Disclosure

- I have nothing to disclose except
- I do work for food
- I promote giving Blood

Blood Components

- Plasma 54%
- White cells and platelets 1%
- Red Cells 45%

White Blood Cells

- Fight infections
- Are increased in infections
- Move inside and outside of blood vessels
- Are made in the bone marrow

White Blood Cells

WBC - White Blood Cells 4.5 - 11.0 K/uL
Low = Leukopenia  High = Leukocytosis

WBC Differential

- Neutrophils - Segs 54 - 62%
- Neutrophils - Bands 3 - 5%
- Lymphocytes - Lymphs 25 - 33%
- Monocytes - Monos 3 - 7%
- Eosinophils - Eos 1 - 3%
- Basophils - Basos 0 - 0.75%
- Atypical Lymphs 0
Platelets

- Primary Hemostasis
- Help clotting cascade
- Made in the bone marrow

Red Blood Cells

- Carry oxygen from the lungs
- Carry carbon dioxide back to the lungs
- Normally live 120 days
- Major acid buffer for pH
- Contains the protein hemoglobin
- Made from iron, folic acid, vitamin B12
- Made in the bone marrow

Microscope View

Red Blood Cells - Shape

Red cells travel through very narrow blood vessels

Red Blood Cells - Adult Hemoglobin

<table>
<thead>
<tr>
<th>Chromosome 16</th>
<th>Chromosome 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>97% = Hemoglobin A</td>
<td>1% = Hemoglobin F (Fetal)</td>
</tr>
<tr>
<td>2% = Hemoglobin A2</td>
<td></td>
</tr>
</tbody>
</table>
Red Blood Cells

Red cells, white cells and platelets are made in the bone marrow.

Red cells are made in the bone marrow.

Red cells live 120 days in the circulation.

Food with iron and vitamins is digested.

Reticulocytes, or Retics are young red cells just released from the bone marrow. The Retic count is the best indicator about how the marrow factory is doing.

Red cells are recycled in the spleen and liver. The iron and proteins are stored and bilirubin is released.

Hepcidin

Increased levels blocks absorption of Iron and cell release - inflammation IL6

Decreased levels increase iron absorption and release from cells - Erythropoietin, low iron

Erythropoietin is made by the kidney as a signal to the bone marrow to make more red cells.
The History

- Weakness
- Tiredness - Fatigue
- Dyspnea
- Dizzy – non vertigo
- Palpitations
- New angina

The History -2

- History of melena, abdominal pain. Aspirin or non-steroidal anti-inflammatory agents (NSAIDs) use, past peptic ulcer disease, then consider GI bleeding, platelet dysfunction.
- In females the menstrual history quantifying the amount of bloodloss, or possible pregnancy should be obtained.
- History of pica or abnormal craving for ice, clay, starch,...; dysphagia then consider iron deficiency.
- Poor diet, then consider iron or folate deficiency, and general malnutrition.
- History of gastric surgery, distal paresthesias, gait problems; consider B12 deficiency.
- History of alcohol abuse; consider folate deficiency or liver disease. If moonshine use or lead paint/pipe exposure, consider lead toxicity.

The History -3

- Family history of blood cell or bleeding disorder: consider Sickle Cell disease, G6PD, Thalassemia, Hemophilia, von Willebrand
- History of jaundice, transfusion, new medication, infection; consider hemolytic process.
- History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease, renal disease; then consider secondary cause.
- History of fever and chills, cough, dyspnea, then consider infection.

Physical Exam

Sclera

Spoon Nails – Fe Def.
Physical Exam

**GENERAL INSPECTION:** clubbing in TB or lung cancer
- Skin: Hypothyroid, SLE, Bruises, lesions, petechiae or purpura.
- Weight: Loss in Cancer, HIV, Chronic disease, gain in hypothyroid
- Vital Signs: Pulse, Respiration, BP, Temperature
  - Fever: Infections, drug reactions.
- HEENT: Jaundice if hemolysis, pallor in conjunctiva
- Mouth: Glossitis and angular stomatitis in iron or B12 deficiency
- Neck: Thyroid enlargement or nodules, lymph nodes
- Heart: Increased output/murmur, consider high output failure
- Lung: Consider infection, lesion
- Abdominal: Liver/spleen size, masses, tenderness, surgical scars
- Rectal: Stool guaiac, prostate exam in men
- Pelvic/Breast: Uterine abnormality, Pap smear, Breast nodule
- Lymph nodes: Consider lymphoma, leukemia, infection, connective tissue disease
- Neurologic: Decreased vibratory and position sense in B12 deficiency

**LAB- INITIAL SCREENING TESTS**

- CBC, red cell morphology and white blood cell differential, Reticulocyte count
- Urinalysis: Hematuria/proteinuria in renal disease, hemoglobinuria in hemolysis.
- Chemistry profile (LDH, Bilirubin- Direct and Indirect, BUN, Creatinine, AST, ALT).
- Hemoglobin Electrophoresis if hereditary hemoglobinopathy is suspected
- IF BLEEDING: Platelet Count, PT, aPTT, PFA

**CBC- Red Cell Measures**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>NORMAL ADULT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB - Hemoglobin</td>
<td>Male = 15.5 +/- 2 mg/dl</td>
<td>Low = Anemia</td>
</tr>
<tr>
<td></td>
<td>Female = 13.5 +/- 2</td>
<td>High = polycythemia</td>
</tr>
<tr>
<td>HCT - Hematocrit</td>
<td>Male = 46.0 +/- 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female = 41.0 +/- 6%</td>
<td></td>
</tr>
<tr>
<td>RBC - Red Blood</td>
<td>Male = 4.3 - 5.9 Million/Ul</td>
<td></td>
</tr>
<tr>
<td>Cell Count</td>
<td>Female = 4.0 - 5.2</td>
<td>High in Thyroid</td>
</tr>
</tbody>
</table>

**Red Cell Indices MCH, MCHC**

- MCH: Mean Corpuscular
  - 27 -32 pg: Low = Hypochromic
  - 30 - 36 gm/dl: Low = R/O Fe def.
- Hemoglobin: High = Hyperchromic
- MCHC: Mean Corpuscular Hemoglobin Concentration
  - High = Spherocytosis

**Red Cell Indices MCV - RDW**

- MCV: Mean Corpuscular Volume
  - 80 - 94 fl: Low = Microcytosis
  - High = Macrocytosis
- RDW: Red Cell Distribution Width
  - 11.5 - 14.5: Variation in RBC size (High in Iron deficiency)
**RBC Morphology**

**Red Cell Morphology**

- **Significance**
  - Burr Cells: Uremia, Low K, artifact, Ca stomach, PUD
  - Spur Cell: Post-splenectomy, Alcoholic liver disease
  - Stomatocyte: Hereditary, Alcoholic liver disease, Immune hemolytic anemia
  - Spherocyte: Hereditary, immune hemolytic anemia, water dilution, post-transfusion
  - Shistocyte - helmet: TTP, DIC, vasculitis, glomerulonephritis, heart valve, burns
  - Elliptocyte - Ovalocyte: Hereditary, Thalassemia, Fe Def., Myelophthistic, megaloblastic anemias
  - Rouleaux formation: Multiple Myeloma
  - Target Cells: Thalassemia, hemoglobinopathies
  - Microcytes: Thalassemia, Iron Def., Lead Toxic
  - Macrocytes: B12 of folate Def.
  - Parasites: Malaria, Babesiosis

**Platelets**

- **Platelet Count** 150 - 400 K cell/µL
  - Low = Thrombocytopenia
  - High = Thrombocytosis

**Retics or Reticulocyte count**

- **Retic - Reticulocyte Count 0.5 - 1.5 %**
  - Low in anemia = low marrow output
  - High = RBC loss

**Correcting the Retic**

- **Absolute reticulocyte count (measured)**
  - reticulocyte (%) = absolute number of reticulocytes + number of RBC x 100
  - reticulocyte index = % reticulocytes x actual hematocrit + normal hematocrit
  - corrected reticulocyte index (corrects for appropriate bone marrow release of reticulocytes) = reticulocyte index + maturation factor
  - maturation factor = 3.25 – (actual hematocrit ÷ 20)
  - if hematocrit 45, maturation factor = 1
  - if hematocrit 35, maturation factor = 1.5
  - if hematocrit 25, maturation factor = 2
  - if hematocrit 15, maturation factor = 2.5

**Corrected Retic Count**

- Retic = Raw Retic
  - index = Percentage x Pt's Hematocrit
  - An example would be if the raw retic percentage reported on the CBC was 6% and the male patient's hematocrit is 23 then:
  - The retic index = 6% x 23/46 or 3%
  - The corrected retic index = 3% x maturation factor of 2 = 1.5%
  - Corrected retic index < 2 indicates bone marrow production problem
  - Corrected retic index >2 indicates acute red cell loss (hemolysis or bleed)

**Diagnostic Pathway**

- **Reticulocyte Production Index**
  - <2 Decreased Production
  - >2 Increased Loss
  - Red Cell Indices MCV
  - Hemolysis
  - Bleeding
  - Coombs Positive
  - Drug Warm Antibody
  - Coombs Negative
  - Membrane Hb
  - Enzyme
**Microcytic**

- MICROCYTIC = "TICS"
  - T-Thalassemias
  - I-Iron Deficiency
  - C-Chronic Inflammation
  - S-Sideroblastic - lead, drug, or hereditary

**Microcytic Tests**

- TESTS TO ORDER:
  - Serum Iron
  - TIBC = Total Iron Binding Capacity = Transferrin binding sites for transporting iron
  - % Saturation = Transferrin saturation with Iron
  - Ferritin = Storage Iron
  - HBE LP = Hemoglobin Electrophoresis
  - Lead level if exposed

**Thalassemia Syndromes.**

- Hereditary – Alpha or Beta chain production
- Decrease Hemoglobin A
- Hemoglobin ELP and normal Iron are diagnostic
- Supportive therapy or BMT
- Target Cells
- Hemolysis signs
- Increased Red cell count

**Iron deficiency**

- Low Serum iron,
  - Low Ferritin, High TIBC
- Find out why – GI bleed, menses, diet
- Treat FeSO4 300mg tid
- F/U in 2-3 weeks for Retic and Ferritin

**Chronic Inflammation**

- Block of normal iron stores transport to bone marrow factory (Hepcidin)
- Normal Ferritin, serum iron and TIBC are low with a low saturation
- 30% Microcytic, 70% Normocytic
- High Sed rate or c-reactive protein
- Treat inflammation – RA, SLE, HIV....

**Sideroblastic**

- Ring sideroblasts in bone marrow
- Serum iron is increased and TIBC normal resulting in a high saturation. Serum ferritin is increased
- Basophilic stippling
- Lead toxicity is suspect
Normocytic Anemia

- Normocytic = "Normal Size"
  - N - Normal Pregnancy
  - O - Over hydration
  - R - Renal Disease
  - M - Myelophthistic
  - A - Acute Blood Loss
  - L - Liver Disease
  - S - Systemic Infection
  - I - Inflammatory Block
  - Z - Zero Production - Aplastic anemia

Normocytic Tests
- Blood Urea Nitrogen (BUN), Creatinine, SGOT, Alkaline Phosphatase, Bilirubin, Erythrocyte Sedimentation Rate (ESR), Urinalysis, and Thyroid profile
- Renal Function tests
- Pregnancy Test
- Bone Marrow Biopsy

Normocytic - Renal Failure
- Anemia caused by decrease erythropoietin production causing decreased bone marrow production
- Can monitor erythropoietin levels
- Treat with epoetin alfa injections weekly or darbepoetin alpha every other week or monthly

Aplastic Anemia
- idiopathic (78% cases)
- hepatitis (5% cases) testing for known hepatitis viruses usually negative
- drugs (2% cases due to gold, 4% due to other drugs)
- Parvo virus B19 (Fifths disease)
- Check WBC and Platelet count
- May need Bone Marrow Bx and supportive therapy

Macrocytic Anemia

- Macrocytic = "big fat red cells"
  - B - B12 Malabsorption
  - I - Inherited
  - G - Gastrointestinal disease or surgery
  - F - Folic Acid Deficiency
  - A - Alcoholism
  - T - Thiamine responsive
  - R - Reticulocytes miscounted as large RBCs
  - E - Endocrine: Hypothyroid, hypoadrenal, hypoandrogen
  - D - Dietary
  - C - Chemotherapeutic Drugs
  - E - Erythro Leukemia
  - L - Liver Disease
  - S - Splenectomy

Macrocytic Tests
- The peripheral blood changes include:
  - Anemia with decreased reticulocyte count, - Increased MCV
  - Neutropenia with hypersegmented neutrophils
  - Thrombocytopenia with large platelets.
- LABS to order:
  - B12, Serum Folate, RBC Folate
  - Methylmalonic acid and homocysteine levels
  - if all normal, consider TSH, and a Bone Marrow Bx.
B12 Cobalamin Deficiency

Physical signs include edema, pallor, jaundice, smooth tongue, decreased vibratory and position sensation. Hypersegmented polys. Low serum B12 level. Metformin, Gastric bypass, or PPI as cause?

Methylmalonic acid and homocysteine levels elevate early. Pernicious anemia - anti-intrinsic factor antibodies. Schilling’s test.

Rx - cobalamin 1000 mg I.M., oral, or Nasal Spray.

Folate Deficiency

- Causes - liver disease, diet vitamin B12 deficiency, and drugs such as methotrexate, ethanol, and dilantin.
- Lab – low serum and RBC Folate - always check B12 (needed for conversion)
- Elevated homocysteine
- Rx – Folate 1mg po qD

Hemolytic Anemia

- HEMOLYTIC = "HEMATOLOGIST"

- H-Hemoglobinopathy: sickle cell disease
- E-Enzyme Deficiency
- M-Medication - drug induced: aldomet, INH
- A-Antibodies - immune attack
- T-Trauma to the red cells: D.I.C, artificial heart valves
- O-O-Osmotic fragility in Hereditary spherocytosis
- G-G6PD Glucose-6-Phosphate Dehydrogenase Deficiency
- I-Infection: malaria, babesiosis
- S-Splenic destruction in hypersplenism
- T-Transfusion
- A-Antibodies - immune attack
- N-Normal, indirect, Coombs positive (transfusion, IgM - cold antibody-infections, IgG warm antibody
- D-D-D D.I.C, artificial heart valves

Hemolysis (HIT)

- Hereditary (HEM)
  - Hemoglobin (sickle cell, thalassemia)
  - Enzyme (G6PD deficiency)
  - Membrane (Spherocytosis, Elliptocytosis)
- Immune attack - Coombs positive (transfusion, IgM – cold antibody-infections, IgG warm antibody – Drug induced, Paroxysmal Nocturnal Hemoglobinuria – complement induced)
- Trauma – Microangiopathic (TTP, ITP, HUS, DIC, HIT, HELLP- Eclampsia, Malaria, Splenomegal)

Hemolytic Signs

- Elevated reticulocyte count, with stable or falling hemoglobin
- Elevated indirect bilirubin
- Elevated serum lactate dehydrogenase (LDH)
- Decreased Haptoglobin levels - Haptoglobin binds hemoglobin released in the plasma from red cell breakdown.
- Hemoglobinemia and hemoglobinuria
- Erythroid hyperplasia in bone marrow
- Abnormal Hemoglobin Electrophoresis

Hemolytic Tests

- The direct antiglobulin (Coombs’) test Direct Coombs test looks for antibody on the red cells. The Indirect Coombs looks for antibody in the serum.
- Hemoglobin electrophoresis
- Heinz body stain
- Osmotic fragility
- Blood smear
- Platelet count in the CBC - thrombocytopenia

anti-CD59 and flow cytometry for Paroxysmal nocturnal hemoglobinuria
Hemoglobinopathy
- Sickle Cell Disease – SS, SC, SD, SE, SOarab, S beta Thal
- Newborn Screening or HbELP
- Daily Penicillin –birth -6yo
- TCD screen prevents strokes
- Hydroxyurea prolongs life, prevents complications
- Hydration, Oxygen, Temperature, and Folate

Resource
- World Wide Web Site - The Sickle Cell Information Center
  http://www.SCInfo.org
  - Information for providers, patients, teachers, employers, administrators
  - Monthly E-mail Newsletter aplatt@emory.edu
  - Listing of Clinics
  - Guidelines

G6PD - Glucose - 6 - Phosphate Dehydrogenase Deficiency
- X linked genetic
- Precipitated by oxidant drugs
- Heinz body stain shows denatured Hb
- Avoid medications such as antimalarials, aspirin, sulfa drugs, and avoid eating fava beans.

Immune Attack
- Coombs Test: IgG and Compliment +/-
- Transfusion reaction: immediate or delayed
  - IgM – (IgG Neg Comp +) cold antibody-infections like, EBV (Mono), HIV, Mycoplasma pneumoniae, influenza B, Cytomegalovirus (CMV), rubella virus, varicella-zoster virus (VZV), parvovirus B19, and Chlamydia psittaci
  - IgG warm antibody – Drug induced – Antibiotics, ibuprofen, Autoimmune diseases
  - PNH Paroxysmal Nocturnal Hemoglobinuria – Red cells attacked by complement. Lack of CD55 or CD59 on RBC surface

Parasites – Malaria - Babesiosis

Membrane problems
- Spherocytosis and Ovalocytosis
To Clot or Not Coagulopathies

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Keep Blood in the Tubing PVC-pipes
- Platelets Adequate number that work right
- Von Willebrand Factor (vWF)
- Clotting Factors
- Pipes - Intact and healthy endothelium

Clotting Process
- Break in vessel wall – smooth muscle contracts
- Platelets with (vWF) stick to collagen and Activate
- More platelets are attracted
- Clotting Factors activate to form Fibrin
- Clot contracts

Clotting system activated
- Normal Blood Flow
- Clot

Endothelium
- Covers collagen, TF
  - vWF
  - tPA
  - Nitric Oxide (NO)
  - Prostacyclin –Cox2 mediated
  - ADPase
  - TF Pathway Inhibitor (TFPI)
  - Heparin

Von Willebrand Factor - vWF
- Super glue of platelets to stick to damaged walls
- Stabilizes and transports Factor VIII
- Made by Endothelial Cells
- Most common genetic bleeding disorder is Von Willebrand Disease
Platelets
- Made in the bone marrow
- Thrombopoetin made in liver stimulates production
- Fragments of megacaryocytes
- No nucleus
- 67% in circulation
- 33% in spleen storage
- Life 8 – 10 days

Platelet Activation
- Collagen
- Tissue factor, TXA2
- Thrombin
- Arachidonic acid
- Cyclooxygenase COX
- TXA2 and ADP released, also PF4
- ADP receptor
- glycoprotein (GP) IIb/IIIa receptor
- Fibrinogen attaches to other platelets

The Shape of Platelets
- Flowing Platelets
- Activated Platelets
- Aggregated - Active Platelets

Clotting Cascade - Factors
- Intrinsic Pathway – Inside the cut
  - Endothelial Injury
  - XII to XII active
  - XI to XI active
  - X to IX active
  - VIII to VIII active
  - Common Pathway
    - X to Xactive with V present
    - II Prothrombin to Thrombin
    - I Fibrinogen to Fibrin
  - Test = aPTT
- Extrinsic Pathway – outside the cut in the plasma
  - Vitamin K - Liver dependant
  - VII to VII active + Tissue factor
  - Common Pathway
    - X to Xactive with V present
    - II Prothrombin to Thrombin
    - I Fibrinogen to Fibrin
  - Test = TT, RT

Built in Clot Blockers and Busters
- Intrinsic Pathway – Inside the cut
  - Endothelial Injury
  - XII to XII active
  - XI to XI active
  - X to IX active
  - VIII to VIII active
  - Common Pathway
    - X to Xactive with V present
    - II Prothrombin to Thrombin
    - I Fibrinogen to Fibrin
  - Antithrombin III
  - Liver made Protein S
  - Tissue Factor Pathway Inhibitor
- Extrinsic Pathway – outside the cut in the plasma
  - Tissue Factor Pathway Inhibitor
  - Antithrombin III
  - Heparin
  - Plasminogen via t-PA/PAI-1 to Plasmin
  - Fibrin split products, D-Dimer
**Increased Bleeding Presentation**

- Bleeding gums
- Easy Bruising
- Prolonged Post-op Bleeding
- Prolonged Bleeding post dental work
- Petechiae or Purpura
- Increased Menstrual Bleeding
- Lab Finding of Low Platelets (under 50,000) or Abnormal PT, aPTT, abnormal platelet function
- G.I. Bleeding

**Increased Clotting Presentation**

- Deep Vein Thromboplebitis (DVT)
- Pulmonary Embolus (PE)
- Myocardial Infarction, Angina
- Miscarrages
- Stroke, or Transient Ischemic Attacks (TIAs)
- High Risk – post operative, pregnancy, atrial fibrilation, congestive heart failure
- Elevated platelets (Over 900,000)

**Bleeding History**

1. Abnormal bleeding from the mucus membranes such as the mouth, nose or vagina suggests platelet defects or von Willebrand’s disease (vWD).
2. Abnormal bleeding into joint spaces and soft tissues implies a defect in the clotting factors.
3. Purpuric lesions are usually caused by vascular wall defects.

**Bleeding History**

- HX - History of melena, abdominal pain, Aspirin or non-steroidal anti-inflammatory agents (NSAIDs) use, past peptic ulcer disease , then consider GI bleeding, platelet dysfunction.
- In females the menstrual history quantifying the amount of bloodloss , or possible pregnancy should be obtained.
- History of alcohol abuse - consider liver disease.
- Family history of blood cell or bleeding disorder: consider Hemophilia, von Willebrand Disease

**Bleeding History**

- History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease, renal disease - then consider secondary cause
- History of fever and chills, cough, dyspnea, then consider Infection.
- History of prolonged bleeding after dental extractions, epistaxis, gum bleeding, easy bruising, then consider low or dysfunctional platelets.
- History of bleeding into joints, then consider hemophilia.
- History of Lupus - Lupus anticoagulant

**Increased Clotting History**

- History of recurrent clots, PEs... consider protein S,C, or Antithrombin III deficient, Factor V Leiden, hyperhomocysteine, prothrombin 20210 mutation
- Pregnancy - Increased blood viscosity, fibrinogen and factor VIII. Post Partum - Hypercoaguable state
- Polycythemia vera - increased viscosity
- Prolonged travel or immobility
Increased Clotting History

- Smoking, Resent Surgery, Diabetes, Congestive Heart Failure, Cancer, Atrial Fibrillation are all high risk
- Autoimmune diseases such as systemic lupus erythematosus, and medications such as procainamide, chlorpromazine, and quinidine.
- Oral contraceptives - Estrogen

Physical Exam

- PHYSICAL EXAM
- GENERAL INSPECTION- clubbing in TB or lung cancer
- Skin- Hypothyroid, SLE, Bruises, lesions, petechiae or purpura.
- Weight - Loss in Cancer, HIV, Chronic disease
- VITAL SIGNS- Pulse: Tachycardia from increased cardiac output
- Respiration: Tachypnea from decreased oxygen transport
- BP: Orthostatic if volume depleted
- Temp: Fever in infections and drug or transfusion reactions,
- HEENT- Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva

Physical Exam 2

- HEENT- Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
- LUNG- consider infection, lesion, rub
- CV - new murmer or CHF , Listen for Bruits
- ABDOMINAL- Liver/spleen size, masses, tenderness, surgical scars
- RECTAL- Stool guaic,
- PELVIC/BREAST- Uterine abnormality, Pap smear, Breast nodule
- LYMPHNODES- consider lymphoma, leukemia, infection, connective tissue disease
- EXTR- Homan’s or calf tenderness/swelling

Platelet Problems or Von Willebrand Disease (vWD)

Clotting Factor Disorders

Hemarthrosis

Vascular Wall Defects

Purpura
Testing PVC-Pipes

Platelets – CBC with platelet count
- Do they work – PFA (Bleeding time)
- vWF – abnormal PFA and aPTT (Factor VIII depends on vWF) do vWF analysis
- Clotting Factors – PT and aPTT - if abnormal do Thrombin Time (TT), Mixing study, Factor levels VIII, IX,….
- Chem Profile, UA (Renal or Hepatic causes)
- Pipes – Vasculitis C-Reative Protein, ESR, Biopsy

Tests to Order – Screen for Clotting ability

- CBC, WBC Differential, Cell Morphology
- Platelet Count - 150,000 - 350,000 cu/mm
- Bleeding can occur if < 50,000
- Danger zone < 20,000
- if > 900,000 Clotting too much
- Chem Profile (Hepatic profile – ALT, AST, Indirect Bili in hemolysis, Renal BUN,Creat)

Tests – Bleeding too much

Platelet Tests
- Platelet Function Analysis (PFA) do platelets work?
- Platelet Aggregometry do platelets stick together (IIb- IIIa)
- Used Less -Bleeding Time - (normal 3-8 minutes) is a measure of platelet function and an intact coagulation cascade.

Do if suspect vWD (abnormal PFA and aPTT)
- Von Willebrand Antigen Measurement
- Ristocetin Cofactor Activity (von Willebrand Activity)
- Factor VIII Activity
- Von Willebrand Multimer Analysis

Bleeding Work-up

First pass – CBC, Chem Profile, UA, Platelet Function Analysis (PFA), PT, aPTT
- Chem Profile – Abnormal Liver enzymes or Renal Failure (BUN,Creat)
- UA – Abnormal Renal function
- CBC Platelets Low – Thrombocytopenia
  - Peripheral Smear and or Bone Marrow Biopsy
  - Are they under attack – Platelet antibody studies, HIT assay if on heparin
  - Is the spleen enlarged?

PT or aPTT abnormal
- Von Willebrand analysis
  - Aspirin or other platelet inhibitors
  - Platelets not working right – Platelet Aggregometry, Chem profile (BUN, Creat), Urimaly, – Uremia
  - Dietary/Herbal history – Fish oil, chocolate, red wine garlic…..

- VWF analysis
  - abnormal PFA and aPTT
  - Mixing study – if corrects then measure Factors, if not Inhibitor is present
  - Both abnormal then do TT Thrombin Time for common pathway and also consider DIC

Clotting Tests for bleeding

<table>
<thead>
<tr>
<th>Test/Disease</th>
<th>PT</th>
<th>aPTT</th>
<th>Mixing study</th>
<th>TF</th>
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</thead>
<tbody>
<tr>
<td>Inhibitor of VIII</td>
<td>Normal</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Normal</td>
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<tr>
<td>IX, XI, XII</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Lupus –aPL antibodies</td>
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<tr>
<td>Hemophilia A</td>
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<td>Normal</td>
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<td>VIII</td>
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<td>Reptilase time normal</td>
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<tr>
<td>Low Fibrinogen</td>
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<tr>
<td>Factor VII deficiency</td>
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</table>
Clotting Tests for bleeding

<table>
<thead>
<tr>
<th>Test/Disease</th>
<th>PT</th>
<th>aPTT</th>
<th>PFA</th>
<th>Platelet Ct</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWD</td>
<td>Normal</td>
<td>Increased (VIII)</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemophilia A/B</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>DIC</td>
<td>Increased</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Uremia</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Aspirin NSAIDs</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver Failure - early</td>
<td>Increased</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Low</td>
</tr>
<tr>
<td>Liver Failure - Late/Severe ITP, TTP, HUS, HIT</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Tests – Clotting too much

- Protein S, C, antithrombin III assay,
- Factor V Leiden assay
- Fasting homocysteine level
- Lupus anticoagulant
- Anticardiolipin antibodies
- Prothrombin 20210 mutation test
- Fibrinogen level
- HIT Assay

Tests – Is Clotting going on

- D-Dimer elevation
- Fibrin Split products
- Peripheral smear may show shistocytes (helmet cells)

Differential Diagnosis – Bleeding too much

- C - Cirrhosis/Liver Disease and Coumadin
- A - Aspirin and other drugs NSAIDs
- F - Factor Deficiency - Hemophilia
- D - Disseminated Intravascular Coagulation
- I - Idiopathic Thrombocytopenic Purpura
- P - Platelet Deficiency (TTP, HUS, DIC, Heparin- HIT) or Platelet Dysfunction (vWD)
- S - Scurvy: Vitamin C Deficiency

Von Willebrand Disease

- Most common inherited bleeding disorder
- Found in approximately 1% of the population
- Most individuals are asymptomatic unless a significant bleeding event occurs
- Blood Group O individuals have significantly lower vWF than other groups (30% lower)
- vWF stabilizes Factor VIII so any decrease in vWF will increase aPTT and platelet function analysis will be abnormal

PVC pipes

- Platelets
  - Not enough below 50,000 – production, destruction, sequestration
  - Not working – ASA, NSAIDs, Uremia, Congenital
- Von Willebrands Disease-Type 1 most common
- Clotting Factors
  - Most common: VIII, IX
  - Vitamin K Deficiency, Liver Disease
  - Inhibitors
- Pipes - Vasculitis, Scurvy, Ehlers-Danlos, Heritary Hemorrhagic Telangiectasias, Steroids
  - Palpable Purpura – Sepsis, Meningococcemia, Henoch-Schonlein purpura, Drugs

Von Willebrand Disease

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- vWF stabilizes Factor VIII so any decrease in vWF will increase aPTT and platelet function analysis will be abnormal
**Von Willebrand Disease**
- Measure vWF antigen (vWF:Ag)
  - How much protein is present?
- Measure vWF activity (Ristocetin Cofactor)
  - How well is the protein working?
- Measure Factor VIII activity
  - How well is vWF stabilizing Factor VIII?
- Evaluate pattern of von Willebrand multimers by electrophoresis
- Treat most common cause with DDAVP

**Hemophilia**
- US 13,320 cases of hemophilia A (VIII) and 3,640 cases of hemophilia B (IX).
- Prolonged aPTT with a normal PT
- Bleeding into joints
- Treat with Recombinant Factor replacement (No longer plasma exposure)
- Three types of Hemophilia A – Genetic, vWD, Inhibitor to factor VIII acquired or developed

**Liver Disease**
- The liver is THE site for coagulation factor synthesis (except Factor VIII)
  - Liver failure leads to multi-factorial coagulopathy
    - Decreased coagulation factors
    - Decreased anti-coagulation factors
    - Decreased fibrinogen
    - Decreased platelets
    - Increased D-dimers (interfere with clot formation)
  - Bleeding from liver failure is a major cause morbidity and mortality
  - Give Vitamin K

**Thrombocytopenia**
- Production
  - Nutritional B12 or Folate Deficiency
  - Congenital – Alports syndrome, Fanconi anemia, Wiscott-Aldrich syndrome
  - Marrow damage – aplastic anemia, chemotherapy, drugs, malignancy – myeloma or leukemia, radiation, myelodysplasia
- Destruction
  - Immune – (Positive Platelet Associated Antibody test or HIT assay) ITP, Drug, HIV, SLE, HIT
  - Non-Immune – DIC, TTP, Preeclampsia, HELLP syndrome Anti-phospholipid syndrome
  - Sequestration - Liver, spleen, marrow -myelofibrosis, cancer

**ITP - Idiopathic Thrombocytopenic Purpura**
- In children linked to viral infection
  - platelet-associated antibodies
  - 80% rapid remission, and does not recur
    - Treatment: steroids and IVIG
  - 10% to 20% develop chronic ITP
    - splenectomy works in 70%
- Adults linked to HIV and Hepatitis C
  - 50% develop chronic ITP
  - Same treatments

**TTP, HUS, DIC, get HEELP!**
- TTP – Thrombotic Thrombocytopenia Purpura with ADAMTS-3 and big vWF
- HUS – Hemolytic Uremic Syndrome with E.Coli 0157:h7
- DIC – Disseminated Intravascular Coagulation – Sepsis, Burns, Trauma
- All of these need ICU/expert care: PUNT to Hematologist
HELLP - Pregnancy
- Hemolysis (high indirect Bilirubin, LDH)
- Elevated Liver Enzymes (AST, ALT)
- Low Platelets
- Severe preeclampsia (BP increased and proteinuria) increased maternal and fetal mortality
- 1 per 1000 pregnancies up to 20% with preeclampsia/eclampsia at 28 – 36 weeks gestation
- Rx Support and Deliver Baby

Thrombocytopenia – Not HIT

<table>
<thead>
<tr>
<th>Issue/Disease</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
<th>TTP</th>
<th>HUS</th>
<th>DIC</th>
<th>HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Children</td>
<td>Adults</td>
<td>Adults</td>
<td>Children</td>
<td>Any</td>
<td>Pregnant</td>
</tr>
<tr>
<td>Cause</td>
<td>Immune</td>
<td>Immune</td>
<td>ADAMTS-3 and tPA</td>
<td>Septic, Bum, trauma</td>
<td>Pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>PFP/PTT</td>
<td>Bleeded</td>
<td>Bleeded</td>
<td>Normal Both</td>
<td>Increased Both</td>
<td>+/- Both</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>both</td>
<td>+/- both</td>
</tr>
<tr>
<td>Hemolysis*</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Organ failure</td>
<td>no</td>
<td>no</td>
<td>CNS &gt; Renal</td>
<td>Renal &gt; CNS</td>
<td>All possible</td>
<td>Liver</td>
</tr>
<tr>
<td>Treatment</td>
<td>None – IVG, Steroids</td>
<td>Steroids</td>
<td>Plasma Exchange + Support, No Plts</td>
<td>FFP, Cryo, platelets</td>
<td>Deliver (MgSO4)</td>
<td></td>
</tr>
</tbody>
</table>

Bleeding Therapy Summary
- Low platelets immune attack – Corticosteroids, splenectomy
- Low platelets – Transfuse platelets (not if HIT, TTP, HUS +/- ITP) thrombopoietin
- vWD – DDAVP
- Hemophilia A – Factor VIII, DDAVP
- DIC/Multiple clotting factors low – FFP or Cryo
- Liver Disease, Coumadin excess – Vitamin K
- HIT – Stop heparin and use heparinoid
- Reverse heparin - protamine

Clotting too much
- Clotting too much - Pulmonary Embolus, Deep Vein Thrombophlebitis, Stroke, Myocardial Infarction

Virchows Triad

<table>
<thead>
<tr>
<th>Stasis</th>
<th>Clot</th>
<th>Hyper-coagulable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Injury</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypercoagulability – PVCs
- Platelets
  - Too many
  - Overactive
- Vascular Injury
- Clotting Factors
  - Anti-clotting factors deficient/ not working
  - Too many factors/triggers
- Stasis and Surgery
Differential Diagnosis - Hycoagulability

- The mnemonic is: 5 Ps HAD CAUSED CLOTS
- P - Pregnancy - Increased blood viscosity, fibrinogen and factor VIII, Post Partum - Hypercoaguable state
- P- Prothrombin 20210 mutation, Protien S, C, deficient – Inherited
- P - Polycythemia vera - increased viscosity
- P - Paroxysmal Nocturnal Hemoglobinuria
- S - Smoking

Heparin-induced thrombocytopenia (HIT)

- Due to an antibody against heparin
- Occurs in 1-3% of adult patients receiving heparin for 1 week or more. heparin binds to platelet factor 4 (PF4), forming a highly reactive antigenic complex on the surface of platelets
- An unexpected fall in platelet count occurring 4-14 days after heparin exposure
- Platelet count usually falls by 50%
- Mean platelet count 60,000 – 100,000/uL
- Platelets become activated and induce clotting
- Associated with thrombosis - 10-30% develop arterial or venous thromboses (usually DVTs or PEs)
- Of those forming a clot, 30% will die or require amputation
- Platelet counts should be monitored while patient is on heparin therapy
- HIT Assay

Who ya gonna Call?

Clot Busters

tPA (tissue Plasminogen Activator)

Drug Clot Busters

tPA – reteplase, alteplase, tenecteplase
Heparin

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active
Common Pathway
X to X active with V present
II Prothrombin to Thrombin
I Fibrinogen to Fibrin

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor
Test = PT
VII to VII active
XIII to XIII active

Antithrombin III

Protamine reverses Heparin

Thrombin Inhibitors

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active
Common Pathway
X to X active with V present
II Prothrombin to Thrombin
I Fibrinogen to Fibrin

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor
Test = PT
VII to VII active
XIII to XIII active

Antithrombin III

Coumadin

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active
Common Pathway
X to X active with V present
II Prothrombin to Thrombin
I Fibrinogen to Fibrin

Extrinsic Pathway – outside the cut in the plasma
Vitamin K - Liver dependant
Test = PT
VII to VII active + III Tissue factor
XIII to XIII active

Antithrombin III

LMW Heparin

Danaparoid, Fondaparinux

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active
Common Pathway
X to X active with V present
II Prothrombin to Thrombin
I Fibrinogen to Fibrin

Extrinsic Pathway – outside the cut in the plasma
LMW Heparin

Danaparoid – (Orgaran)
Fondapurix

Protamine reverses Heparin

Novel Oral Anticoagulants - Thrombin and Factor Xa inhibitors

NOACs

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
XI to XI active
IX to IX active
VIII to VIII active
Common Pathway
X to X active with V present
II Prothrombin to Thrombin
I Fibrinogen to Fibrin

Apixaban
Rivaroxaban
Edoxaban
Dabigatran (DTI)

May replace Coumadin with fewer side effects. Risk of MI may be increased

Reversal agent / antidote available for major bleeding
4 none

The new oral anticoagulants for VTE – Comparison (Advantages, Disadvantages)

Dabigatran
(Pradaxa)
Rivaroxaban
(Xarelto)
Apixaban
(Eliquis)
Edoxaban
(Savaysa)

Started immediately upon diagnosis of VTE
yes
yes
yes
yes

Dosing
Twice daily
Twice daily
Twice daily
Twice daily

Renal clearance
80%
33%
25%
35%

Efficacy compared to warfarin (treatment VTE)
same
same
same
same

Safety compared to warfarin (inpatient VTE)
same
same
same
same

Reversal available to warfarin (inpatient VTE)
same
same
same
same

Reversal agents available for major bleeding
1
1
1
1

FDA approved for VTE treatment
yes
yes
yes
yes

1 “Major bleeding” same as with warfarin in DVT trial, but less in PE trial
2 Less “major bleeding” with apixaban
3 Less “clinically relevant bleeding” with edoxaban, same “major bleeding”
4 Reversal agents are in early clinical development for all 4 anticoagulants

Sources: http://professionalsblog.clotconnect.org/2015/01/08/4th-noac-fda-approved-for-dvt-pe-and-atrial-fibrillation saysas-

9/8/2017

Platelet Activation Blockers

- **Vorapaxar** – Zontivity, protease-activated receptor-1 (PAR-1) Thrombin antagonist
- **Abciximab** (ReoPro), **Tiriliziban** (Aggrastat), and **Eptifibatide** (Integrelin).

**Von Willebrand Factor**

- Factor vWF

**Arachidonic acid**

- Collagen, TXA2, Thrombin, TXA2

**Aspirin, NSAIDS**

- COX, TXA2 and ADP released

**Endothelium**

- ADP receptor

**TXA2 and ADP released**

- Aspirin, NSAIDS, Dipyridamole (Persantine and Aggrenox – ASA combo)

**Von Willebrand Factor**

- Factor vWF

**Endothelium**

- ADP receptor

**TXA2 and ADP released**

- Aspirin, NSAIDS, Dipyridamole (Persantine and Aggrenox – ASA combo)

**ADP receptor**

- Ticlopidine

**TXA2 and ADP released**

- Clopidogrel (Plavix), Prasugrel (Effient), Ticagrelor, Vorapaxar

**2B3A blockers IV**

- Stop Clotting and Clot prevention – (DVT, PE, MI, AFib, Genetic…)

- Heparin (Reversed with Protamine)

- LMW Heparin and factor Xa blockers

- Coumadin (Reversed with Vitamin K)

- New Thrombin and F10a inhibitors

**Anti-Clotting Therapy**

- To block Platelets (MI and Stoke)

- **To avoid**

- Antiplatelet agents – aspirin or clopidogrel, or aspirin + dipyridamole New agents Prasugrel (Effient), Ticagrelor, Vorapaxar

- **2B3A blockers IV**

- Stop Clotting and Clot prevention – (DVT, PE, MI, AFib, Genetic…)

- Heparin (Reversed with Protamine)

- LMW Heparin and factor Xa blockers

- Coumadin (Reversed with vitamin K)

- New Thrombin and F10a inhibitors

**To Bust Clots** (PE, MI, Thrombotic Stroke)

- tPA

**Lymphadenopathy**

- L- Lymphoma, Leukemia

- Y-Yersinia Pestis (Plague)

- M-Mononucleosis or CMV

- P-Parasite - Toxoplasmosis

- H-Hodgkins Disease or HIV infection

- N-Neoplasm or metastasis

- O-Obvious local infection or inflammation

- -Other systemic infections: Hep B, Rubella, Tularemia, Cat scratch

- D-Drug - Procainamide (Pronestyl), Phenylbutylamine (Dilantin)

- E-Endocrine - Addisons, Hypothyroid

- S- Syphils

- -SLE/Rheumatoil arthrits

- -Serum sickness

- -Sarcoid

**Mono - continued**

**Hodgkins Disease**

- Emory University Physician Assistant Program

- **Lymphadenopathy**

- **Mononucleosis**

- **Hodgkins Disease**

- Emory University Physician Assistant Program
Multiple Myeloma
- Symptoms and Signs - Itching, Bone pain, weakness, anemia, lytic bone lesions, increased protein, M-Spike, Bence Jones protein in urine, Renal failure, rouleaux formation

Primary - Polycythemia vera
- Sx: Pruritis HA, Dizziness, vertigo, visual disturbance, tinnitus
- PE: Rubor, BP increased, splenomegaly or hepatomegaly
- Lab: HCT >55 Increased platelets and WBC count
- RX: Phlebotomy, Hydroxyurea

Secondary Polycythemia
- Increase erythropoietin due to hypoxia (COPD, smokers, high altitude), tumors of kidney, ovary, liver, brain, drugs: steroids, androgen, dehydration, burns
- PE: No hepatosplenomegaly unless tumor

Leukemia and Lymphoma
- ALL: Acute Lymphocytic Leukemia (Usually in Children)
- AML: Acute Myelogenous Leukemia
- CLL: Chronic Lymphocytic Leukemia
- CML: Chronic Myelogenous Leukemia
- Lymphomas, Hodgkin's
- Hx: Fatigue, anorexia, wt loss, fever, bone pain, headaches, lymphadenopathy, non healing infections, thrush, bleeding
- PE: Pallor, gingival hyperplasia, Candida infections, lymphadenopathy, hepatosplenomegaly, lung infiltrates, bleeding, bruising
- Lab: CBC, elevated WBC, low platelets, low Ht, WBC Differential, Chem 18, Bone Marrow Biopsy
- Philadelphia Chromosome seen in CML
- Auer bodies or rods in AML
- Lymph node BX: Reed-Sternberg cells in Hodgkin's Disease
- CT - MRI chest and abdomen
- CXR - Chest Infiltration, pneumonias
- RX: Chemotherapy, Bone Marrow Transplant

ALL - Blasts