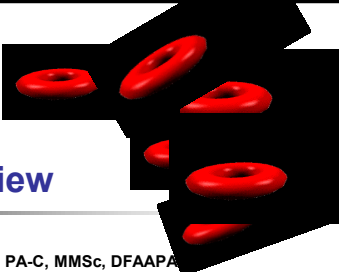



Heme Review






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Disclosure

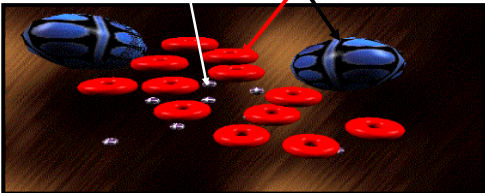
- I have nothing to disclose except
 - I do work for food
 - I promote giving Blood





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Blood

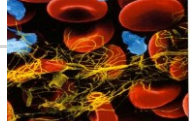


- Blood has red cells (erythrocytes)
- White cells (leukocytes)
- Platelets (thrombocytes)




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Blood Components

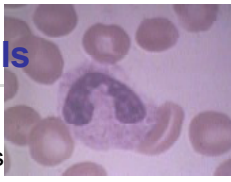
- Plasma 54%
- White cells and platelets 1%
- Red Cells 45%






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White Blood Cells

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



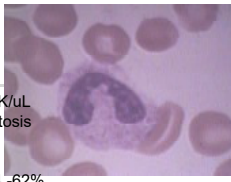
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White Blood Cells

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

WBC Differential

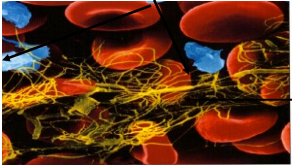
Neutrophils - Segs	54 - 62%
Neutrophils - Bands	3 - 5%
Lymphocytes - Lymphs	25 - 33%
Monocytes - Monos	3 - 7%
Eosinophils - Eos	1 - 3%
Basophils - Basos	0 - 0.75%
Atypical Lymphs	0




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Platelets

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





Fibrin



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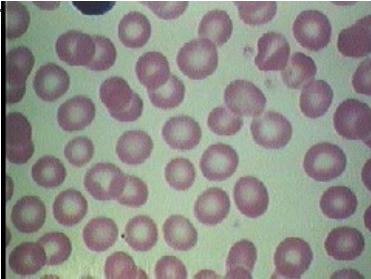

Red Blood Cells

- 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

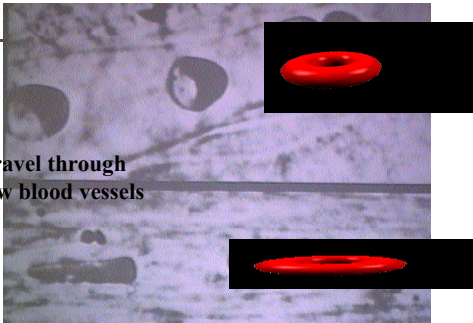
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Microscope View





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Red Blood Cells - Shape



Red cells travel through very narrow blood vessels

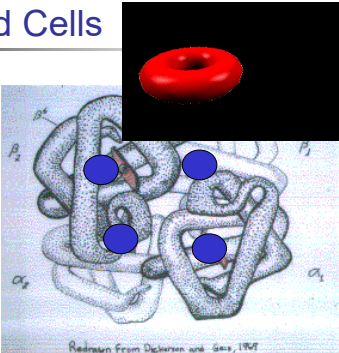



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Red Blood Cells

- Oxygen


Hemoglobin, the main protein in red cells holds four oxygen molecules

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Red Blood Cells - Adult Hemoglobin

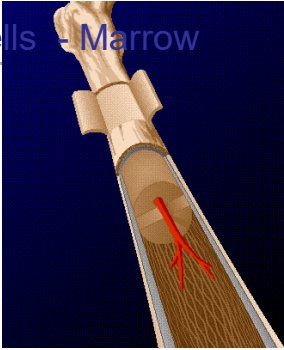

Chromosome 16		Chromosome 11			
Alpha	Alpha	Gamma	Gamma	Delta	Beta
Alpha	Alpha	Gamma	Gamma	Delta	Beta
Alpha	Alpha	97% = Hemoglobin A			
Beta	Beta				
Alpha	Alpha	1% = Hemoglobin F (Fetal)			
Gamma	Gamma				
Alpha	Alpha	2% = Hemoglobin A2			
Delta	Delta				



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Red Blood Cells - Marrow


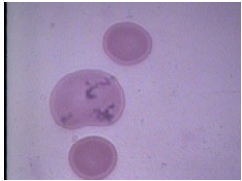
Red cells, white cells and platelets are made in the bone marrow

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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.

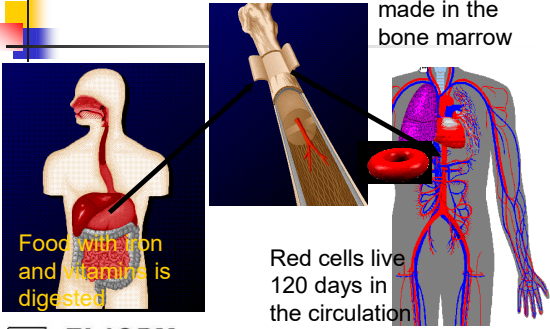
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Red Blood Cells

Red cells are made in the bone marrow

Food with iron and vitamins is digested

Red cells live 120 days in the circulation



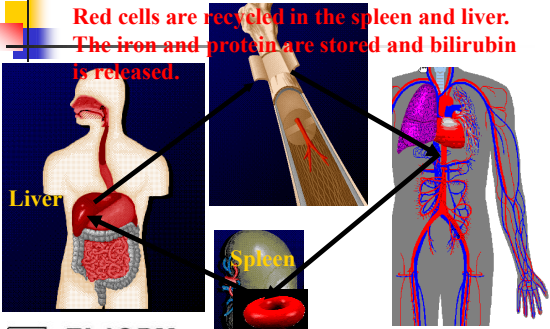
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Red Blood Cells - Recycled

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

Liver

Spleen



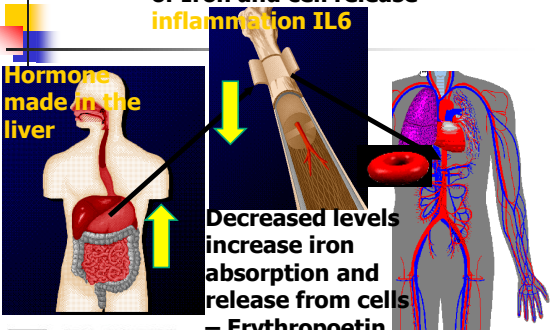
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Hepcidin

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

Hormone made in the liver

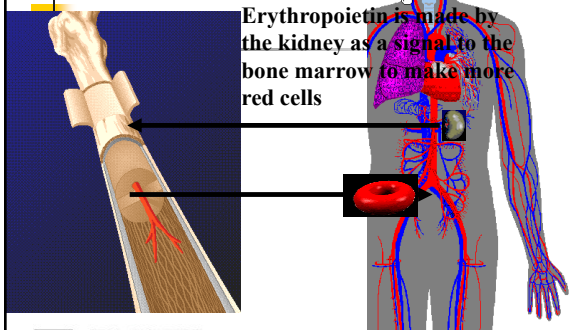
Decreased levels increase iron absorption and release from cells - Erythropoietin, low iron



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Red Blood Cells - The Kidney

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



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The History

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



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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.



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The History -3

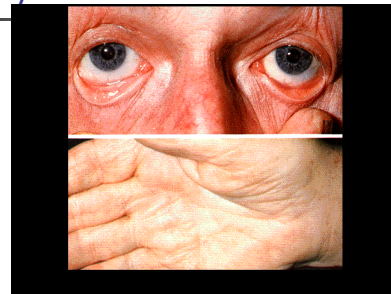
- - Family history of blood cell or bleeding disorder: consider Sickle Cell disease, G6PD, Thalassemia, Hemophilia, von Willebrand
- - History of jaundice, transfusion, new medication, infection - consider hemolytic process
- - History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease,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



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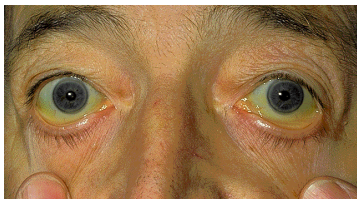
Physical Exam



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Sclera



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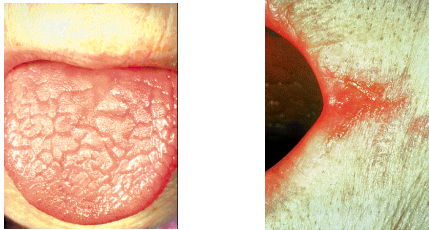
Spoon Nails – Fe Def.



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Glossitis and Chelosis – Fe and B12



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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: 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
 - 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
- LYMPHNODES:** consider lymphoma, leukemia, infection, connective tissue Disease
- NEUROLOGIC:** Decreased vibratory and position sense in B12 deficiency

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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



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CBC- Red Cell Measures

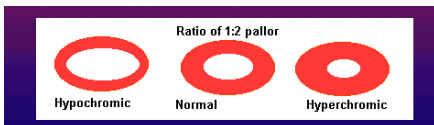
PARAMETER	NORMAL ADULT	COMMENTS
HB - Hemoglobin	Male= 15.5 +/- 2 mg/dl Female = 13.5 +/- 2	Low = Anemia High = polycythemia
HCT - Hematocrit	Male= 46.0 +/- 6% Female= 41.0 +/- 6%	" "
RBC - Red Blood Cell Count	Male = 4.3 - 5.9 Million/uL Female = 4.0 - 5.2 "	" High in Tha

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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

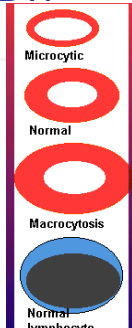
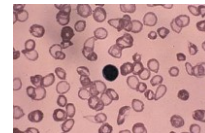


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Red Cell Indices MCV - RDW

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)



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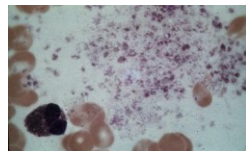
RBC Morphology


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,
Spherocyte	Hereditary, Immune hemolytic anemia, water dilution, post-transfusion
Shistocyte - helmet	TTP, DIC, vasculitis, glomerulonephritis, heart valve, burns
Eliptocyte - Ovalocyte	Hereditary, Thalassemia, Fe Def., Myelophthistic, megaloblastic anemias
Rouleaux formation	Multiple Myeloma
Target Cells	Thalassemias, hemoglobinopathies
Microcytes	Thalassemia, Iron Def., Lead Toxic,
Macrocytes	B12 of Folate Def.
Parasites	Malaria, Babesiosis

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Platelets

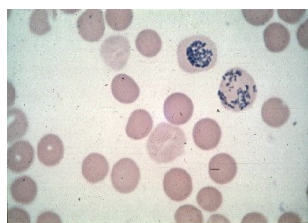
- Platelet Count 150 - 400 K cell/uL
- Low = Thrombocytopenia
- High = Thrombocytosis




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Retics or Reticulocyte count


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



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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

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Corrected Retic Count

$$\text{Retic index} = \frac{\text{Raw Retic Percentage}}{\text{Pt's Hematocrit}} \times 46 \text{ Male or } 41 \text{ Female}$$

- 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% × 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)


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Diagnostic Pathway

Reticulocyte Production Index

```

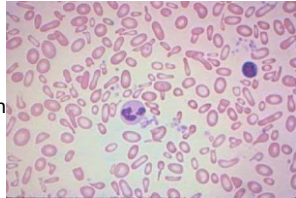
    graph TD
      RPI[Reticulocyte Production Index] --> D2["<2 Decreased Production"]
      RPI --> G2[">2 Increased Loss"]
      
      D2 --> RCI["Red Cell Indices MCV"]
      RCI --> RCI94[">94 Macro"]
      RCI --> RCI80["80-94 Normo"]
      RCI --> RCI80["<80 Micro"]
      
      G2 --> Hemolysis
      G2 --> Bleeding
      
      Hemolysis --> Extrinsic
      Hemolysis --> Intrinsic
      
      Extrinsic --> CoombsPositive["Coombs Positive"]
      Extrinsic --> CoombsNegative["Coombs Negative"]
      
      CoombsPositive --> Drug
      CoombsPositive --> WarmAntibody["Warm Antibody"]
      CoombsPositive --> ColdAntibody["Cold Antibody"]
      
      Intrinsic --> Membrane
      Intrinsic --> Hb
      Intrinsic --> Enzyme
    
```

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Microcytic

■ MICROCYTIC = "TICS"

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



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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
- HBELP = Hemoglobin Electrophoresis
- Lead level if exposed

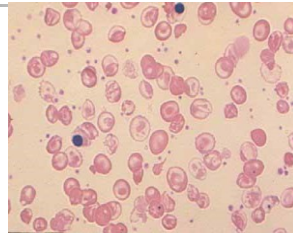


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Thalassemia Syndromes.

- 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

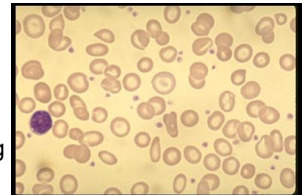


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Iron deficiency

- 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



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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....

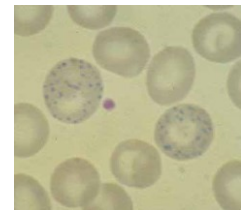


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Sideroblastic

- 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



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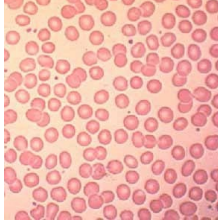
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Normocytic Anemia

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



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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



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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



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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



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Macrocytic Anemia

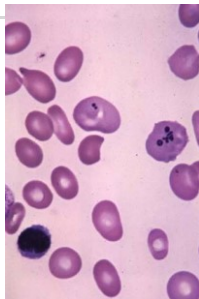
MACROCYTIC = "BIG FAT RED CELLS"

- **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
- D-Dietary

- C-Chemotherapeutic Drugs
- E-Erythro Leukemia
- L- Liver Disease
- L- Lesch-Nyhan Syndrome
- S-Splenectomy



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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.



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B12 Cobalamin Deficiency

Physical signs include edema, pallor, jaundice, smooth tongue, decreased vibratory and position sensation

Hypersegmented polys

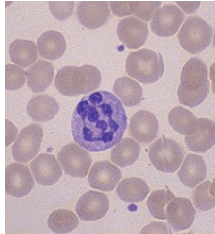
Low serum B12 level

Metformin, Gastric bypass, or PPI as cause?

Methylmalonic acid and homocysteine levels elevate early

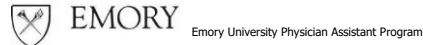
Pernicious anemia - anti- intrinsic factor antibodies Schilling's test

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



Folate Deficiency

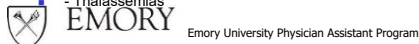
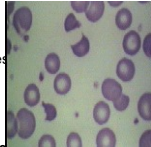
- Causes - liver disease, diet vitamin B12 deficiency, and drugs such as methotrexate, ethanol, and dilantin.
- Lab – low serum and RBC Folate - always check B12 (needed for conversion)
- elevated homocysteine
- Rx – Folate 1mg po qD



Hemolytic Anemia

HEMOLYTIC = "HEMATOLOGIST"

- H-Hemoglobinopathy: sickle cell disease**
 - 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
- O-Osmotic fragility in Hereditary spherocytosis and in Hereditary Elliptocytosis
- G-G6PD Glucose-6-Phosphate Dehydrogenase Deficiency**
 - I-Infection: malaria, babesiosis
 - S-Splenic destruction in hypersplenism
- T-Transfusion**
 - Thalassemias



Hemolysis (HIT)

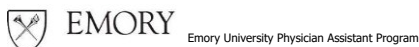
- Hereditary (HEM)**
 - Hemoglobin (sickle cell, thalassemia)
 - Enzyme (G6PD deficiency)
 - Membrane (Spherocytosis, Elliptocytosis)
- Immune attack** – Coombs positive (transfusion, IgM – cold antibody-infections, IgG warm antibody – Drug induced, Paroxysmal Nocturnal Hemoglobinuria – complement induced)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



Hemolytic Signs



- 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 test 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

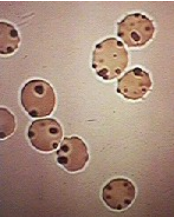
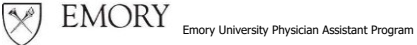
World Wide Web Site - The Sickle Cell Information Center
<http://www.SCInfo.org>

- 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.

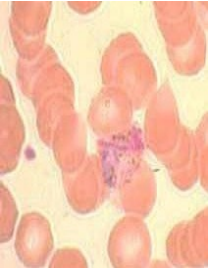
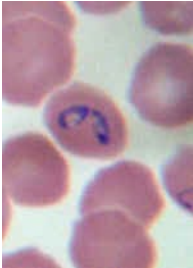
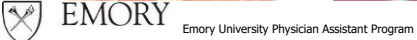



Immune Attack

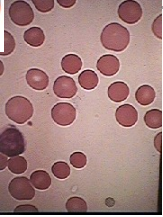
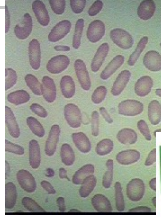


- Coombs Test: IgG and Complement +/-
- Transfusion reaction: immediate or delayed
- IgM – (IgG Neg Comp +) cold antibody-infections like, EBV (Mono), HIV, *Mycoplasma pneumoniae*, influenza B, Cytomegalovirus (CMV), rubella virus, varicella-zoster virus (VZV), parvovirus B19, and *Chlamydia psittaci*
- 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



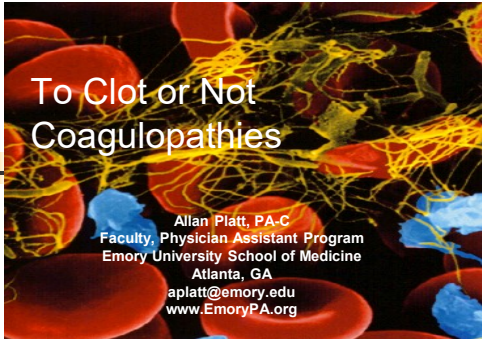
Parasites – Malaria - Babesiosis

Membrane problems spherocytosis and Ovalocytosis

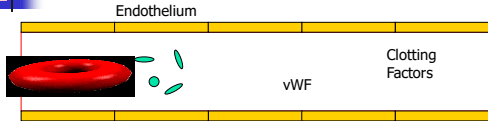
To Clot or Not Coagulopathies



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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

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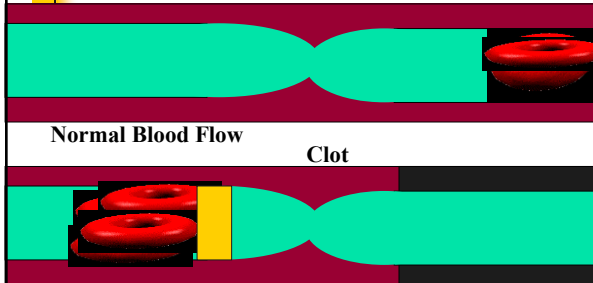
Clotting Process



- 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

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Clotting system activated

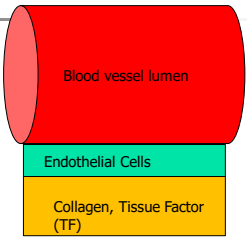


Normal Blood Flow **Clot**

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Endothelium

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



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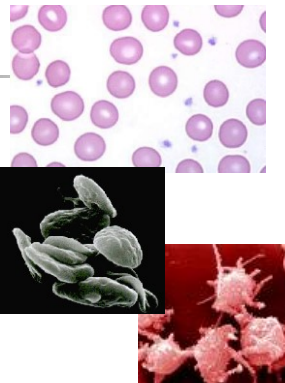

Von Willebrand Factor - vWF

- 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

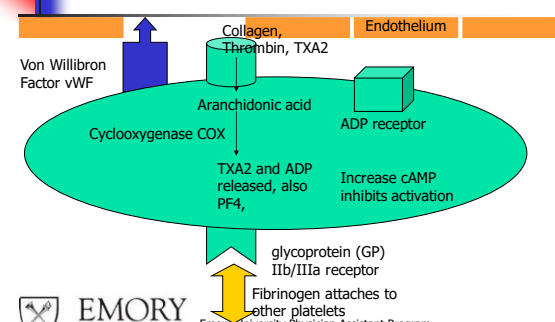

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Platelets

- 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

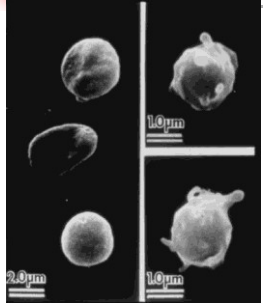



Platelet Activation

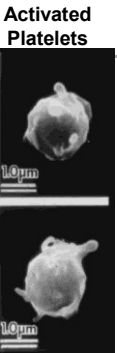



The Shape of Platelets

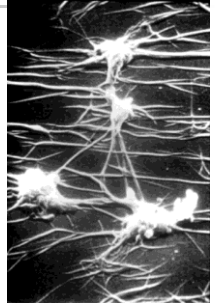
Flowing Platelets



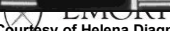
Activated Platelets



Aggregated - Active Platelets



Courtesy of Helena Diagnostics



Clotting Cascade - Factors

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

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 X active with V present
II Prothromin to Thrombin
I Fibrinogen to Fibrin

Test = TT, RT

XIII to XIII active stabilizer to crosslink fibrin



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

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor

VII to VII active

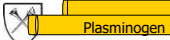
Common Pathway

X to X active with V present
II Prothromin to Thrombin
I Fibrinogen to Fibrin

Plasminogen via t-PA/ PAI-1 to Plasmin

Fibrin split products, D-Dimer

Blockers/Busters: Liver made Protein S, Protein C; Tissue Factor Pathway Inhibitor; Antithrombin III



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

Extrinsic Pathway – outside the cut in the plasma – Tissue Factor

VII to VII active


Common Pathway

X to X active with V present
II Prothromin to Thrombin
I Fibrinogen to Fibrin

Plasminogen via t-PA/PAI-1 to Plasmin

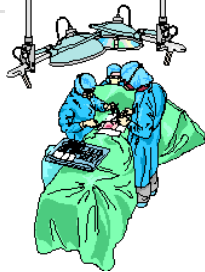
Fibrin split products, D-Dimer

Blockers/Busters: Heparin; Antithrombin III



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

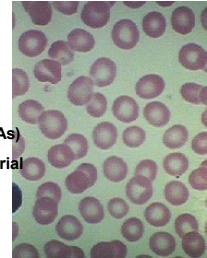


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Increased Clotting Presentation

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



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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.



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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 blood loss, 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



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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



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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 - Hypercoagulable state
- Polycythemia vera - increased viscosity
- Prolonged travel or immobility



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Increased Clotting History

- Smoking, Recent 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



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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



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Physical Exam 2



- HEENT- Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
- LUNG- consider infection, lesion, rub
- CV - new murmur 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



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Platelet Problems or Von Willebrand Disease (vWD)

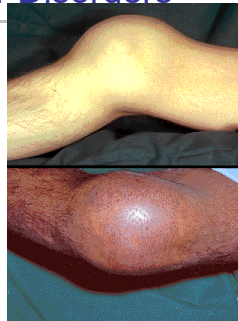


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Clotting Factor Disorders

Hemarthrosis

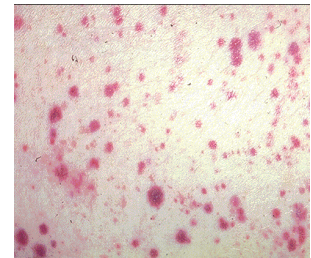


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Vascular Wall Defects

Purpura




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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-Reactive 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 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 a 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 (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



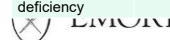
Bleeding Work-up

- 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?
- 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 inhibitor is present
 - Both abnormal then do TT Thrombin Time for common pathway and also consider DIC



Clotting Tests for bleeding

Test/Disease	PT	aPTT	Mixing study	TT
Inhibitor of VIII IX, XI, XII, Lupus –aPL antibodies	Normal	Increased	Abnormal	Normal
Hemophilia A VIII	Normal	Increased	Normal	Normal
Hemophilia B IX	Normal	Increased	Normal	Normal
DIC	Increased	Increased	Normal	Increased
Heparin	Normal	Increased	Abnormal	Increased Reptilase time normal
Low Fibrinogen	Increased	Increased	Normal	Increased
Factor VII deficiency	Increased	Normal	Normal	Normal



Clotting Tests for bleeding

Test/Disease	PT	aPTT	PFA	Platelet Ct
vWD	Normal	Increased (VIII)	Abnormal	Normal
Hemophilia A/B	Normal	Increased	Normal	Normal
DIC	Increased	Increased	Abnormal	Low
Uremia	Normal	Normal	Abnormal	Normal
Aspirin NSAIDs	Normal	Normal	Abnormal	Normal
Liver Failure - early	Increased	Normal	Normal	Normal
Liver Failure – Late/Severe	Increased	Increased	Abnormal	Low
ITP, TTP, HUS, HIT	Normal	Normal	Normal	Low



Tests – Clotting too much

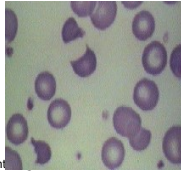
- Protein S, C, antithrombin III assay,
- Factor V Leiden assay
- Fasting homocysteine level
- Lupus anticoagulant
- Anticardiolipin antibodies
- Prothrombin 20210 mutation test
- Fibrinogen level
- HIT Assay



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Tests – Is Clotting going on

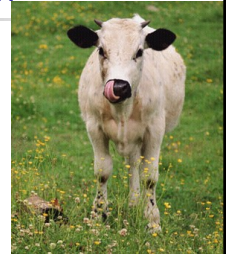
- D-Dimer elevation
- Fibrin Split products
- Peripheral smear may show schistocytes (helmet cells)



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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



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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, Meningococemia, 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



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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



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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



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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



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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



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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



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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

Issue/Disease	Acute ITP	Chronic ITP	TTP	HUS	DIC	HELLP
Age	Children	Adults	Adults	Children	Any	Pregnant
Cause	Immune Post viral	Immune HIV Hep C, SLE	ADAMTS-3 and big vWF	Infections E.Coli 0157:h7	Sepsis, Burns trauma	Pre-eclampsia
PT/PTT	Normal	Normal	Normal	Normal	Increased	+/-
Bleed/clot	Bleed	Bleed	Both	Both	Both	Both
Fever	no	no	yes	yes	depends	+/_
Hemolysis*	no	no	yes	yes	yes	yes
Organ failure	no	no	CNS > Renal	Renal > CNS	All possible	Liver
Treatment	None – IVIG, Steroids	Steroids Splenectomy	Plasma Exchange	Support, No Plts	FFP, Cryo, platelets	Deliver (MgSO ₄)

Hemolysis* - Microangiopathic: increased indirect Bilirubin/LDH/Shistocytes/Reticulocytes



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, DDVAP
- DIC/Multiple clotting factors low – FFP or Cryo
- Liver Disease, Coumadin excess – Vitamin K
- HIT – Stop heparin and use non heparinoid
- Reverse heparin - protamine



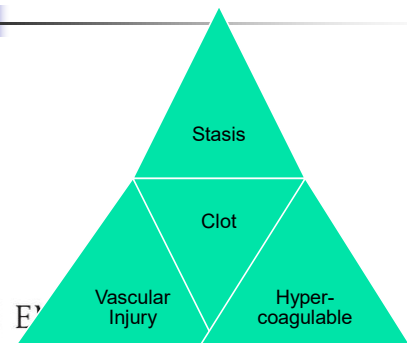
Clotting too much

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



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Virchows Triad



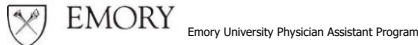
Hypercoagulability – PVCs

- Platelets
 - Too many
 - Overactive
- Vascular Injury
- Clotting Factors
 - Anti-clotting factors deficient/ not working
 - Too many factors/triggers
- Stasis and Surgery



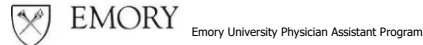
Differential Diagnosis - Hycoagulability

- 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,
- Protien 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
- U - Uremia - Chronic Renal Failure
- S - Surgery - Orthopedic is greatest risk
- **E - Estrogen - Oral Contraceptives or replacement Rx**
- D - Diabetes



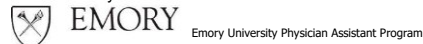
Differential Diagnosis

- 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



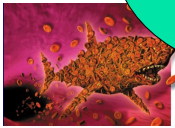
Heparin-induced thrombocytopenia (HIT)

- 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

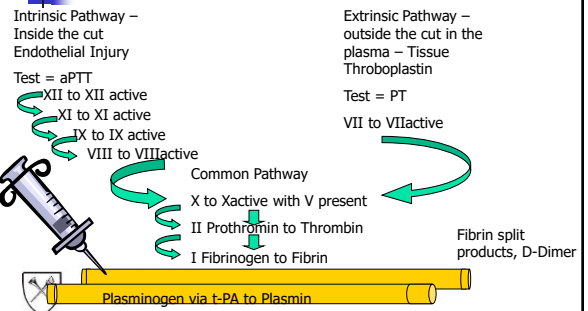


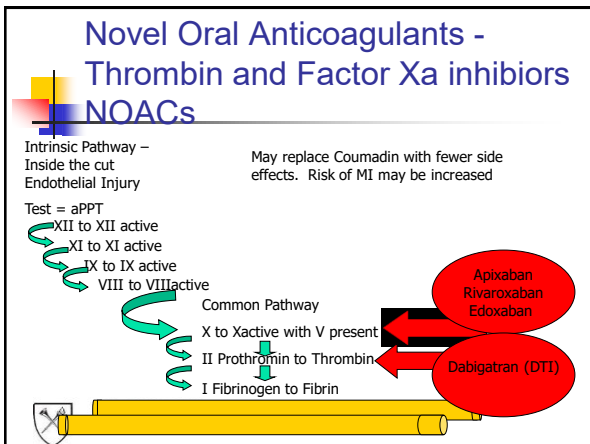
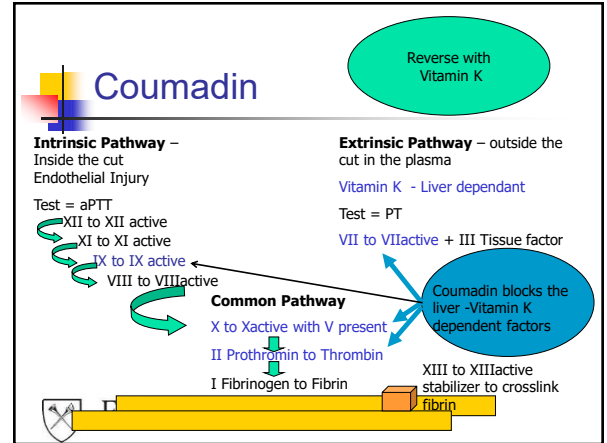
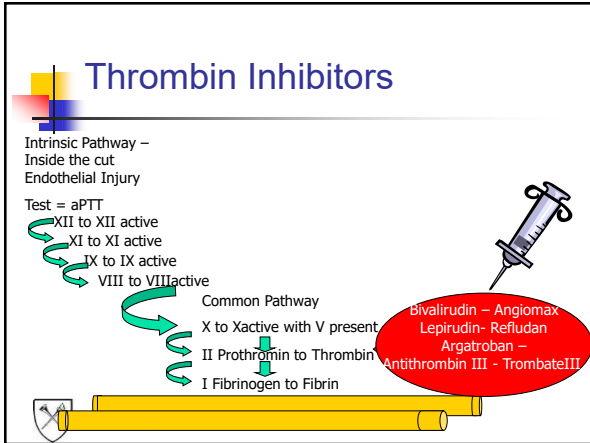
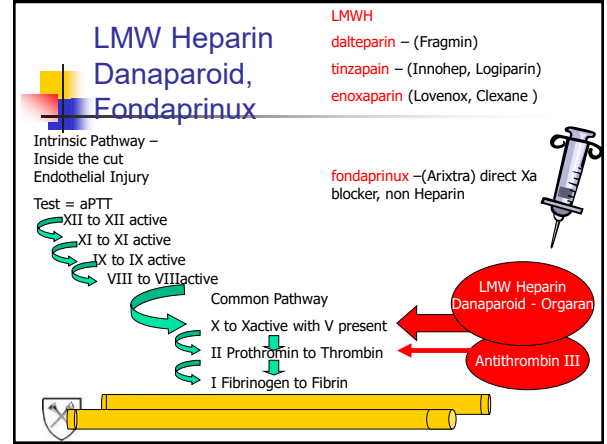
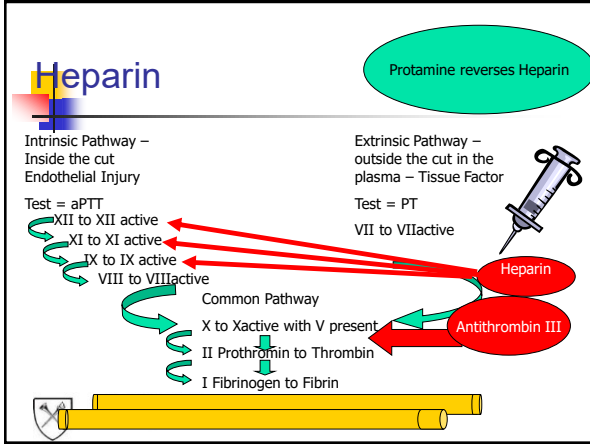
Who ya gonna Call?

Clot Busters
tPA (tissue Plasminogen Activator)



Drug Clot Busters tPA - reteplase, alteplase, tenecteplase



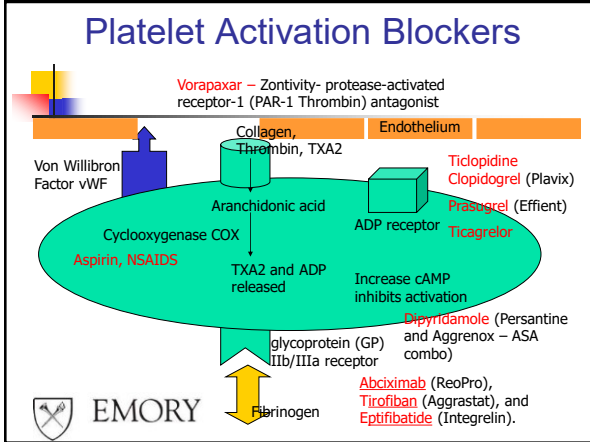


The new oral anticoagulants for VTE – Comparison (Advantages, Disadvantages)

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
Started immediately upon diagnosis of VTE	no	yes	yes	no
Dosing	twice daily	once daily	twice daily	once daily
Renal clearance	80 %	33 %	25 %	35 %
Efficacy compared to warfarin (recurrent VTE)	same	same	same	same
Safety compared to warfarin in respect to relevant bleeding	same	same/better ¹	better ²	better ³
Reversal agent / antidote available for major bleeding ⁴	Yes - Praxbind	none	none	none
FDA approved for VTE treatment	yes	yes	yes	yes

¹ Major bleeding¹ 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

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Anti- Clotting Therapy

- To block Platelets** (MI and Stroke prevention)
 - 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 -

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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 (Pronesty), Phenytoin (Dilantin)
- E-Endocrine - Addisons, Hypothyroid
- S- Syphilis
- SLE/Rheumatoid arthritis
- Serum sickness
- Sarcoid

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Mononucleosis

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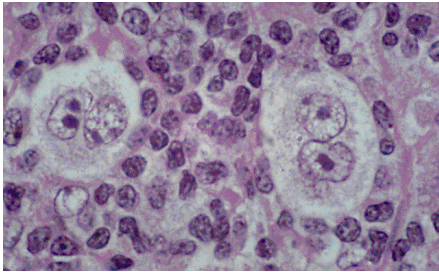
Mono - continued

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Hodgkins Disease

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Hodgkins – Reed Sternberg cells

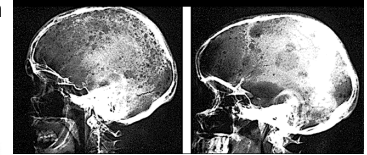
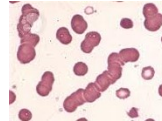


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Multiple Myeloma

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



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Primary - Polycythemia vera

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



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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



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Leukemia and Lymphoma

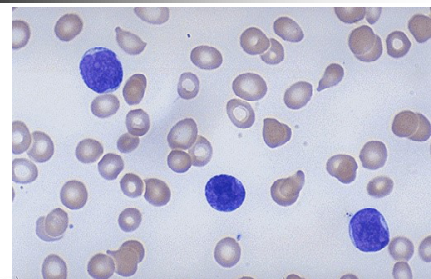
- ALL: Acute Lymphocytic Leukemia (Usually in Children)
- AML: Acute Myelogenous Leukemia
- CLL: Chronic Lymphocytic Leukemia
- CML: Chronic Myelogenous Leukemia
- Lymphomas, Hodgkins
- HX: Fatigue, anorexia, wt loss, fever, bone pain, headaches, lymphadenopathy, non healing infections, thrush, bleeding
- PE: Pallor, gingival hyperplasia, Candida infections, lymphadenopathy, hepatosplenomegaly, lung infiltrates, bleeding, bruising
- LAB: CBC: elevated WBC/ low platelets, low 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 Hodgkins Disease
- CT - MRI chest and abdomen
- CXR - Chest infiltration, pneumonias
- RX: Chemotherapy, Bone Marrow Transplant



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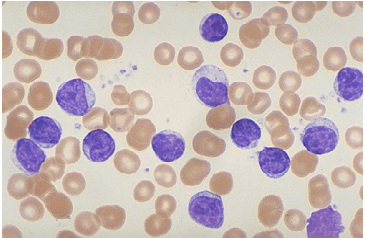
ALL - Blasts



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CLL - Blasts



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This slide features a microscopic image of CLL blasts. The title 'CLL - Blasts' is positioned at the top left, accompanied by a small graphic of overlapping colored squares. The image shows several large, atypical lymphocytes with high nuclear-to-cytoplasmic ratios and irregular nuclei, characteristic of CLL blasts, set against a background of smaller, normal red blood cells. The Emory University logo and program name are located at the bottom left.

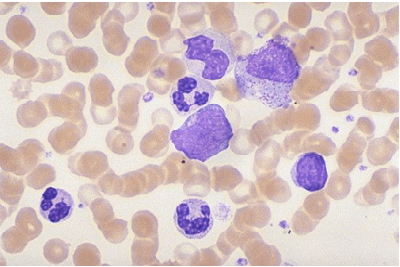
AML Auer Rod



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This slide features a microscopic image of AML blasts with an Auer rod. The title 'AML Auer Rod' is at the top left with a graphic. The image shows a large blast cell with a prominent, needle-shaped cleft (Auer rod) extending through the nucleus, a key diagnostic feature of AML. The background contains numerous red blood cells. The Emory University logo and program name are at the bottom left.

CML



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This slide features a microscopic image of CML. The title 'CML' is at the top left with a graphic. The image shows a field of leukocytes, including several large, atypical myeloid cells with high nuclear-to-cytoplasmic ratios and prominent nucleoli, typical of CML. The background is filled with red blood cells. The Emory University logo and program name are at the bottom left.