF
- Non-recombinant FVIII (i.e. NOT synthetic)
- Cryoprecipitate
- ***No FFP (very little vWF)**
- Antifibrinolytics: prevent conversion of plasminogen to plasmin inhibiting breakdown of clots (2nd or 3rd line)
    - ε amino-caproic acid (Amicar): 5gm IV over 1 hour, then 1gm/hr gtt
    - Tranexamic acid:  10mg/kg IV q6--8h
- Estrogens: increase vWF and FVIII; can use OCPs chronically, but mainly used IV for an acute bleed
- Topicals: Surgiseal, thrombin spray or powder, fibrin glue

## *Pearls*

- Coagulation hemostasis: 1) vessel constriction; 2) primary hemostasis (platelet plug); 3) secondary hemostasis (fibrin clot)
- Hemophilias are x-linked: **hemarthroses =** hallmark symptom
- Hemophilia A (factor VIII) more common (85% cases) than Hemophilia B (Factor IX)
- CNS bleeds kill hemophilia patients
- Hemophilia best treated with factor
- Factor **V**III = “V” = 2 (FVIII raises activity 2% for every U/kg)
- Factor **I**X = “I” = 1 (FIX raises activity 1% for every U/kg)
- Backup factor replacement for hemophilia patients include DDAVP (factor VIII), fresh frozen plasma, and cryoprecipitate
- Von Willebrand’s Disease (vWD) is most common bleeding disorder; responds well to topical tx; can tx with recombinant vWF, DDAVP, or cryoprecipitate, but NO FFP

# Hemostatic Disorders - Iatrogenic

## *Heparin*

- Mechanism of Action: binds and activates anti-thrombin III → completely inactivates factor Xa and thrombin
    - Half life of 30--150 minutes
    - Monitor with PTT
- Bleeding?
    - Stop heparin
    - Think about anemia/thrombocytopenia and whether to transfuse

    - Consider protamine
- Reversal Agent: Protamine
    - Actually an anticoagulant, but binds up heparin and neither can work
    - Dose: 1mg protamine for every 100U heparin given in previous 4 hours
        - max 50mg
    - Give SLOWLY to avoid anaphylactoid reaction

## *LMWH (Enoxaparin)*

- Mechanism of Action: also binds to anti-thrombin III, but the resultant complex inactivates only Xa (NOT thrombin)
    - Half life is 3--4 hours
    - Monitor with Xa levels, not PTT
- Reversal: also protamine! But …
    - Only reverses about 60% of function
    - Dose depends on timing after enoxaparin given and amount given
    - Max is 50mg
    - Give slowly to avoid anaphylactoid reaction

| Hours post lovenox | Dose |
|---|---|
| <8 | 1mg:1mg |
| 8-12 | 1mg: 0.5mg |
| >12 | none |

## *Coumadin (sodium warfarin)*

- Mechanism of Action: inhibits vitamin K dependent clotting factors (II, VII, IX, and X), and proteins C and S
    - Half life of 36 hours
    - Monitor with INR

### Reversal

- FFP: contains all coagulation factors/proteins present in the initial unit of blood
- Vitamin K: coagulation factor substrate; given PO/SQ/IV; takes >24 hours for full effect (time to remake factors)
- Prothrombin complex concentrate (PCC): derived from human plasma and rich in II, VII, IX, X
    - Works in <30 min
    - Minimal risk of thrombotic complications
    - Dose 25-50 U/kg IV
    - Effective, quick, but not FDA approved
- When to reverse?
    - If INR <5, no bleeding → skip next dose of coumadin
    - If INR >5 but <9, no bleeding → skip 1 or 2 doses, can give vitamin K (up to 5mg PO) if increased bleeding risk, follow up with PMD
    - If INR > 9, no bleeding → hold warfarin until therapeutic; give vitamin K 5-10mg

PO
    - **Any serious bleeding at any INR → hold warfarin, give vitamin K 5-10mg IV, and give FFP or PCC**
    - **Life threatening bleeding → hold warfarin, give vitamin K 5-10mg IV, AND PCC or factor VIIa**
- Reversal Pros and Cons
    - These patients are on anti-coagulation for a reason
    - Chance of thrombosis
    - High risk vs low risk
        - High risk patients for reversal: patients with mechanical valves, or defective native valves + afib
        - Low risk patients: DVT and a-fib with normal valves

## *Tissue Plasminogen Activator (tPA)*

- Mechanism of Action: converts plasminogen to plasmin → clot breakdown
- Bleeding?
    - Give everything!
    - Transfuse blood, 10u cryo, 2-4u FFP, 10u platelets
    - PCC, Factor VIIa, ε amino-caproic acid (Amicar), Tranexamic acid

## *Clopidogrel (Plavix)*

- Oral antiplatelet agent
- Mechanism of Action: prodrug converted by liver; blocks glycoprotein IIb/IIIa → prevents cross-linking of platelets by fibrin
- Can cause bleeding and TTP
- Reversal: nothing really; can give platelets

## *Dabigatran (Pradaxa)*

- Mechanism: direct thrombin inhibitor
- RE-LY trial showed slightly better stroke rate but more patients withdrew from side effects related to the drug
- **Associated with GI bleeds
- Reversal: nothing; platelets won't work; it **is dialyzable**; can try activating thrombin with PCC, FFP, cryo

## *Xabans (apixaban, rivaroxaban)*

- Mechanism: Oral factor Xa inhibitor (like LMWH)
- Studies show non-inferiority to LMWH but not studied vs warfarin
- Also approved for non-valvular a-fib and post-op DVT prevention
- Reversal: in progress; can try thrombin activation as with pradaxa; cannot be dialyzed

## *Pearls*

- Reverse heparin/LMWH with protamine (give slowly)
- Warfarin reversal → if not bleeding, oral vitamin K; if bleeding, give fresh frozen

plasma/prothrombin complex concentrate + IV vitamin K
- Give tPA bleeders everything you can think of
- Plavix reversal → give platelets
- Direct thrombin inhibitors reversal → thrombin activators + dialysis
- Xabans reversal → thrombin activators

# Blood Disorders

## *Multiple Myeloma*

- Definition: monoclonal immunoglobulin produced by single clone of neoplastic cells → clone proliferates in bone marrow
- Sx: elderly with chronic bony/back pain, lytic lesions on xrays
- Associated Symptoms
    - Anemia (bone marrow infiltration)
    - Renal disease ("cast nephropathy" "myeloma kidney")
    - Hypercalcemia (can result in **LOW anion gap)**
- Diagnosis
    - Serum and urine for monoclonal protein
        - **Abnormal SPEP & UPEP** (electrophoresis to ID protein); **Bence-Jones Protein** (in urine)
    - +/- skeletal survey
    - **Rouleaux** formation on blood smear
    - Elevated ESR

## *Lymphoma*

- Definition: cancer of lymphocytes; presents as a solid tumor (static tumor)
- Two Categories: Hodgkins Lymphoma, Non-Hodgkins Lymphoma (NHL)
- **B-Symptoms (if present, more aggressive): Fever, Night Sweats, Lymphadenopathy**
- Dx: lymph node biopsy

### Non-Hodgkins Lymphoma (NHL)

- **Follicular Lymphoma** (40% of lymphomas in adults)
    - **Indolent** = often wide spread at presentation
    - Not curable, but slow growing
    - Who: older adults
    - Can transform to aggressive form with high mortality (patient has B symptoms)
- **Diffuse Large B cell Lymphoma** (40-50% of lymphomas in adults)
    - **Aggressive = symptomatic**
    - About half are curable
    - Rapidly spreads outside of lymph nodes
    - Who: all ages, more common in older adults

### Hodgkins Lymphoma

- Less common than NHL
- Who: male, bimodal age distribution (age 20-40 and >55), strong family history, relation to viral infection
- Rapid treatment = high cure rates
- Dx: B symptoms + **Local spread** to contiguous LN (different from NHL)
- Pathology: **Reed-Sternberg cell** on biopsy

## *Leukemia*

- Definition: cancer of the blood or bone marrow – neoplastic proliferation of hematopoietic or lymphoid cells
- Dx: bone marrow aspiration

### Types: Acute vs Chronic and Lymphocytic vs Myelogenous

- Acute: CHILDREN; rapid increase in blasts → crowds out other cells in marrow → blasts spill into blood
- Chronic: ELDERLY; slow onset, progress over yrs; mature abnormal WBCs; not emergency
- Lymphocytic: cancer of cells that become lymphocytes (T or B cells;mostly B cells)
- Myelogenous: cancer of cells that become RBCs, platelets, other WBCs

### Putting this together we get 4 main types of leukemia

- Acute Lymphocytic Leukemia (ALL): bony pain, **lymphadenopathy**, spleno/hepatomegaly, fatigue (anemia), bleeding/petechiae (thrombocytopenia) and infections (functional immunosuppression); blasts
- Acute Myelogenous Leukemia (AML): **same as ALL except NO lymphadenopathy**, MILD splenomegaly; infiltration into gums; **Auer rods** on smear; blasts
- Chronic Lymphocytic Leukemia (CLL): adults (> 50yrs); slow onset; usually incidental **(elevated WBC for no good reason)**; advanced disease = swollen LN/spleen, anemia and infections
- Chronic Myelogenous Leukemia (CML): similar to CLL + **high platelets**

## *Leukemia/Lymphoma Emergencies*

### Leukostasis

- Real emergency!
- WBC > 100K, usually AML or CML in blast crisis
- Viscous blood plugs circulation
- Symptoms: severe hypoxia, headache, dizziness, visual changes, AMS → SICK!
- Tx: induction chemotherapy
    - Temporize with leukapheresis
    - Allopurinol (prevent TLS), hydroxyurea

### Tumor Lysis Syndrome

- Death of many CA cells at once → massive release of intracellular contents → metabolic derangements → final pathway is renal failure
- Who: aggressive heme malignancies (high-grade lymphomas - Burkitt; ALL), large solid

tumor burden (breast), tumors with high proliferative rates
    - Post induction therapy (1-5 days)
    - Radiation therapy
    - New cancer diagnosis
    - High sensitivity to treatment
- Symptoms: non-specific and related to the electrolyte issue
    - Hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia → renal insufficiency
- Lab: **Uric acid level, potassium, phosphorous, calcium**
- Clinical: laboratory TLS plus one of the following: elevated creatinine, cardiac arrhythmia, seizure, sudden death
- Tx: aggressive fluid resuscitation, treat electrolyte abnormalities, prevent ARF, cardiac monitoring, labs every 6 hours
    - Hyperuricemia (**suspect TLS = send uric acid level**; uric acid crystals obstruct renal tubules → renal failure)
        - Allopurinol blocks metabolism to uric acid; oral or IV; slow onset; does not work on existing uric acid crystals
        - Rasburicase oxidizes uric acid to water soluble form; IV only; rapid onset; works on existing uric acid; save for sicker patients
    - Hyperphosphatemia
        - Phosphate binders (i.e. aluminum hydroxide)
        - Dialysis
    - Hyperkalemia
        - Potassium shifters (Insulin/glucose, albuterol, bicarb)
        - Potassium excreters (lasix, kayexalate, dialysis)
        - Cardio-protection if wide QRS (calcium)
    - Hypocalcemia (secondary to high phosphate levels)
        - Do not treat until phosphate levels normal
        - Only treat if symptomatic (seizure, heart failure, long QT, syncope)
        - Calcium gluconate 50-200mg IV

## *Pearls*

- Multiple myeloma: Chronic Bony pain, SPEP, UPEP, Bence Jones, Rouleaux formation, Low Anion Gap.
- Lymphoma: Hodgkins vs NHL
- Follicular NHL = indolent > Large B cell; NHL = Aggressive
- Hodgkins Lymphoma: Reed Sternberg Cell, local spread
- Leukemia: 4 types: AML (auer rods, gums), ALL, CML, CLL
- Leukostasis → sludging → hypoxia + neuro + sick → leukapheresis + induction chemo
- TLS: electrolyte and metabolic abn → renal failure. Uric acid level. tx with IVF, tx electrolyte abn. Allopurinol and Rasburicase.

# Platelet Disorders - Thrombocytopenia

## *Idiopathic Thrombocytopenic Purpura (ITP)*

- Relatively rare
- Isolated thrombocytopenia, other labs normal; patient well appearing
- 2 forms: childhood and adult
    - Childhood form: acute, self limiting, 2-3 weeks post immunization or infection
    - Adult form: insidious, chronic, no preceding illness
- Pathophysiology: impaired platelet production; T cell mediated destruction, B cell clone antibodies, splenic clearance of IgG coated platelets
- Treatment
    - 1st line: corticosteroids (2/3 of patients will respond)
    - IVIG: works fast but short lived; expensive
    - Platelets: temporary hemostatic support; will be destroyed; use in critically ill patients
    - Splenectomy
    - RhoGAM: induces mild hemolysis in Rh+ patients → decreases macrophage activity, spares IgG coated platelets from splenic destruction
    - Chemotherapeutic agents: Rituximab
    - New drugs: Eltrombopag and Romiplostim (stimulate platelet production; lifelong)

## *Thrombotic Thrombocytopenic Purpura (TTP)*

- Pathophysiology: long platelet chains clog blood vessels and prevent RBC passage
- “The Evil Pentad”: low platelets, anemia, fever, acute renal failure, neuro symptoms (fever and renal failure rare in reality)
- Presentation: symptoms wax and wane (b/c cause of TTP is platelet plugs that are not very stable)
    - brain, heart, adrenal gland, kidney, pancreas
- Consider this diagnosis if patient has thrombocytopenia, MAHA, +/- CNS, no other obvious cause (don’t wait for full pentad!)
- Risk factors: obese, African-American, female, HIV, SLE, drugs (Quinine, Clopidogrel, Ticlopidine)
- Rare disease but high mortality if missed and low mortality if treated
- Laboratory Abnormalities: thrombocytopenia, anemia, increased unconjugated bilirubin, increased LDH, normal fibrin/fibrinogen, ADAMTS-13 tests, vWF gel electrophoresis, DNA analysis; hematuria
- Treatment
    - Give FFP, **PET**, immunosuppressants (steroids, chemo agents), splenectomy, IVIG, anti-platelet agents, Hematology consult
    - DO NOT give platelets (will worsen emboli; exception in life-threatening ICH)

## *Hemolytic Uremic Syndrome (HUS)*

- Childhood: 6 months - 4 years

- Triad: MAHA, thrombocytopenia, ARF
- 95% of cases have diarrhea
- 80-90% caused by E. Coli 0157:H7 (shiga-like toxin)
    - Endothelial damage → Thrombin generation promoted → Fibrin deposition → Platelet-Fibrin clots
    - Seen in outbreaks
- Risk Factors: history of rare hamburger, petting zoo, unpasteurized fruits/juices, unchlorinated water, daycare, long-term care facility
- Classic presentation: bacteria ingested → 3 days → non-bloody diarrhea → 2 days → painful bloody diarrhea → platelet-fibrin clots → end organ damage (thrombocytopenia, MAHA, ARF)
- Diagnosis: presumptive; stool and urine for shiga toxin
- Laboratory Findings: schistocytes, thrombocytopenia, increased UC bili and LDH, normal fibrin/fibrinogen, negative direct coombs, negative blood cultures for E. Coli
- Treatment: mainly supportive
    - Admission for IVFs, PRBC for HgB <6 or unstable VS, HD/PD for anuria
    - PET for rare severe cases
    - No platelets!
    - Antibiotics can increase toxin release
    - New drug: Eculizumab

## *Heparin Induced Thrombocytopenia (HIT)*

- Definition: platelets <150K OR >50% drop from baseline
- 1-3% of patients on Heparin; can occur with LMWH (<1%)
- 3 Types … Type 2 most important (presents 4-14 days after starting Heparin)
- Pathophysiology: autoimmune process that forms plugs
- Clinical manifestations: CLOTS
    - Venous/arterial thrombosis, skin lesions, acute reaction, DIC
    - DVT, PE, adrenal thrombosis, cerebral venous/sinus thrombosis, venous limb gangrene, stroke, MI, skin necrosis, erythematous plaques,
- Diagnosis: 4T's - **T**hrombocytopenia, **T**ime of onset (5-14 days), **T**hrombosis, no o**T**her cause
- Laboratory Tests: Heparin-induced platelet aggregation assay, other immunoassays
- Treatment
    - Stop heparin, no platelets, no coumadin (until platelet count normal)
    - Change to direct thrombin inhibitor: Argatroban IV; Dabigatran (pradaxa) PO

## *DIC*

### Basics

- Characterized by widespread microvascular thrombosis
    - Consumption of clotting factors and platelets (common)
    - Decreased blood flow to vital organs → organ failure (rare)
- THEY ARE SICK!
- *Not a primary disease, a consequence of one
- Independent predictor of mortality in sepsis and trauma

### Pathophysiology

- Massive inflammation → endothelial damage → cytokine release (TNF, IL-6) → impaired anti-coagulation & consumption of clotting factors

### Lab Findings

- ↓Platelets, ↑D-Dimer, ↑PT/INR, ↓Fibrinogen

### Treatment

- Identify and treat underlying cause
- Give platelets if <10-20K or if risk of bleeding and <50K
- ? low-dose heparin

## *Key Points*

- DIC is not a primary disease
- Shiga Toxin E. Coli can cause HUS via UTI or diarrhea
- You must think of HIT to diagnose it
- Gross hematuria may be a clue to MAHA, and MAHA is enough to suspect TTP
- In TTP, give FFP while waiting for PET
- No platelets for TTP, HUS, HIT

## *Lab Summary of Thrombocytopenia*

| Lab-Summary | ITP | TTP | HUS | HIT | DIC |
|---|---|---|---|---|---|
| ↓Platelets | Yes | Yes | Yes | Yes | Yes |
| ↑PT/INR | No | No | No | +/- | Yes |
| MAHA | No | Yes | Yes | No | No |
| NL fibrin/fibrinogen | Yes | Yes | Yes | Yes | No |
| Big Spleen | No | Yes | No | No | No |
| “Sick” | No | Yes | +/- | No | Yes |
| Ok to give Platelets | Yes | No | No | No | Yes |
| Clots Common | No | No | No | Yes | No |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | |

### *Pearls*

- Disseminated Intravascular Coagulopathy (DIC) is not a primary disease, and the patients are sick
- Hemolytic Uremic Syndrome (HUS) may be caused by Shiga-toxin/shigtoxigenic E coli from a diarrheal illness or UTI
- Give a direct thrombin inhibitor in heparin-induced thrombocytopenia (HIT), and stop heparin
- No platelets for thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), or heparin-induced thrombocytopenia (HIT)

# Red Blood Cell Disorders - Anemia

## *Definitions*

- Hemoglobin (Hgb): grams of Hgb per 100ml of blood
- Hematocrit (Hct): RBC% in sample of whole blood
- MCV: Mean Corpuscular Volume
    - Macrocytic (>100), Microcytic (<80)
- RDW: RBC Distribution Width
    - Elevated RDW = RBCs of different sizes
- Reticulocyte: immature red blood cell; 1% of all RBCs; last one day in circulation before maturing
- Anemia: decreased oxygen carrying capacity due to decreased RBC mass
    - Males: Hgb <13.5 g/dl, Hct<41%
    - Females: Hgb <12g/dL, Hct <36% (at baseline females have less RBCs)

## *Remember ...*

- Acute blood loss may not drop Hgb and Hct → need time for fluid shifts to occur → serial measurements required
- Special populations
    - Smokers have ↑Hgb and ↑Hct (polycythemia)
    - African Americans have slightly lower than normal RBC count
    - Athletes have higher than normal RBC count
- Pancytopenia?
    - Anemia, thrombocytopenia, neutropenia
    - DDX: infections (specifically HIV), medications, **leukemia**

## *Symptoms of Anemia*

- Decreased Oxygenation
    - Dyspnea on exertion/rest, general fatigue, palpitations, altered mental status, CHF/angina/MI
- Hypovolemia
    - Muscle cramps, orthostasis, syncope, shock, death

## *Causes of Anemia*

- Kinetic Approach
    - Bleeding
    - RBC destruction (inherited and acquired conditions)
    - Impaired RBC production (nutrients, marrow suppression, hormones)
- Morphologic Approach
    - Microcytic: iron deficiency, thalassemia, chronic disease
    - Macrocytic: folate, vitamin B12
    - Normocytic: acute blood loss
    - **Need a peripheral smear to differentiate**

## *Microcytic Anemias*

### Iron Deficiency

- ↓reticulocyte count, ↓ferritin, ↓total iron, ↑TIBC

### Thalassemia

- Defective hemoglobin chains
- Alpha (**Africa**, Mediterranean, Middle East, Asia)
- Beta (**India**, Mediterranean, South East Asia)
- ↑reticulocyte count, **target cells**, normal/↑ferritin, normal/↑iron

### Chronic Lead Poisoning

- Headache, abdominal pain, memory loss
- From paint, soil, water
- **Burton's line:** blue line on gums
- Leads to **Basophilic RBC stippling**

## *Normocytic Anemia*

### Anemia of Chronic Disease

- Variety of causes
- ↓reticulocytes, ↓total iron, ↑TIBC

## *Macrocytic Anemia*

### Vitamin B12 Deficiency

- Vit B12 comes from animal products

- Who: Crohns, genetics, proton pump inhibitors, **vegan diet**
- Neurologic changes
- **Hypersegmented neutrophils**

### Folate Deficiency

- Folate comes from animal products & green, leafy vegetables)
- Alcoholics (impaired absorption and poor nutrition)
- **NO neurologic changes**
- **Hypersegmented neutrophils**

## *Sickle Cell Anemia*

- Sickled red blood cells
- **Valine for glutamine** switch at position 6 in hemoglobin amino acid sequence
- Genetic condition; autosomal recessive
    - **Heterozygous:** carriers of disease**;** 8-9% of African Americans; essentially asymptomatic
    - **Homozygous** = have real disease

### Clinical Emergencies of Sickle Cell Disease

VASOOCCLUSIVE CRISES

- **Acute Dactylitis:** the most common initial manifestation of SCD
    - 6-18months old (uncommon after age 6)
    - Pain and swelling of feet and hands (d/t RBC production occurring in small bones) → Infarction, not infection
- **Bone Pain**: in adults, occurs in long bones, back, chest
    - Can see avascular necrosis of femoral/humeral head
    - Most common reason for ED visit
    - Treat with narcotics +/- fluid

## *Pearls*

- 3 large groups of anemias: Microcytic, Normocytic, Macrocytic
- Symptoms of anemia can be separated into: 1) decreased organ oxygenation and 2) hypovolemia
- If pancytopenia is present, think about: 1) Infections (HIV); 2) Medications; 3) Leukemia
- Macrocytic anemias can be differentiated clinically by presence/absence of neurologic symptoms
- Bone pain in sickle cell disease is due to infarction, not infection, and occurs in small bones in children, and long bones in adults

### Clinical Emergencies of Sickle Cell Disease

VASOOCCLUSIVE CRISES (con't)

- **Priapism**: low flow state → venous, ischemic
    - Erect painful penis with soft glans
    - Treatment ("Time is Penis" = rapid treatment)
        - Aspiration of corpus cavernosum bilaterally (6 and 9 o'clock)
        - Intra-cavernous phenylephrine
        - Surgical drainage if unsuccessful medical management
- **Stroke:** CVA in young patients; usually affects large arteries → devastating deficits
    - Management: **emergent exchange transfusion**
    - Hydroxyurea: increases Fetal hemoglobin (Hgb)
    - Can also see bleeds in older adults due to rupture of vessels at sites of prior infarction
- **Acute Chest Syndrome**
    - Clinical: fever, SOB, **must see infiltrate on CXR**
    - **High mortality rate!**
    - Caused by combination of infection, micro-occlusive disease, fat embolism (from bone marrow necrosis → fat emboli to lungs → inflammation → hypoxia → more sickling → more vasoocclusion)
    - Management: antibiotics, IVF, analgesia, O2
        - If sick enough, then packed red blood cell (PRBC) transfusion or exchange transfusion

HEMATOLOGIC CRISES

- **Hemolysis**
    - SCD RBC lifespan short: 1-2 weeks
    - Baseline HGB 8 g/dL (patients compensate and tolerate this level well)
    - Any acute process (infx) may drop HGB dramatically
- **Aplastic Crisis**
    - Rapid drop in RBCs; most common in pediatric patients; usually self-limiting
    - Caused by parvovirus
    - Low reticulocyte count
    - Transfuse PRBC's for severe symptoms
- **Splenic  Sequestration**
    - Occurs in kids (before spleen infarcts)
    - Sudden enlargement of spleen with rapid drop in HGB (LUQ pain)
    - Management: aggressive IVF and transfusion +/- exchange transfusion

INFECTIOUS CRISES

- **More susceptible to encapsulated organisms 2/2 lack of functioning spleen** (S. pneumo, H. flu)
    - Meningitis, sepsis, PNA, UTIs, osteomyelitis

## *Pearls*

- Sickle cell disease: there are 3 major types of crises
    - Vaso-occlusive (dactylitis, bone pain, priapism, stroke, acute chest)
    - Hematologic (more common in children than adults)
    - Infectious (due to encapsulated organisms)