

Hematology Pathophysiology

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Anemias

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| <p>Most often women, esp. from developing country (ex. India)</p> <ul style="list-style-type: none"> ➤ Fatigue (Sometimes out of proportion to anemia) ➤ Atrophic glossitis (atrophy of tongue) ➤ Pica (eating weird crap) ➤ Koilonychia (Nail spooning) ➤ Esophageal web (rare – but specific to anemia) | <p>Progression of findings:</p> <ul style="list-style-type: none"> ➤ Stainable iron, bone marrow aspirate (Serum iron low) ➤ Serum ferritin – LOW ➤ Desaturation of transferrin ➤ Transferrin (Iron binding capacity) INCREASES ➤ Anemia | <p>RBCs:</p> <ul style="list-style-type: none"> ➤ Micocytic ➤ Hypochromic ➤ Anisocytosis ➤ Poikilocytosis | <p><u>Iron Deficiency Anemia</u></p> <p>Causes:</p> <ul style="list-style-type: none"> ➤ Blood loss (ex. GI bleed most common cause in U.S.) ➤ Increased iron utilization ➤ Malabsorption ➤ Dietary inadequacy (almost never the solitary cause) ➤ Combo of above | <p>Iron Therapy</p> <ul style="list-style-type: none"> ➤ Not well tolerated, not well absorbed (requires acidic environment) ➤ Initial response – 7-14 days ➤ Modest reticulocytosis ➤ Correction of anemia takes 2-3 months <p>Correction of underlying cause</p> |
| | <ul style="list-style-type: none"> ➤ Serum iron low ➤ Serum ferritin – HIGH ➤ Transferrin DECREASED ➤ Mild non-progressive anemia (Hgb c. 10, Hct c. 30%) ➤ Other counts normal ➤ Somewhat shortened RBC survival ➤ Normal reticulocyte count (low for anemia) ➤ Normal bilirubin ➤ EPO levels increased but blunted | <p>RBC's:</p> <ul style="list-style-type: none"> ➤ Normochromic/ normocytic ➤ (30% hypochromic/microcytic) | <p><u>Anemia of Chronic Disease</u></p> <p>Iron inappropriately shunted to storage.</p> <p>Causes (mostly inflammatory → IL-1, TNF → Mac's to prevent transferrin production, and increase ferritin levels → iron shunted away from transport path into storage):</p> <ul style="list-style-type: none"> ➤ Thyroid disease ➤ Collagen vascular disease ➤ Inflammatory bowel disease ➤ Malignancy ➤ Chronic infectious diseases ➤ Familial Mediterranean Fever | <p>Reduce inflammation</p> |

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| | <ul style="list-style-type: none"> ➤ ↑ bilirubin and lactate dehydrogenase (LDH) (Autohemolysis in the bone marrow due to ineffective erythropoiesis) | <p>RBC's</p> <ul style="list-style-type: none"> ➤ Oval macrocytosis (MCV >110) <p>PMN's</p> <ul style="list-style-type: none"> ➤ Hypersegmented <p>Bone Marrow</p> <ul style="list-style-type: none"> ➤ Megaloblastic hyperplasia (megaloblasts in the bone marrow lead to macrocytes in the peripheral blood) | <p><u>Megaloblastic Anemias: in general</u></p> <ul style="list-style-type: none"> ➤ Caused by impaired DNA synthesis (delayed mitosis) while RNA is not impaired resulting in a nuclear-cytoplasmic asynchrony that affects all rapidly proliferating cell lines, including cells of the bone marrow, GI, and GYN | |
| <ul style="list-style-type: none"> ➤ No neurologic abnormalities ➤ Sever dietary deprivation ➤ Pregnancy ➤ Intestinal malabsorption | <ul style="list-style-type: none"> ➤ Pancytopenia ➤ Reticulocytopenia, elevated LDH (90%) ➤ normal or elevated serum iron ➤ Decreased serum folate levels ➤ Increased serum homocysteine | <p>RBC's</p> <ul style="list-style-type: none"> ➤ Oval macrocytosis (MCV >110) <p>PMN's</p> <ul style="list-style-type: none"> ➤ Hypersegmented | <p><u>Megaloblastic Anemia: Folic Acid Deficiency</u></p> <p>Cause:</p> <ul style="list-style-type: none"> ➤ Dietary deficiency ↓ intake, dietary deficiency in this case only takes months to develop - Seen more in chronic alcoholics and the elderly <p>Folic acid is important for thymine and purine biosynthesis</p> <ul style="list-style-type: none"> ➤ Critical for DNA synthesis ➤ Critical for one carbon transfer metabolic reactions ➤ The primary transport for of folic acid in the blood is N5 methyl THF ➤ ↓ absorption (folate is absorbed in the duodenum) by the deconjugation of poly-Glu) <ul style="list-style-type: none"> ➤ Conditions where the need for folate ↑ such as pregnancy (can be a cause of neural tube defects, will cause increase in α-fetoprotein can result in myeloceles, spina bifida, etc) <ul style="list-style-type: none"> ➤ Conditions where there is ↓ use of folate ➤ Folate antagonists are used in chemotherapy (methotrexate) | <ul style="list-style-type: none"> ➤ Start with Folate and B12 until you know which one it is, otherwise, if you have B12 deficiency and are just given folate, the neurological deficit can progress further |

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| <ul style="list-style-type: none"> ➤ Insidious onset – weakness ➤ Lemon-yellow skin color ➤ Stomatitis and glossitis - due to generalized epithelial atrophy ➤ Subacute degeneration of the spinal cord (ataxia, hyperreflexia with extensor plantar reflexes, etc.) | <ul style="list-style-type: none"> ➤ Anti-intrinsic factor antibodies ➤ Abnormal Schilling test Schilling test – radioactive oral Vit. B is given with a concurrent IM injection of non-radioactive B12 at the same time and then measure urine for radioactive B12 ➤ Low serum B12 ➤ ↑ serum homocysteine (risk factor for atherosclerosis) ➤ ↑ methylmalonic acid in urine (since it can not be broken down to succinylCoA) | <p>RBC's</p> <ul style="list-style-type: none"> ➤ Oval macrocytosis (MCV >110) <p>PMN's</p> <ul style="list-style-type: none"> ➤ Hypersegmented | <p><u>Megaloblastic Anemia: Cobalamin Deficiency</u></p> <ul style="list-style-type: none"> ➤ Cause: usually autoimmunity: Pernicious anemia – abnormality corrected with IF administration ➤ (impaired absorption of B12 not corrected by IF; normal absorption due to dietary deprivation in vegans) ➤ Bacterial overgrowth – not corrected for even with IF, but is corrected if given antibiotic therapy | <ul style="list-style-type: none"> ➤ First draw blood before anything, then begin therapy with B12 and folate ➤ Avoid transfusions unless the patient has some heart disease or unless hemodynamic compromise is present ➤ Post IM injection of Vit. B12, reticulocytes will increase in number in about 5 days |
| | <ul style="list-style-type: none"> ➤ Disappearance of serum haptoglobins ➤ hemoglobinuria, hemoglobinemia ➤ ↑ LDH and ↑ unconjugated (indirect reacting) bilirubin → may lead to pigment-containing gallstones as a late complication | <p>RBC's:</p> <ul style="list-style-type: none"> ➤ Normocytic, normochromic peripheral blood ➤ Reticulocytosis <p>Bone marrow:</p> <ul style="list-style-type: none"> ➤ Normoblastic erythroid hyperplasia | <p><u>Hemolytic Anemia (in general)</u></p> <ul style="list-style-type: none"> ➤ Shortened RBC survival, reticulocytosis due to increased destruction | |
| <ul style="list-style-type: none"> ➤ No splenomegaly | <ul style="list-style-type: none"> ➤ ↑ bilirubin from the RBC causes jaundice and an increased risk of pigment gall stones ➤ Release of Hb into the blood causes Hemoglobinemia and hemoglobinuria ➤ Hb may be oxidized to methemoglobin which causes methemoglobinuria and methemoglobinemia ➤ Markedly decreased Hb binding proteins in the blood such as Haptoglobin and hemopexin | | <p><u>Hemolytic Anemia: Intracorpuscular Hemolysis</u></p> <p>Causes:</p> <ul style="list-style-type: none"> ➤ Membrane abnormalities ➤ Metabolic abnormalities ➤ Hemoglobinopathies | |

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| <ul style="list-style-type: none"> ➤ Splenomegaly present (extracorporeal sign related to intracorporeal hemolysis) | <ul style="list-style-type: none"> ➤ Increased osmotic fragility to hypotonic saline ➤ Normal MCH with an increased MCHC (mean corpuscular hemoglobin conc.) | | <p><u>Hereditary Spherocytosis (membrane defect)</u></p> <p>Microskeletal defect:</p> <p>Defective or absent spectrin molecule leading to loss of the RBC surface membrane leading to spherocytosis.</p> <ul style="list-style-type: none"> ➤ Autosomal dominant disorder ➤ ↓ deformability and flexibility of the cell resulting in increase osmotic fragility (at a given difference of osmolarity, its is more prone to hemolysis than a normal RBC) and clearance by spleen Macrophages which can result in symptoms of extracorporeal hemolysis ➤ Filtered and hemolysis in the spleen can occur leading to splenomegaly, increased bilirubin and increased risk for jaundice and pigment gallstones | <ul style="list-style-type: none"> ➤ Tx – Splenectomy |
| | | | <p><u>Hereditary stomatocytosis</u></p> <p>Membrane permeability defect</p> | |
| <ul style="list-style-type: none"> ➤ Breathlessness at night <p>Complications:</p> <ul style="list-style-type: none"> ➤ aplastic anemia ➤ leukemia ➤ venous thrombosis | <ul style="list-style-type: none"> ➤ Positive Ham Test (acid hemolysis) ➤ Flow cytometry: CD 59 negative (their RBCs are without CD 59 – a product of the PIG-A gene) | <ul style="list-style-type: none"> ➤ Pancytopenia | <p><u>Paroxysmal Nocturnal Hemoglobinuria (membrane defect)</u></p> <p>Increased sensitivity to complement. Uncommon acquired intracorporeal defect from somatic mutation in PIG-A gene.</p> <p>Caused by decreased GPI proteins especially DAF</p> <ul style="list-style-type: none"> ➤ DAF usually binds to GPIs on the RBC surface to breakdown complement components from lysing the cell (specifically C3 convertase). DAF deficiency results in increased complement activity ➤ Clonal cell disorder (so effects all cell lines), with ongoing intravascular and extravascular hemolysis, classically at night (this may be due to the fact that people become slightly acidotic during sleep and complement components are more active in the ↓ in pH (so exercise can also cause this to occur)) | <ul style="list-style-type: none"> ➤ |

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| <ul style="list-style-type: none"> ➤ Shows an X-linked inheritance commonly found in African Americans and Mediterraneans ➤ Acute self-limited intravascular hemolytic anemia ➤ At times of oxidative stress are infection, medication, fava beans | <p>Hemoglobinemia and hemoglobinuria caused by oxidative stress</p> | <ul style="list-style-type: none"> ➤ Heinz body formation – from Oxidative stress. Can be seen with methylene blue ➤ Bite cells - these cells get eaten up by the splenic macrophages (extravascular hemolysis) | <p><u>G6PD Deficiency (Enzyme defect)</u></p> <p>Defect in EM path</p> <ul style="list-style-type: none"> ➤ G6PD deficiency results in decreased levels of the antioxidant glutathione (GSH), and thus RBCs become sensitive to oxidant stresses leading to hemolysis ➤ G6PD is the rate-limiting enzyme in the hexose-monophosphate shunt ➤ G6PD also produces NADPH which keeps glutathione reduced and then glutathione can protect by breaking down hydrogen peroxide ➤ The actual deficiency is not due to the absence of the enzyme, but rather a defective protein folding, resulting in the protein having a decrease half-life, so towards the later stages of an RBCs life (more than 20 days), the functional levels of the enzyme start to decline ➤ Mediterranean version is associated with fava bean ingestion and shows a more severe hemolysis because all the RBCs have decreased G6PD activity due to decreased synthesis and stability ➤ African American version is associated with intermittent hemolysis since old the older RBCs have decreased levels of G6PD and usually occurs in response to oxidative states such as infections | |
| <ul style="list-style-type: none"> ➤ Splenomegaly (if the extravascular hemolysis occurs in the spleen) ➤ Hepatomegaly results if the extravascular hemolysis occurs in the liver | <ul style="list-style-type: none"> ➤ ↑ bilirubin and ↓ haptoglobin occurs (just not as much as IV hemolysis) ➤ There is no hemolobinemia, hemoglobinuric and methemoglobin formation | | <p><u>Hemolytic Anemia: Extracorporeal hemolysis</u></p> <p>Causes:</p> <ul style="list-style-type: none"> ➤ Nonimmune ➤ Immune | |
| | | <p>RBC's :</p> <ul style="list-style-type: none"> ➤ Schistocytes ➤ Helmet cells | <p><u>Microangiopathic Hemolytic Anemia</u></p> <ul style="list-style-type: none"> ➤ Caused by vascular abnormalities (such as AV fistula, Cavernous hemangioma), renal lesions, vasculitis ➤ Due to mechanical disruption of circulating erythrocytes ➤ DIC and thrombotic thrombocytopenic purpura are associated with this condition | |

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| | <p>Coombs test Direct Test – looks for Ig and/or complement on the surface of the RBC</p> <ul style="list-style-type: none"> ➤ Coombs reagent has anti-human Ig and anti-human complement ➤ Mix it with patient, and if those immune components are on the cell surface, then, you will get agglutination due to the Coombs reagent <p>Indirect Test – looks for Anti-RBC Ab in the patients serum, using a panel of RBCs with known surface Ags</p> <ul style="list-style-type: none"> ➤ Combine patient's serum with cells from a panel of RBCs with known antigens ➤ Add combs reagent to the mixture ➤ If anti-RBC antigens are in serum, agglutination occurs | | <p><u>Immune Hemolytic Anemia (In general)</u></p> <ul style="list-style-type: none"> ➤ All require antigen-Ab interactions, and the types of reactions depend on the class of Ab, amount of antigen on the cell surface, complement availability, functional status of the reticuloendothelial system ➤ Can manifest as intravascular or extravascular hemolysis ➤ Ab combines with RBC to activate complement (results in intravascular hemolysis) or opsinize the RBC for cell mediated endocytosis (Macrophages recognize the Fc portion of the Ig and/or C3b and then this results in extravascular hemolysis) | |
| <ul style="list-style-type: none"> ➤ Quinidine, quinine, Isoniazid ➤ Penicillins, cephalosporin ➤ Methyldopa, L-dopa, Procainamide, Ibuprofen | | | <p><u>Drug-related Immune Hemolysis</u></p> <ul style="list-style-type: none"> ➤ Immune complex mechanism (quinidine, quinine, Isoniazid) ➤ Drug and Ab bind in the plasma ➤ Immune complexes activate complement in the plasma, or sit on the RBC, and that is recognized by Macrophages and results in destruction of the immune complex, and the RBC lyses for being an innocent bystander ➤ Haptenic Immune mechanism – penicillins, cephalosporins ➤ Drug binds to and reacts with red cell surface proteins, antibodies recognize the altered protein/drug as foreign and initiate immune processes ➤ True Auto-immune Mechanism – Methyldopa, L-dopa, Procainamide, Ibuprofen ➤ Not known etiology, but the drug causes antibodies to for against antigens found normally on the RBC surface | |

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| <ul style="list-style-type: none"> ➤ Immediate (back pain, fever, HTN and DIC) ➤ Slow (usually with only mild symptoms)r ➤ <i>Delayed</i> presentation this is usually asymptomatic | <ul style="list-style-type: none"> ➤ Need to pre-test ABO and Rh type for both the donor and recipient ➤ Antibody screen of donor and recipient including indirect Coombs | | <p><u>Allo-immune Hemolysis</u> Hemolytic transfusion reaction – caused by recognition of foreign antigens on transfused blood cells - Several subtypes.</p> <ul style="list-style-type: none"> ➤ Immediate intravascular hemolysis (occurs in minutes) in reaction to pre-formed anti-bodies – this is life-threatening ➤ Slow extravascular hemolysis (occurs over days) in reaction to repeat exposure to a foreign antigen to which there was previous exposure – ➤ Delayed sensitization (occurs over weeks) as a result of 1st exposure to an antigen; | |
| <ul style="list-style-type: none"> ➤ Usually occurs in the 2nd or later pregnancy ➤ Can cause severe anemia in the fetus with erythroblastosis and heart failure | <ul style="list-style-type: none"> ➤ Hyperbilirubinemia can lead to severe brain damage (kernicterus) if not promptly treated | | <p><u>Hemolytic disease of the newborn</u></p> <ul style="list-style-type: none"> ➤ Occurs due to incompatibility between the mother negative for an antigen and fetus/father positive for that antigen. Rh and ABO incompatibilities are most common causes ➤ Requires maternal IgG antibodies vs. RBC antigens in fetus ➤ Note that IgM doesn't cross the placenta | <ul style="list-style-type: none"> ➤ Can be prevented if caused by an Rh incompatibility by administration of anti-Rh D to Rh negative mothers after each pregnancy |
| <ul style="list-style-type: none"> ➤ General features of anemia | <ul style="list-style-type: none"> ➤ Positive direct Coombs test | <p>RBC's</p> <ul style="list-style-type: none"> ➤ Spherocytosis (progressive loss of membrane protein from being Ab coated while passing through the spleen) | <p><u>Autoimmune Hemolysis: Warm Type</u></p> <p>Occurs due to formation of Abs that attack self RBCs</p> <ul style="list-style-type: none"> ➤ Auto Abs allow for complement fixation on the RBC ➤ Warm type – usually due to IgG Abs, with complement fixation to level of C3, if at all. ➤ Ig binding occurs at all temperatures, Fc receptors and C3b receptors on Macrophages cause extravascular hemolysis. ➤ 70% of cases are associated with other illnesses – lymphoproliferative disease or collagen vascular disease | <ul style="list-style-type: none"> ➤ Responsive to steroids and splenectomy |
| | | | <p><u>Autoimmune Hemolysis: Cold Type</u></p> <ul style="list-style-type: none"> ➤ Usually IgM mediated with Abs binding at 30 degrees or lower. ➤ Complement is responsible for this with the formation of the MAC leading to RBC lysis intravascularly. ➤ 90% is associated with other illnesses – eg. Infectious mono or mycoplasma pneumoniae | <ul style="list-style-type: none"> ➤ Poorly responsive to steroids or splenectomy but is responsive to plasmaphoresis |

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| <ul style="list-style-type: none"> ➤ Patients are initially normal at birth because HbF levels are high enough to compensate, ➤ But at about 6 months, when Hb F levels start to fall, patients start to show symptoms ➤ Marked anemia ➤ Distortion of skull, facial bones (“chipmunk face”), and long bones ➤ Hepatosplenomegaly ➤ Requirement for blood transfusions ➤ Cooley's Anemia = Mediterranean Anemia | <ul style="list-style-type: none"> ➤ Erythroid hyperplasia in the bone marrow (visible in imaging) ➤ Hb electrophoresis will show ↑ Hb F (90%), ↑ Hb A2 and ↓ Hb A ➤ Generalized hemosiderosis | <p>RBC's:</p> <ul style="list-style-type: none"> ➤ Microcytic/hypochromic (due to ↓ β globin) anemia, ➤ Target cells (which are due to increased RBC membrane) ➤ Extensive changes in size and shape ➤ Increase in reticulocytes | <p><u>Cooley's Anemia (Homozygous B Thalassemia)</u></p> <ul style="list-style-type: none"> ➤ β-thalassemia has decreased β globin chains with excess α-chains → extra-vascular hemolysis ➤ Eventually results in a iron overload ➤ Is due to a point mutation forms either some β-chains (β+) or none (β0) – usually a result of a point mutation to form a stop codon, or a point mutation which results in an abnormal mRNA processing at the splice junctions ➤ Genetically there are a total of 2 β-globin chain genes which are expressed only post-natally and therefore no pre-natal disease occurs ➤ The decreased RBC lifespan results in severe hemolytic anemia – intermedullary destruction (within the bone marrow → in ineffective erythropoiesis, and the hemolysis → increases bilirubin levels → increases the likelihood of jaundice → gall stones) ➤ CHF is the most common cause of death | <ul style="list-style-type: none"> ➤ Life long transfusions which can result in secondary hemochromatosis ➤ Tx will rely on chelator (desferrioxamine) use concurrently, ➤ Hydroxyurea to increase HbF |
| <ul style="list-style-type: none"> ➤ Asymptomatic condition or may manifest as mild anemia | <ul style="list-style-type: none"> ➤ Increased HbA2 (8%) – Diagnostic | <p>RBC's:</p> <ul style="list-style-type: none"> ➤ Minimal hypochromic microcytic anemia | <p><u>β-thalassemia minor</u></p> <ul style="list-style-type: none"> ➤ Rule out: iron deficiency anemia and anemia of chronic disease | |
| <ul style="list-style-type: none"> ➤ Most common form of thalassemia in Southeast Asia | | | <p><u>Alpha Thalassemia</u></p> <ul style="list-style-type: none"> ➤ α-thalassemia has decreased α globin chains with excess β-chains ➤ Normal people have 4 α genes and 100% α chains. silent carriers have 1 deletion à total of 3 α genes, which produces 75% of normal α chains. these individuals are completely normal and asymptomatic with normal lab values as well ➤ α-Thalassemia minor patients have 2 α genes either in a cis (on same gene missing – more common in Asians) or trans (on different loci missing – more common in African Americans) ➤ Since blacks have the trans form, their off spring can never get H disease or hydrops while Asians can have offspring with hydrops fetalis ➤ Hb H disease patients have 3 deletions (if there is a newborn with severe anemia, run gel electrophoresis and look for Hb H). These patient have 1 α gene which results in 25% of the α chains | |

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| | | | <p>being produced</p> <ul style="list-style-type: none"> ➤ Results in increased Hb H which has 4 β subunits, and forms Heinz bodies which can be seen with crystal blue stain ➤ Hydrops fetalis – these patients have 4 deletions and the condition is lethal in utero, they have 0 α genes and thus, 0% α chains. This condition results in increased γ4 (Bart’s Hemoglobin) ➤ Hb H and Hb Bart are better than the free α globin chains seen in β thalassemia, however, they have an increased affinity for O2 which results in a poorer O2 delivery | |
| <ul style="list-style-type: none"> ➤ Severe hemolytic anemia ➤ Chronic leg ulcers ➤ Painful crises ➤ Repeated infarcts of lungs and spleen ➤ Aplastic crises – parvovirus infection ➤ Infectious complications – Salmonella osteomyelitis | <ul style="list-style-type: none"> ➤ Erythroid hyperplasia in the bone marrow, jaundice and ↑ bilirubin levels - With low O2 tension, the RBC sickles, but with repeated sickling, Ca enters the RBC and H2O and K+ leave the RBC resulting in irreversible sickling which will result in chronic extra-vascular hemolysis. ➤ The chronic hemolysis will result in reticulocytosis and hyperbilirubinemia ➤ Prenatal: Chorionic villus biopsy and amniocentesis | <p>RBC's:</p> <ul style="list-style-type: none"> ➤ Sickle cells ➤ Howell Jolly bodies | <p><u>Sickle Cell Disease</u></p> <ul style="list-style-type: none"> ➤ Hb S – (sickle cell anemia with a β-globin chain which has a valine (neutral) substituted for glutamate (-) at the 6th position of the chain) ➤ Hypoxia, dehydration (Increasing HbS concentrations inside the RBC will induce sickling, while thalassemia will make it better), acidosis (↓ pH decreases O2 affinity and will induce sickling) and infection triggers sickling ➤ Capillaries blocked by sickled cells will cause a vaso-occlusive crisis (painful crisis), hand-foot syndrome (swelling in children), Autosplenectomy due to chronic infarcts and subsequent ischemic necrosis and fibrosis of the spleen (this will result in increased susceptibility to infections by encapsulated organisms and Howell Jolly bodies in peripheral blood smear) ➤ Heterozygous (AS) trait à patients are normal until they reach high altitudes ➤ About 8% of African Americans are heterozygotes for Hb S. These patients have about 40% HbS and since most (60%) is Hb A which does not interact well with HbS, sickling does not occur too often ➤ Patients with sickle trait have fewer symptoms than those with sickle disease and they also have resistance to P. Falciparum (malaria) ➤ Hb F does not interact well with Hb S and so perinatal infants will be asymptomatic until about 6 months ➤ Hb C is another β globin mutant which interacts well with HbS, and so this can be problematic because it will induce sickling | <ul style="list-style-type: none"> ➤ Tx – hydroxyurea in order to induce more Hb F which will increase O2 in the blood and will also reduce inflammation which reduces RBC stasis and sickling prone situations |

Hemorrhagic Disorders

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| | <ul style="list-style-type: none"> ➤ Prolonged bleeding time, ➤ Normal PT but Prolonged aPTT, abnormal platelet response to ristocetin (which causes thrombocytopenia) ➤ Low vWF and factor VIII | <ul style="list-style-type: none"> ➤ Normal platelet count | <p>Platelet Adhesion Defect: Von Willebrand Disease</p> <ul style="list-style-type: none"> ➤ Autosomal dominant inheritance with variable penetrance, generally a mild bleeding disorder with variable test results (hemophilia is X-linked) ➤ Results from reduced or dysfunctional vWF (prevalence 1-2%) which is normally produced by endothelial cells and megakaryocytes ➤ Factor VIII is stabilized by vWF, and without it, the half life of Factor VIII is minutes, but binding to vWF makes it 12 hrs ➤ vWF made by endothelial cells and megakaryocytes (compared to Factor VIII synthesized in liver) <p>Bernard Soulier Disease – very rare abnormal GpIb-IX complex (vWF receptor) on platelets so does not bind vWF</p> <ul style="list-style-type: none"> ➤ The vWF receptor is the only adhesion mediator in high shear stress | <ul style="list-style-type: none"> ➤ Tx is with Desmopressin (an ADH analog which releases vWF from Weibel Palade bodies) |
| | | | <p>Platelet release defect – congenital</p> <p>Platelet function defects – release defects resulting in a mild bleeding disorder and a definite decrease in platelet aggregation</p> <ul style="list-style-type: none"> ➤ Δ granule storage pool disease – failure to form dense granules so no ADP, Ca, Serotonin is release upon activation so you also fail in recruiting platelets for aggregation ➤ Gray-platelet syndrome – failure to package α granules so you don't release fibrinogen and other platelet aggregatory factors | |
| | | | <p>Platelet aggregation defect – congenital</p> <p>Aggregation defects – congenital</p> <p>Glanzmann's thrombasthenia –</p> <ul style="list-style-type: none"> ➤ Autosomal recessive ➤ Lack of fibrinogen receptor Gp IIb/IIIa – platelets can not aggregate and bleeding can be severe | |

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| <ul style="list-style-type: none"> ➤ Alcohol (a lot is needed, about 1 liter everyday for 2 months), ➤ Prostaglandin Synthetase Inhibitors (i.e. NSAIDS, Dipyridamole) ➤ ADP receptor inhibitors (clopidogrel, ticlopidine) ➤ β-lactam antibiotics, Heparin | | | <p><u>Platelet – prolonged bleeding time</u></p> <p>Acquired defects – Drug Induced</p> | |
| | | | <p><u>Thrombocytopenia</u></p> <p>Decreased production</p> <ul style="list-style-type: none"> ➤ Decreased number of megakaryocytes – good response to platelet transfusion ➤ Neoplastic causes such as aplastic anemia, leukemia, metastatic carcinoma, drugs, radiotherapy, or primary bone marrow disorders such as megaloblastic anemias, myelodysplastic or myeloproliferative disorders <p>Increased destruction</p> <ul style="list-style-type: none"> ➤ Shortened platelet lifespan, increase megakaryocytes, macroplatelets and bad response to platelet transfusion ➤ Causes can be immune – ITP, lymphoma, drugs, or ↑ consumption, or septicemia (since infection causes endothelial cells to expose subendothelial collagen) | |
| | <ul style="list-style-type: none"> ➤ Decreased platelet count ➤ Prolonged bleeding time ➤ Normal PT and aPTT time | <p>Thrombocytopenia and enlarged immature platelets</p> <p>Bone marrow:</p> <ul style="list-style-type: none"> ➤ Increased numbers of megakaryocytes with immature forms | <p><u>ITP (immune thrombocytopenic purpura)</u></p> <ul style="list-style-type: none"> ➤ Antiplatelet antibodies made in the spleen against platelet antigens such as Gp IIb/IIIa and Gp Ib/IX ➤ Platelets are destroyed upon reaching the spleen in circulation because of the Fc receptors on M-phages that bind to IgG coated platelets ➤ Acute form – occurs in children after viral infection and is self-limited ➤ Chronic form usually seen in women of childbearing years, may be the first manifestation of SLE, symptoms include petechiae, ecchymoses, menorrhagia and nosebleeds | <ul style="list-style-type: none"> ➤ Tx – corticosteroids (to ↓ Ab production), ➤ Ig therapy which flood Fc receptors on splenic M-phages or ➤ Splenectomy (removing the site of platelet destruction and Ab production) |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| | | | <p><u>HIV associated thrombocytopenia</u></p> <ul style="list-style-type: none"> ➤ Early on – immune mediated, marrow is within normal limits and Tx is with anti-retroviral therapy ➤ Later on – virus infiltrates marrow, get pancytopenia, results in association with infection or neoplasm, and is poorly responsive to all treatments | |
| | <ul style="list-style-type: none"> ➤ Normal vWF, ➤ Type A lacks factor VIII, type B lacks IX ➤ Bleeding time is normal (as compared to VWD when it is prolonged) ➤ aPTT is prolonged | | <p><u>Hemophilia</u></p> <ul style="list-style-type: none"> ➤ Hemophilia – incidence is .02% - not the most common, but most serious disorder ➤ Sex-linked recessive disease, types A and B are clinically indistinguishable except by factor analysis and is genetically lethal without replacement therapy. New, current mutations can lead to this. (VWD is autosomal dominant) <p>Clinical severity correlated with factor level:</p> <ul style="list-style-type: none"> ➤ Mild hemophilia is with a >5% factor level (bleeding only occurs with significant trauma or surgery) ➤ Moderate is 1-5% factor level (bleeding with mild trauma, hemarthroses with trauma) or spontaneously – occasionally), ➤ Severe is < 1% factor level – often see spontaneous mucosal and spontaneous bleeding ➤ Factor VIII synthesized in liver (compared to VWF made by endothelial cells and megakaryocytes) | <ul style="list-style-type: none"> ➤ Tx rules – treat first, ask later, if there is bleeding into closed spaces let it be, avoid emergent procedures if possible ➤ Type A is treated with replacing Factor VIII ➤ Type B, you need to double the doses because factor IX distributed into total body water also |
| | <ul style="list-style-type: none"> ➤ PT goes up 1st, secondary to factor VII's short half life | | <p><u>Acquired Clotting Disorders: Vit. K deficiency</u></p> <ul style="list-style-type: none"> ➤ Usually in hospitalized patients because ↓ dietary consumption and concurrent ↓ in normal gut flora is needed for this to happen | <ul style="list-style-type: none"> ➤ Tx is to replace Vit. K and a response should be noted in 24-48 hours |
| | <ul style="list-style-type: none"> ➤ ↑ fibrin split products due to impaired clearance which can result in inhibition of the clotting process ➤ ↑ PT, aPTT, TT ➤ ↓ platelets (hypersplenism) ➤ In liver disease vWF is normal while in DIC, vWF is ↓ | | <p><u>Acquired Clotting Disorders: Liver disease</u> – one of the major causes of bleeding disorders. Results in factor deficiencies secondary to decreased synthesis.</p> <ul style="list-style-type: none"> ➤ ↓ synthesis of Vit. K dependent proteins ➤ ↓ clearance of activated clotting factors so you can see ↑ clotting in some cases ➤ ↑ fibrinolysis secondary to ↓ PAIs and anti-plasmin, and an increase t-PA ➤ Dysfibrinogenemia secondary to synthesis of abnormal fibrinogen. Abnormal fibrinogen results in excess sialic acid lysing fibrin, prolonged TT which means that there are abnormally low levels of fibrinogen | <ul style="list-style-type: none"> ➤ Tx – replacement therapy but is reserved for a bleeding procedure since the half life of the factors is very short, normally a very high volume and frequency is needed in order to use it otherwise |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| | | | <p><u>Anticoagulant Protein Deficiency</u></p> <p>Heterozygous Protein Deficiency</p> <ul style="list-style-type: none"> ➤ Increased venous thrombosis ➤ Occasional increased arterial thrombosis ➤ Warfarin induced skin necrosis (protein C deficiency) <p>Homozygous Protein Deficiency</p> <ul style="list-style-type: none"> ➤ Neonatal purpura fulminans ➤ Fibrinogenolysis ➤ Chronic DIC | |
| <ul style="list-style-type: none"> ➤ Extremely common (5-20% of the white population with this mutation) | <ul style="list-style-type: none"> ➤ Failure for activated protein C to prolong aPTT (98% of the time due to a mutation of Arg 506 to glutamine which is the cleavage site where APC cleaves Va) | | <p><u>Factor V Leiden Deficiency: Protein C Resistance</u></p> <ul style="list-style-type: none"> ➤ Normally, APC cleaves and inactivates Va and also VIIIa ➤ 4X increased risk in heterozygotes for thromboemboli and even more so in homozygotes ➤ Can exist in combination with other disorders and when they do exist, their effects have a synergistic effect | |
| <ul style="list-style-type: none"> ➤ Anticardiolipin Syndrome ➤ Malignancy ➤ Immobilization ➤ TTP ➤ DIC ➤ Oral Contraceptive Therapy ➤ Prosthetic valves ➤ PNH ➤ Myeloproliferative disease ➤ Nephrotic Syndrome ➤ Inflammatory Diseases ➤ Atherosclerosis ➤ Surgery ➤ Diabetes mellitus | | | <p><u>Acquired Hypercoagulable States</u></p> <p>C4b Binding protein – acute phase reactant synthesized under inflammatory states</p> <ul style="list-style-type: none"> ➤ Increases in inflammatory diseases ➤ Binds to protein S resulting in a decrease in effective Protein S (since bound Protein S is inactive as a cofactor) <p>Inflammation increases IL-1 and TNF-α</p> <ul style="list-style-type: none"> ➤ Both of these cytokines downregulate thrombomodulin by increasing its internalization and decreasing its translation ➤ Thrombin as a result only exerts its pro-coagulant functions b/c of the lack of thrombomodulin (so thrombin does not activate protein C at all) | |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| | | | <p><u>Heparin or anti-coagulation therapy</u></p> <p>Lepirudin/Argatroban Direct thrombin inhibitors which inhibit thrombin bound to fibrin</p> <ul style="list-style-type: none"> ➤ Inhibits thrombin activation of platelets so may cause more bleeding than heparin ➤ Usually used in place for heparin if there is severe thrombocytopenia <p>Coumadin Inhibits Vit. K dependent Carboxylase activity, preventing the reduction of Vit. K, but does not affect proteins already synthesized</p> <ul style="list-style-type: none"> ➤ Initially may cause a hypercoagulable state because protein C will drop first because of its shorter half life, so you need to give heparin concomitantly for the first 1-2 days ➤ Dose is monitored with PT time ➤ Multiple drug interactions, toxicity is reversed with high dose Vit. K <p>Thrombolytic therapy</p> <ul style="list-style-type: none"> ➤ Streptokinase – purified from streptococcus and functions in binding to plasminogen and then starts to convert another plasminogen molecule into plasmin ➤ Urokinase – purified from urine initially and functions in activating plasminogen directly ➤ t-PA – made by endothelial cells with an increased affinity for fibrin bound plasminogen with relative fibrin specificity and activates plasminogen directly – results in lysis of clots ➤ Thrombolytic therapy has a high incidence of intracerebral hemorrhage ➤ Results in lowered plasma fibrinogen ➤ Used in MI to lyse coronary thrombi ➤ t-PA has a high incidence of re-occlusion disease | |
| <p>Always occurs secondary to another disorder:</p> <ul style="list-style-type: none"> ➤ Obstetric complications (placental tissue factor activates clotting) ➤ Sepsis (LPS), ➤ Adenocarcinomas (mucin activates clotting) ➤ AML-M3 aka APL (cytoplasmic granules in neoplastic promyelocytes activate clotting) | <ul style="list-style-type: none"> ➤ ↓ platelets, ➤ Prolonged PT and aPTT, ➤ ↓ fibrinogen, ↑ fibrin split products – fragment D especially since this occurs in patients only with active thrombosis occurring and fragment X can be seen in anyone with fibrinolysis (so the D-dimers is the most conclusive) – this one confirms DIC | <p>RBC</p> <ul style="list-style-type: none"> ➤ Schistocytes <p>Platelets</p> <ul style="list-style-type: none"> ➤ Decreased <p>WBC</p> <ul style="list-style-type: none"> ➤ Increased. Bands, metamyelocytes | <p>DIC</p> <ul style="list-style-type: none"> ➤ Results in widespread microthrombi and the consumption of platelets and clotting factors causes hemorrhage ➤ In acute DIC – bleeding is a concern – a decrease in both coagulants and anti-coagulants ➤ Chronic DIC – thrombosis is a concern <p>Defibrination Can occur due to release of tissue procoagulants (tumors, fetal, placental, prostatic, pancreatic, Shock), damage to the vascular tree (as in sepsis, aortic aneurysm, hemanigoma, tumor emboli) and ↓ clearance seen with liver disease</p> | <ul style="list-style-type: none"> ➤ Tx is to fix the underlying disorder, ➤ If bleeding, treat with replacement therapy – cryoprecipitate (fibrinogen), fresh frozen plasma, and platelets ➤ If manifestation = thrombosis, treat with anticoagulants ➤ Heparin is rarely indicated for bleeding problems, but can be used occasionally (esp. for APL, adenocarcinoma) |

Malignancies

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| <p>Commonest form of malignancy in children (B-cell lineage)</p> <p>Marrow involvement → pancytopenia</p> <ul style="list-style-type: none"> ➤ Infections, weakness, bleeding. ➤ Cause of death often hemorrhage (ex. Subarachnoid) ➤ Bone pain <p>Organ infiltration</p> <ul style="list-style-type: none"> ➤ hepatosplenomegaly, adenopathy, hypertrophied gums, meningeal infiltration <p>Increased peripheral WBC → leukostasis in small vessels</p> <ul style="list-style-type: none"> ➤ Tachypnea, dyspnea, tinnitus, lethargy, stupor <p>Hyperurecemia (purines)</p> <ul style="list-style-type: none"> ➤ renal tubular damage ➤ Acute renal failure | <ul style="list-style-type: none"> ➤ Increased “buffy coat” (% volume of WBC > % vol of RBCs) ➤ Myeloperoxidase (-) ➤ tdT (+) ➤ Cell surface Ag’s: B cell (CD10, CALL-A, CD19) or T cell ➤ Ig or T cell receptor, gene arrangement (+) | <p>Peripheral blood:</p> <ul style="list-style-type: none"> ➤ Predominance of lymphoblasts ➤ No Auer rods (-) <p>Bone marrow</p> <ul style="list-style-type: none"> ➤ Lymphoblasts | <p>Acute Lymphoblastic Leukemia: ALL</p> <p>Precursor B and T cell Neoplasms</p> <ul style="list-style-type: none"> ➤ Arises in early progenitor B or T cell (4:1 ratio) ➤ Lymphoblasts are positive for terminal deoxyltransferase (TdT – determined by using a nuclear stain), PAS and acid phosphatase <p>B cell lineage – based on the presence or absence of cytoplasmic or cell surface markers</p> <ul style="list-style-type: none"> ➤ Surface Ig present in mature B cell ALL ➤ Cytoplasmic μ present in pre B cell ALL ➤ Genetically heterogeneous – 90% have chromosomal abnormalities <p>T cell lineage – associated with a mediastinal mass in adult males (Thymic enlargement)</p> | <ul style="list-style-type: none"> ➤ Form of acute leukemia most responsive to therapy, children (90% remission) more than adults ➤ Tx – combination therapy, chemo is continued beyond remission. CNS prophylaxis. ➤ Bone marrow transplantation, ➤ Supportive therapy (RBC, platelet transfusions and antibiotics) |
| <ul style="list-style-type: none"> ➤ More common in adults than children ➤ DIC is especially common with APL ➤ Symptoms and signs similar to ALL ➤ Choloromas – press skin, turns green (from myeloperoxidase) | <ul style="list-style-type: none"> ➤ Myeloperoxidase (+) ➤ tdT (-) ➤ Cell surface Ag’s: myeloid ➤ Ig or T cell receptor (-) ➤ Cytogenetics: 15:17 translocation | <ul style="list-style-type: none"> ➤ Auer rods (+) | <p>Acute Non-Lymphoblastic Leukemias (ANLL), aka Acute Myelogenous Leukemias (AML)</p> <ul style="list-style-type: none"> ➤ Key example: Acute Promyelocytic Leukemia (APL), M3 of AML, (comprises 7% of ANLL) ➤ Malignant clones show early differentiation and cells contain Auer rods ➤ 15;17 translocation is often present ➤ The retinoic acid receptor-α gene is on chromosome 17q, (normally a transcription enhancer upon retinoic acid binding, for cell differentiation) and this translocation with the pml gene on 15 causes failure for promyelocytes to differentiate and blocks apoptosis | <ul style="list-style-type: none"> ➤ In general, AML prognosis not as good as ALL ➤ Therapy shows sensitivity to arsenical trioxide and retinoic acid (induces remission in APL, cells turn into PMN) |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| <ul style="list-style-type: none"> ➤ Age in 60s, often first presentation is with recurrent infections (an indication of their hypo-Ig condition) ➤ Lymphadenopathy (60%), splenomegaly (50%), Hepatomegaly (<40%) ➤ Hypogammaglobulinemia --> increased risk of infections, ➤ Some patients develop autoimmune antibodies (10%) and most develop a decrease in one or more Ig types ➤ Minor impairments in cell mediated immunity will lead to reoccurrence of infections such as shingles, herpetic lesions, etc. ➤ CLL rarely transforms into a worse disease such as prolymphocytic leukemia or large cell lymphoma (Richter Syndrome) | <ul style="list-style-type: none"> ➤ B-CLL (98% of cases) à has B cell markers like CD 19 and 20, one T cell marker (CD5) is also present à cells are CD23+ and CD10 negative. ➤ T-CLL (1-2% of cases) à has T cell markers | <p>Peripheral blood:</p> <ul style="list-style-type: none"> ➤ ↑ # of normal appearing lymphocytes, Smudge cells (parachute cells) which result from the fact that neoplastic lymphocytes are fragile ➤ Spherocytes - CLL is associated with warm autoimmune hemolytic anemia (AIHA) in 10% of cases and will cause to be observed in peripheral blood (a major complication) <p>Bone Marrow</p> <ul style="list-style-type: none"> ➤ Numerous normal appearing neoplastic lymphocytes <p>Lymph node:</p> <ul style="list-style-type: none"> ➤ Diffuse pattern (not nodular), but proliferation centers are present | <p><u>Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)</u></p> <p>CLL is very similar to SLL</p> <ul style="list-style-type: none"> ➤ Patients presenting with blood findings à CLL ➤ Patients presenting with lymph node finding à SLL ➤ Lymph node involvement is also common in CLL (50%) <p>SLL is a proliferation of small B lymphocytes, which have B cell markers and one T cell marker (CD5), like B-CLL</p> <p>Classification of CLL</p> <ul style="list-style-type: none"> ➤ CLL is a progressive accumulation of neoplastic, immunologically incompetent, clonal lymphocytes ➤ Cytological abnormalities – no specific mutation, but trisomy 21 is common and some involve translocations of the long arm of 14 (14q) which is the site of heavy chain gene, and usually, involvement of this area is prognostic of progressive disease ➤ If B cell monoclonality, then you will only see a κ or a λ chain but not both due to light chain restriction | <ul style="list-style-type: none"> ➤ Staging system is indicative of prognosis and depends on the presence of lymphocytosis in addition to lymphadenopathy, splenomegaly, anemia or thrombocytopenia ➤ Tx – no evidence that therapy prolongs survival, but if you are asymptomatic, you watch and wait, if you are symptomatic, you get radiation for local complications, chemotherapy, monoclonal antibodies or stem cell transplantation |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| <p>Increasing incidence with peak age at 70 with Blacks : whites 2:1 (unknown etiology)</p> <ul style="list-style-type: none"> ➤ Lytic disease of the bone → bone pain, spontaneous fractures; ➤ Anemia ➤ Infection ➤ Ascites ➤ Circulatory insufficiency ➤ Dyspnea, congestion, <p>Patients who present early end up with an incidental diagnosis and are asymptomatic while patients who present later present with lower back pain, recurrent infections and systemic symptoms related to their anemia, renal failure and hypercalcemia</p> | <p>Diagnosis is made from blood test and protein electrophoresis</p> <ul style="list-style-type: none"> ➤ 75-80 % have serum monoclonal IgG, IgA, (M protein) ➤ 10-20% make light chains only and rapid renal excretion allows for urine electrophoresis (Bence Jones protein) ➤ (note that CLL, lymphoma, benign monoclonal gammopathy can also have monoclonal Igs) ➤ Hypercalcemia – secondary to bone destruction ➤ Renal insufficiency from Bence Jones protein ➤ Amyloidosis | <p>Blood smear</p> <ul style="list-style-type: none"> ➤ Multinucleated plasma cells with dysplastic cytoplasm <p>Bone marrow</p> <ul style="list-style-type: none"> ➤ Plasmacytosis– >10% plasma cells (usually much higher) often present in sheets (keep in mind that inflammation, cirrhosis and AIDS can be other sources of plasmacytosis) | <p>Multiple Myeloma</p> <ul style="list-style-type: none"> ➤ A clonal malignancy of Plasma Cells ➤ Monoclonal Ig and light chains, ↓ levels of normal Ig's (hypogammaglobulinemia), cellular immune responses however are preserved and bacterial infections are common – early (Strep Pneumoniae) and Later (S. Aureus, Gram negative rods) <p>Bone disease in Myeloma</p> <ul style="list-style-type: none"> ➤ Results from unbalanced osteoclast activity usually visible on radiograph and ↑ bone breakdown results in hypercalcemia and hypercalciuria <p>Ascites can result from amyloid damage of the kidney</p> <p>Hyperviscosity Syndrome</p> <ul style="list-style-type: none"> ➤ Due to aggregated M protein and results in circulatory insufficiency, and abnormal hemostasis ➤ Dyspnea with congestion evident on CXR, encephalopathy and visual disturbances (see fundoscopic abnormalities indicative of hyperviscosity – dilatation and segmentation of the retinal vein) and bleeding <p>Amyloidosis in Myeloma</p> <ul style="list-style-type: none"> ➤ Due to light chain deposition in tissues with a greater incidence of lambda amyloid and frequently manifests in skin, tongue, GI, soft tissue, peripheral nerves, heart, kidneys | <p>No effective Tx out there</p> <ul style="list-style-type: none"> ➤ Tx – viphosphonates (pamidronate, zoledronate), ➤ Radiotherapy, corticosteroids and ➤ Conventional chemotherapy, thalidomide (anti-angiogenic), Bortezomib (proteasome inhibitor) ➤ Stem cell transplantation |
| | | | <p>Benign Monoclonal Gammopathy</p> <p>Benign Monoclonal Gammopathy is more common than multiple myeloma, but there is no concomitant bone or kidney disease and no anemia, most patients remain stable and about 10% develop multiple myeloma – usually though, monoclonal Ig is an isolated finding</p> | |
| <ul style="list-style-type: none"> ➤ Ages 35-50 ➤ Insidious onset ➤ Massive splenomegaly (extramedullary hematopoiesis) ➤ Terminal: Blast crisis | <ul style="list-style-type: none"> ➤ Marked ↓ leukocyte alkaline phosphatase activity | <p>Blood Smear</p> <ul style="list-style-type: none"> ➤ Leukocytosis - ↑ # of neutrophils, band and metamyelocytes, ↑ eosinophils and basophils <p>Bone marrow</p> <ul style="list-style-type: none"> ➤ Hypercellular with all cell lines increased in number | <p>Chronic Myelogenous Leukemia (CML)</p> <p>Clonal proliferation of pluripotent stem cells</p> <ul style="list-style-type: none"> ➤ Unique characteristic is the chromosomal translocation ➤ Philadelphia chromosome – t(9;22) ➤ Chromosome 9 has abl (an oncogene) while 22 has bcr (breakpoint cluster region) resulting in formation of a new protein P210 that has tyrosine kinase activity | <ul style="list-style-type: none"> ➤ Tx – control with hydroxyurea, bone marrow transplant ➤ Prognosis: Slow progression (50% develop accelerated phase < 5 years) ➤ Blast crisis – non-responsive to chemotherapy |

| Clinical Presentation | Labs | Morphology (Blood Smear / Bone Marrow) | Pathophysiology | Management |
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| <ul style="list-style-type: none"> ➤ Uncommon before 60's ➤ Progressive anemia with marked splenic enlargement (secondary hematopoiesis) ➤ Fatigue, weight loss, night sweats, etc. | <ul style="list-style-type: none"> ➤ WBC count – reduced, normal, or elevated ➤ Same WBC differential as CML | Blood smear <ul style="list-style-type: none"> ➤ Anisopoikilocytosis ➤ Tear-drop RBC's ➤ Nucleated RBC's Marrow <ul style="list-style-type: none"> ➤ Fibrosis (not part of clone) | <u>Myeloid metaplasia with myelofibrosis</u> <ul style="list-style-type: none"> ➤ Also arises from transformed multipotent myeloid stem cell | |
| <ul style="list-style-type: none"> ➤ Abnormal blood flow (from increase in RBC mass) ➤ Splenomegaly ➤ Chronic hypoxia | <ul style="list-style-type: none"> ➤ Hct. 60% or more ➤ Decreased erythropoetin (distinguishes it from other forms of polycythemia) | Blood smear <ul style="list-style-type: none"> ➤ Marked erythrocytosis, granulocytosis, and thrombocytosis ➤ Basophilia, neutrophilia Bone Marrow <ul style="list-style-type: none"> ➤ Hypercellular | <u>Polycythemia vera</u> <ul style="list-style-type: none"> ➤ Also arises from transformed multipotent myeloid stem cell | <ul style="list-style-type: none"> ➤ Maintain crit in normal range with phlebotomy |
| <ul style="list-style-type: none"> ➤ Age over 60 ➤ Bleeding and thrombosis | <ul style="list-style-type: none"> ➤ Platelet count > 600,000 | Blood smear <ul style="list-style-type: none"> ➤ Lots of platelets | <u>Essential thrombocythemia</u> <ul style="list-style-type: none"> > Like polycythemia vera, but for platelets | |
| | | | <u>Leukemoid reaction</u> <ul style="list-style-type: none"> Reaction to infection | |