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- Education: 1977 graduate in Health Systems, Georgia Institute of Technology
- 1979 graduate of the Emory University PA Program
- 2006 graduate of the Career Masters in Physician Assistant at Emory

- Currently: Faculty member of the Emory PA Program, Advanced Didactic Co-Coordinator, Awarded the Clinical Teacher of the Year Award by the graduating class of 1993, 2002 AAPA Paragon Teacher of the year award, SAAPA Presidents award, Course Director of the Behavioral Medicine and Professional issues courses for the Emory didactic PA students.

Heme Review

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Blood

- Blood has red cells (erythrocytes)
- White cells (leukocytes)
- Platelets (thrombocytes)

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 -8 %
- 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
- Contains the protein hemoglobin
- Made from iron, folic acid, vitamin B12
- Made in the bone marrow

Red Blood Cells
- Red cells look like doughnuts that are very flexible

Microscope View

Red Blood Cells - Shape
- Red cells travel through very narrow blood vessels

Red Blood Cells
- Red Cell Flow
- Blood Vessel
Hemoglobin, the main protein in red cells holds four oxygen molecules.

Red Blood Cells - Adult Hemoglobin

- Oxygen

Red Blood Cells - Marrow

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

Red Blood Cells - Retics

- 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 Blood Cells - Recycled

- Red cells are recycled in the spleen and liver. The iron and protein 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 – Erythropoetin, low iron

Erythropoetin

- Made in the liver
- Erythropoetin 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

- Check for pallor, jaundice, splenomegaly, lymphadenopathy.
Emory University Physician Assistant Program

Sclera

Spoon Nails – Fe Def.

Glossitis and Chelosis – Fe and B12

Physical Exam

1. 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
2. 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,
3. HEENT:
   - Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
   - Mouth: Glossitis and angular stomatitis in iron or B12 deficiency
4. NECK:
   - Thyroid enlargement or nodules, lymph nodes
5. HEART:
   - Increased output/murmur - consider high output failure
6. LUNG:
   - consider infection, lesion
7. ABDOMINAL:
   - Liver/spleen size, masses, tenderness, surgical scars
8. RECTAL:
   - Stool guaiac, prostate exam in men
9. PELVIC/BREAST:
   - Uterine abnormality, Pap smear, Breast nodule
10. LYMPH NODES:
    - consider lymphoma, leukemia, infection, connective tissue disease
11. 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 Thalassemia</td>
</tr>
</tbody>
</table>
**Red Cell Indices MCH, MCHC**

- **MCH** - Mean Corpuscular Hemoglobin: 27 - 32 pg
  - Low = Hypochromic
  - High = Hyperchromic

- **MCHC** - Mean Corpuscular Hemoglobin Concentration: 30 - 36 gm/dl
  - Low = R/O Fe def.
  - High = Spherocytosis

**RBC Morphology**

- **SIGNIFICANCE**
  - **Burr Cells**: Uremia, Low K, artifact, Ca stomach, PUD
  - **Spur Cell**: Post-splenectomy, Alcoholic liver disease
  - **Stomatocyte**: Hereditary, Alcoholic liver disease, Hereditary, Immune hemolytic anemia, water dilution, post-transfusion
  - **Spherocyte**: TTP, DIC, vasculitis, glomerulonephritis, heart valve, burns
  - **Spherocyte - helmet**: Hereditary, Thalassemia, Fe Def.
  - **Eliptocyte - Ovalocyte**: Myeloplastic, megaloblastic anemias
  - **Sickle Cells**: Sickle cell disease
  - **Target Cells**: Thalassemias, hemoglobinopathies
  - **Microcytes**: Thalassemia, Iron Def., Lead Toxic
  - **Macrocytes**: B12 of Folate Def.
  - **Parasites**: Malaria, Babesiosis

**Platelets**

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

**Correcting the Retic**

- **absolute reticulocyte count (measured)**
  - reticulocyte (%) = absolute number of reticulocytes × number of RBC × 100
  - reticulocyte index = % reticulocytes × 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 index = Raw Retic percentage x 46 Male or 41 Female

- 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% / 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

- **MCV**
  - >94
  - 80-94
  - <80

- **Macro**
- **Normo**
- **Micro**

- **Extrinsic**
- **Intrinsic**

- **Coombs**
  - Positive
  - Negative

- **Drug**
  - Warm
  - Cold

- **Antibody**
  - 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
  - HBEPO = 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
- 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
- E-Endocrine: Hypothyroid, hypoadrenal, hypoandrogen

**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 erythropoetin production causing decreased bone marrow production
- Can monitor erythropoetin 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
**Macrocyclic Anemia**

- MACROCYTIC = "BIG FAT RED CELLS"
- B - B12 Malabsorption
- S - Sideroblastic (Alcohol)
- T - Thalassemia
- D - Dietary
- C - Chemotherapeutic Drugs
- E - Erythroleukemia
- L - Liver Disease
- I - Inherited
- G - Gastrointestinal disease or surgery
- H - Hemoglobinopathy (sickle cell disease)

**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
  - 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
- 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 (Heart disease?)
- Rx – Folate 1mg po qD

**Hemolytic Anemia**

- HEMOLYTIC = "HEMATOLOGIST"
- H - Hemoglobinopathy: sickle cell disease
- - Hemoglobinuria: Paroxysmal Nocturnal Hemoglobinuria
- 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 - Ovalocytosis
- L - Liver disease
- G - G6PD Glucose-6-Phosphate Dehydrogenase Deficiency
- I - Infection: malaria, babesiosis
- S - Spleenic destruction in hypersplenism

**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, Splenomegaly)
Hemolytic Signs

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

Hemolytic Tests

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

anti-CD59 and flow cytometry for Paroxysmal nocturnal hemoglobinuria

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

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

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, M. pneumoniae, influenza B, Cytomegalovirus (CMV), rubella virus, varicella-zoster virus (VZV), parovirus 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

Keep Blood in the Tubing PVC-pipes

Clotting Process

Clotting system activated
Endothelium

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

Collagen, Tissue Factor (TF)

Blood vessel lumen

Endothelial Cells

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
- Thrombopoietin made in liver stimulates production
- Fragments of megacaryocytes
- No nucleus
- 67% in circulation
- 33% in spleen storage
- Life 8 – 10 days

Platelet Activation

- von Willibron Factor vWF
- Arachidonic acid
- TXA2
- TXA2 and ADP released, also PF4
- Increase cAMP inhibits activation

Fibrinogen attaches to other platelets

Platelet Activation

The Shape of Platelets

Flowing Platelets
Activated Platelets
Aggregated - Active Platelets

The Shape of Platelets

Clotting Cascade - Factors

Intrinsic Pathway – Inside the cut Endothelial Injury
Test = aPTT
XII to XII active
X to XI active
X to IX active
VIII to VIII active
vWF stabilizes Factor VIII

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

Common Pathway
X to Xactive with V present
II Prothrombin to Thrombin
Fibrinogen to Fibrin

XIII to XIII active stabilizer to crosslink

9/7/2012
**Built in Clot Blockers and Busters**

**Intrinsic Pathway**
- Inside the cut
- Endothelial Injury
  - 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
  - VII to VII active

**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

**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.

**Increased Clotting Presentation**

- Deep Vein Thrombophlebitis (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**

- 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, Recent Surgery, Diabetes, Congestive Heart Failure, Cancer, Atrial Fibrillation are all high risk
- Autoimmune diseases such as systemic lupus erythematosis, 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
  - Respirations: 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 guaiac,
- 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 of 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 Bill in hemolysis, Renal BUN, Creat)

Tests to Order – Screen for Clotting ability

- Clotting Cascade Tests
  - PT -Prothrombin Time - +/- 2 of control = 11 - 16 sec. Extrinsic system monitor for coumadin therapy. INR is International Normalization Ratio. 1 is normal, 2.3 for Coumadin Therapy, 2.5 - 3.5 if heart valve (if abnormal do Mixing Study)
  - aPTT - activated Partial Thromboplastin Time- 25 - 38 sec. Intrinsic system. Used to monitor Heparin therapy (if abnormal do Mixing study, Factor analysis and consider vWD)
  - Mixing Study – do if abnormal PT or aPTT (add normal plasma to patient plasma re do PT and aPTT) – if PT or aPTT do not correct then there is an inhibitor present and not a factor deficiency. If PT or aPTT correct look for a factor deficiency
  - If both PT and aPTT are abnormal do Thrombin Time (fibrinogen or heparin), Reptilase Time (normal with heparin)

Tests – Bleeding too much

- Platelet Tests
  - Platelet Function Analysis (PFA) do platelets work?
  - Platelet Aggregometry do platelets stick together (llb- illa)
  - 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,
  - 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?
  - Platelet Function Analysis abnormal
  - Von Willebrand analysis
  - Aspirin or other platelet inhibitors
  - Platelets not working right – Platelet Aggregometry, Chem profile (BUN, Creat), Urinalysis – Uremia
  - Dietary/Herbal history – Fish oil, chocolate, red wine, garlic…..
  - PT or aPTT abnormal
  - Von Willebrand analysis (if aPTT abnormal and PFA abnormal)
  - Mixing study – if corrects then measure Factors, if not present Heparin - then do TT Thrombin Time for common pathway and also

**Clotting Tests for bleeding**

<table>
<thead>
<tr>
<th>Test/Disease</th>
<th>PT</th>
<th>aPTT</th>
<th>Mixing study</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor of VIII (IX, XI, XII), Lupus –aPL antibodies</td>
<td>Normal</td>
<td>Increased</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemophilia A VIII</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Hemophilia B IX</td>
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<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
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<tr>
<td>DIC</td>
<td>Increased</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Increased</td>
</tr>
<tr>
<td>Heparin</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
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<tr>
<td>Low Fibrinogen</td>
<td>Increased</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>Increased</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
- L - Leukemia, Lupus anticoagulant
- 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
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, Hereditary Hemorrhagic Telangiectasias, Steroids
  - Palpable Purpura – Sepsis, Meningococcemia, Henoch-Schonlein purpura, Drugs

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

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 Thrombocytopenic 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

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

Clothing too much
- Cloaking too much - Pulmonary Embolus, Deep Vein Thrombophlebitis, Stroke, Myocardial Infarction
Virchow’s Triad

- Stasis
- Vascular Injury
- Hypercoagulability

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 - Hypercoagulable state
- P - Prothrombin 20210 mutation,
- Protein S, C, deficient – Inherited
- P - Polycythemia vera - increased viscosity
- P - Paroxysmal Nocturnal Hemoglobinuria
- S - Smoking

Differential Diagnosis - Hycoagulability

- H – HIT Heparin Induced Thrombocytopenia
- H – H Hyperhomocysteinemia
- A – Antithrombin III Deficiency
- D – Dysfibrinogenemia
- C – CHF or Congestive Heart Failure
- A – Antiphospholipid Syndrome
- S – Surgery – Orthopedic is greatest risk
- E – Estrogen – Oral Contraceptives or replacement Rx
- D - Diabetes

Differential Diagnosis

- C - Cancer - pro-coagulant effects, Trousseau’s syndrome
- L – Leiden Factor V mutation – Activated Protein C resistance
- O – Obesity and Cholesterol elevation
- T - Trauma, Travel (immobility) - Stasis of blood flow and release of tissue thromboplastin in trauma
- T – Thyroid disease hyper or hypo
- S - Sepsis

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

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

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

Common Pathway
X to X active with V present
II Prothrombin to Thrombin
III Fibrinogen to Fibrin

Plasminogen via t-PA to Plasmin

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

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

Common Pathway
X to X active with V present
II Prothrombin to Thrombin
III Fibrinogen to Fibrin

Heparin

Protamine reverses Heparin

LMW Heparin
Danaparoid, Fondaparinux

LMWH
dalteparin – (Fragmin)
tinzaparin – (Innohep, Logiparin)
enoxaparin (Lovenox, Clexane)

Bivalirudin – Angiomax
Lepirudin- Refludan
Argatroban – Antithrombin III - Trombate III

Coumadin

Reverse with Vitamin K

Common Pathway
X to X active with V present
II Prothrombin to Thrombin
III Fibrinogen to Fibrin

Vitamin K
Liver dependant
Test = PT
VII to VII active + III Tissue factor

Common Pathway
X to X active with V present
II Prothrombin to Thrombin
III Fibrinogen to Fibrin

Coumadin blocks the liver -Vitamin K dependent factors

XIII to XIII active stabilizer to crosslink fibrin
New Oral Thrombin and Factor Xa inhibitors

May replace Coumadin with fewer side effects. All 3 are in extensive clinical trials now.

Platelet Activation Blockers

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 Xactive with V present
II Prothrombin to Thrombin
1 Fibrinogen to Fibrin

Apixaban
Rivaroxaban
Dabigatran

May replace Coumadin with fewer side effects. All 3 are in extensive clinical trials now.

Anticoagulant Therapy

To block Platelets (MI and Stroke)

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

Lymphadenopathy

- L- Lymphoma, Leukemia
- Y-Yersinia Pestis (Plague)
- M-Mononucleosis or CMV
- P-Parasite - Toxoplasmosis
- H-Hodgkin's Disease or HIV infection
- N-Neoplasm or metastasis
- O-Obvious local infection or inflammation
- -Other systemic infections: Hep B, Rubella, Tularaemia, Cat scratch
- D-Drug - Procainamide (Pronestyl), Phenytoin (Dilantin)
- E-Endocrine - Addison’s, Hypothyroid
- S- Syphilis
- -SLE/Rheumatoid arthritis
- -Serum sickness
- -Sarcoid

Mononucleosis

 Mono - continued
Hodgkin's Disease

- Symptoms and Signs: Itching, Bone pain, weakness, anemia, lytic bone lesions, increased protein, M-Spike, Bence Jones protein in urine, Renal failure

Multiple Myeloma

- Symptoms and Signs:
  - Pruritis
  - HA, Dizziness, vertigo, visual disturbance, tinnitus
- Physical Examination:
  - Rubor
  - BP increased
  - Splenomegaly
- Laboratory:
  - HCT >55
  - Increased platelets and WBC count
- Treatment:
  - Phlebotomy
  - Hydroxyurea

Primary Polycythemia

- Increase erythropoietin due to hypoxia (COPD, smokers, high altitude), tumors of kidney, ovary, liver, brain, drugs: steroids, androgen, dehydration, burns
- Physical Examination:
  - No hepatosplenomegaly unless tumor
- Laboratory:
  - CBC: elevated WBC/low platelets, low Hct
  - WBC Differential, Chem 18, Bone Marrow Biopsy
- Philadelphia Chromosome seen in CML
- Auer bodies or rods in AML

Secondary Polycythemia

- Increase erythropoietin due to hypoxia (COPD, smokers, high altitude), tumors of kidney, ovary, liver, brain, drugs: steroids, androgen, dehydration, burns
- Physical Examination: No hepatosplenomegaly unless tumor
- Laboratory:
  - CBC: elevated WBC/low platelets, low Hct
  - WBC Differential, Chem 18, Bone Marrow Biopsy

Leukemia and Lymphoma

- ALL: Acute Lymphocytic Leukemia (Usually in Children)
- AML: Acute Myelogenous Leukemia
- CLL: Chronic Lymphocytic Leukemia
- CML: Chronic Myelogenous Leukemia
- Hodgkin's
- Symptoms and Signs:
  - Fatigue, anorexia, wt loss, fever, bone pain, headaches, lymphadenopathy, non healing infections, thrush, bleeding
  - Physical Examination:
  - Pallor
  - Gingival hyperplasia, Candida infections, lymphadenopathy, hepatosplenomegaly, lung infiltrates, bleeding, bruising
  - Laboratory:
  - CBC, elevated WBC, low platelets, low Hct, 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 Inflation, pneumonias
  - RX: Chemotherapy, Bone Marrow Transplant