The Physician Pharmacist: Hematology/Oncology

Fetal Erythropoiesis:
- Yolk Sac = 3-8 w
- Liver = 6 w - birth
- Spleen = 10-28 w
- Bone Marrow = 18 w - Adult

Fetal Hb = a2g2
- Higher affinity for O2 due to less avid binding of 2,3 BPG (allows HbF to extract O2 from maternal Hb)

Adult Hb = a2B2

Blood Groups:
- **A** = RBCs have A antigens on surface, and B antibodies flowing in blood
- **B** = RBCs have B antigens on surface, and A antibodies in blood
- **AB** = Both A+B antigens on RBC surface, and NO antibodies in plasma
  - (**Universal Recipient**)
- **O** = no antigens on surface, but Anti-A and Anti-B antibodies present in blood
  - (**Universal Donor**) - can only receive from O
- **Rh(+)** = Rh(D) on RBC surface, no antibodies present
- **Rh(-)** = no antigens on surface, so Anti-D antibodies in blood (IgG)

Erythroblastosis Fetalis:
-Rh(-) patient has an Rh(+) fetus…blood exchange causes mothers antibodies to attack fetus
-Often requires first pregnancy exposure (IgG antibodies; often form secondary response - also only Abs to cross placenta)
-**Hydrops Fetalis** = Jaundice/Kernicterus
-Tx = Rhogam (Anti-D IgG) given in 3rd trimester, and shortly after delivery (Prevents maternal production of anti-D IgG)

ABO Hemolytic Dx:
-Type O pregnant patient (circulating anti-A/B) has A or B blood type child
-IgGs cross placenta and attack child
-Key = Can occur with 1st pregnancy (unlike EBF)
-Often less severe
-Tx = Phototherapy or exchange transfusion

Lymphoid Stem Cell (Lymphopoiesis)
- B cells → plasma Cells
- T cells → T-helper + T-cytotoxic
- NK Cells

Myeloid Stem Cell:
- Erythropoiesis = Erythroblast → Reticulocyte → Erythrocyte
- THrombopoiesis = Megakaryoblast → Megakaryocyte → Platelets
- Granulocytopoiesis = Myeloblast
  - Band → Neutrophil
  - Basophil
  - Eosinophil
- Monocytopoiesis = Monoblast → Monocyte → Macrophage

Neutrophils:
-(+)Chemotaxis = **C5a, LTB4, IL-8, 5-HETE**, Kallikrein, Platelet-Activating Factor (PAF), N-formylmethionine (bacterial)
-Hypersegmented Nucleus? = B12/Folate Def
-Left Shift (Bands) = myeloid proliferation (inflammation, CML)
-Leukoerythroblastic Rxn = Left Shift + Immature RBCs (Myelofibrosis, Metastasis)

Erythrocytes:
-Anucleate, No MHC I
-120 d adult t1/2 (60-90d neonates)
-Glycolysis primary energy supply
-Erythrocytosis (Hct) = Polycythemia
-Anisocytosis = varying sizes
-Poikilocytosis = varying shapes
-Reticulocyte = immature RBC (reflect erythroid proliferation)
-Polychromasia = reticulocytes w/ residual ribosomal RNA

Platelets:
-needed for primary hemostasis
-anucleate (has MHC I)
-Megakaryocyte origin
-8-10d lifespan (Pl8lets)
-Dense Granules (**CASH**; Ca2+, ADP, Serotonin, Histamine)
-**a Granules** (vWF, Fibrinogen, Fibronectin, Platelet Factor 4)
-Petechiae = thrombocytopenia
-vWF Receptor = GP Ib
-Fibrinogen Receptor = GP IIb/IIIa

Monocytes:
-found in blood, differentiate into Macrophages in tissue
-One nucleus

Macrophages:
-IFN-g = activates
-APC w/ MHC II
-Form Granulomas (TB, Sarcoid), fusing to form Giant Cells
-Bacterial LPS binds **CD14** to initiate septic shock
-Kupffer Cell = Liver Macrophage
-Histiocytes = Connective Tissue
-Langerhans = Skin
-Osteoclasts = Bone
-Microglial = brain

Eosinophils:
-Helminthic infxn (Major Basic Protein)
-IL-4 stimulated
-Bilobed nucleus
-Produces = Histaminase, Major basic Protein (MBP - kills helminths), Eosinophil Peroxidase, Cationic Protein, Eos-Derived Neurotoxin
-Eosinophilia Causes; PACMANE
- Parasites
- Asthma
- Chronic Adrenal Insuff
- Myeloproliferative dx
- Allergic process
- Neoplasia (Lymphoma)
- Eosinophilic Granulomatosis w/ Polyangiitis

Basophils:
-mediate allergic rxn
-Contain = Heparin + Histamine
-Basophilia = uncommon (CML)

Dendritic Cells:
-highly phagocytic APCs
-"professional APCs" - travel to Lymph nodes to activate T-cells
-Link btw Innate + Adaptive Immune Sys
-Express MHC II + MHC I (Cross-presentation)

Mast Cells:
-mediate local tissue allergic rxns (bind Fc portion of IgE)
-C3a, C5a, Surface IgE cross-link (aggregation) → degranulation → Histamine, Heparin, Tryptase, Eosinophil Chemotactic factors
-**Type I HSR**
-Cromolyn Sodium = prevents degranulation
-Vacomycin, Morphine (Opioids), Radiocontrast dye = elicit IgE-Independent Mast Cell Degranulation
-Mastocytosis (Rare) - *c-KIT mutations*

Lymphocytes:
-B, T, NK cells (B + T part of Adaptive Immunity, NKC part of innate)
NKC:
-Perfoin, granzymes
-**CD56, CD16**
B-cells:
-Humoral response
-bone marrow origin
-migrate to peripheral lymphoid tissue (follicle of LN, White pulp of spleen)
-exposed to antigen, differentiates into Plasma Cells(Ab prod, Memory Cells)
-Can function as APC
T-cells:
-originate form bone marrow, but mature in Thymus
-CD4+ T cells = MHC II
-CD8+ T cells = MHC I
-Both need costimulatory activation of CD28 (often w/ B7 - CD80/86)
Plasma Cells:
-produce antibody
-"Clock face" chromatin distribution + eccentric nucleus
-Abundant RER, well developed Golgi
-Found in bone marrow, normally don't circulate in blood

Hemoglobin Electrophoresis:
-HbA migrates farthest > HbF > HbS > HbC
-Cathode (-)→ Anode (+)
-missense mutation in HbS/C replaces glutamic acid (-) w/ valine or Lysine

Coombs Test: "detects presence of Abs against RBCs"
-Direct Coombs = anti-Ig Ab added, if RBCs already coated w/ Ig they will agglutinate (ddx - AIHA)
-Indirect Coombs = Normal RBCs added to pt serum, if serum has anti-RBC surface Ig→ agglutinates (used for Pretransfusio

Platelet Plug Formation:
1. Injury:
-endothelial damage → transient vasoconstriction (endothelin release)
2. Exposure:
-vWF binds exposed collagen
-vWF comes from a-Granules from Platelets + Weibel-Palade Bodies of Endothelial cells
3. Adhesion:
-platelets bind vWF via GP Ib receptor → conformational platelet change
-platelets release ADP + Ca2+ (inducing Coag cascade), and TXA2
-ADP helps platelets adhere to endothelium
4. Activation:
-ADP binding to P2Y12 receptor → induces GpIIb/IIIa expression at platelet surface
5. Aggregation:
-Fibrinogen binds GP IIb/IIIa receptors + links platelets

Notes:
-Pro-aggregation Factors: (TXA2 from platelets decreases blood flow + increases aggregation)
-Anti-Aggregation Factors: (PGI2 + NO from endothelial cells tries to increase blood flow, and decrease aggregation)
-Temporary plug STOPS bleeding BUT is very UNSTABLE (coagulation cascade provides secondary hemostasis)

Pharm:
-ASA = irreversible inhibition of COX (no TXA2 synth)
-Clopidogrel, Prasugrel, Ticagrelor, Ticlopidine =
- block P2Y12 receptor (Inhibiting ADP-Induced expression of GpIIb/IIIa)

-Abciximab, Eptifibatide, Tirofiban:
- Inhibit GpIIb/IIIa directly

-Ristocetin:
- Normally activates vWF to bind Gp Ib
- Failure to aggregate w/ Ristocetin assay = vonWillebrand Dx (no vWF)or Bernard-Soulier Syndrome (no GpIb receptor)

-Desmopressin = promotes vWF + VIII release from endothelial cells

Vitamin K Def:
-decreased synth of II, VII, IX, X, Protein C and S

-Warfarin inhibits Vit K Epoxide Reductase
-Neonates lack enteric bacteria (normally produce vit K)
-Factor VII (7) = Shortest t1/2
-Factor II (Thrombin) = Longest t1/2
-Antithrombin (AT3) = blocks Thrombin (IIa), VIIa, IXa, Xa, XIa, XIIa
-Heparin enhances activity of Antithrombin
-Factor V Leiden = factor V is resistant to inhibition by Protein C (perpetual clotting)

RBC Morphology:
-**Acanthocytes** (Spur Cells) = Asymmetric projections (liver dx, abetalipoproteinemia, vit E def)
-**Echinocytes** (Burr Cells) = even/uniform projections (Liver dx, ESRD, Pyruvate kinase def)
-**Dacrocytes** (Teardrop) = "squeezed out of bone marrow" (Myelofibrosis)

-**Schistocytes** (Helmet) = Fragmented RBCs (DIC, TTP, HUS, HELLP Synd, Heart Valve Hemolysis)

-**Degmacytes** (Bite Cells) = removal of Heinz bodies by splenic macrophages "degging them out" (G6PD def)

-**Elliptocytes** (ovals) = Spectrin mutation needed to maintain shape of membrane (Hereditary Elliptocytosis)

-**Spherocytes** = small, spherical cells w/o central pallor, SA to Vol ratio (hereditary spherocytosis, autoimmune hemolytic anemia)
-**Macro-ovalocytes** = megaloblastic anemia
-**Target Cells** (Bullseye) = SA to Vol ratio (HALT; HbC dx, Asplenia, Liver dx, Thalassemia)
-**Sickle Cell** = occurs w/ low O2 conditions (High altitude/acidosis - Sickle Cell Anemia)

RBC Inclusions:

1. Iron Granules
-perinuclear mitochondria w/ excess iron (ringed-sideroblasts)
-Prussian Blue Stain
-Dx = Sideroblastic Anemias (Lead Poisoning, Myelodysplastic Syndromes, Chronic ALcohol Overuse)

2. Howell-Jolly Bodies:
-Basophilic nuclear remnants
-Normally removed by splenic macrophages
-Dx = Functional Hyposplenia (Sickle Cell), Asplenia

3. Basophilic Stippling:
-basophilic ribosomal precipitates
-Dx = Sideroblastic anemias, Thalassemias

4. Pappenheimer Bodies:
-Basophilic granules
-Dx = Sideroblastic anemias

5. Heinz Bodies:
-Denatured + precipitated Hb (contain iron)
-phagocytic removal of Heinz bodies ⇒ Bite Cells
-Crystal Violet Staining
-Dx = G6PD

Microcytic, Hypochromic Anemias: (MCV < 80)

Iron Deficiency (IDA):
-low iron due to chronic bleeding (GI loss, Menorrhagia), Malnutrition, Absorption disorders, GI surgery (gastrectomy), increased demand (Pregnancy)
-decreased final step in heme synthesis
- **Iron, TIBC, Ferritin, Free Erythrocyte Protoporphyrin, RDW, RI (reticulocyte index)**
-Microcytosis + Hypochromia (Increased Central Pallor)
-Sxs = fatigue, conjunctival pallor, Pica, Spoon nails (Koilonychia)
-Plummer-Vinson Syndrome (IDA, Esophageal Webs, Dysphagia)

A-Thalassemia:
-a-globin gene deletions on Chr 16 → a-globin synthesis
-Normal aa/aa
-often RBC count (in contrast to IDA)

1. (aa/a-) = a-thalassemia minima
-No anemia (silent carrier)

2. (a-/a-; trans) or (aa/--;cis) = a-Thalassemia minor:
-Mild microcytic
-hypochromic anemia; Cis deleation may worsen outcome for the carrier's offspring

3. (--/-a) Hemoglobin H dx (HbB):
-excess B-globin forms B4
-Mod-severe microcytic hypochromic anemia

4. (--/--) Hemoglobin Barts Dx
-no a-globin, excess gamma-globin forms gamma4
-Hydrops fetalis; incompatible w/ life

B-Thalassemia:
-Point mutations in splice sites + promoter sequences on Chr11 → B-globin synthesis
- prevalence in people of mediterranean descent

1. B-thalassemia Minor:
-Heterozygote
-B-chain is underproduced (usually asymptomatic)
-ddx = confirmed by HbA2 on electrophoresis

2. B-thalassemia Major:
-Homozygote
-B chain is absent → severe microcytic, hypochromic anemia w/ target cells
-Marrow expansion, skeletal deformities
-extramedullary hematopoiesis → hepatosplenomegaly
- risk of Parvovirus B19 induced Aplastic Crisis
HbF (a2g2), HbA2 (a2delta2)
-HbF is protective in the infant (only becomes symptomatic after 6 months)

3. HbS/B-thalassemia heterozygote:
-mild-mod sickle cell dx depending on amount of B-globin production

Lead Poisoning;
-lead inhibits ferrochelatase + ALA Dehydrogenase → heme synthesis + RBC protoporphyrin
-Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling)
Sxs: "**LEAD"**
-Lead Lines on Gingiva (Burton Lines) + long bones
-Encephalopathy + Erythrocyte Basophilic Stippling
-Abdominal Colic + Sideroblastic Anemia
-Drops - wrist/foot drop
Tx: Chelation (Succimer, EDTA, Dimercaprol)

Sideroblastic Anemia:
-Causes = Genetic (X-linked defect in ALA synthase), Acquired (MDS), Reversible (Alcohol, Lead Poisoning, Vit B6 def, Copper Def, Drugs [Isoniazid, Linezolid])
- Iron, Norma/ TIBC, Ferritin
-Ringed sideroblasts (iron-laden, prussian blue-stained mitochondria) in Bone Marrow
-Peripheral blood = basophilic stippling of RBCs
Tx: Pyridoxine (B6, Cofactor for ALA Synthase)

Transferrin = transports iron in blood
TIBC = indirectly measures transferrin
Ferritin = primary iron stores

IDA:
Iron
TIBC
Ferritin,
%Transferrin saturation

Chronic Dx:
Iron
TIBC
Ferritin
%Transferrin saturation

Hemochromatosis:
Iron
TIBC
Ferritin
% Transferrin Saturation

Pregnancy/OCP Use:
- Iron
TIBC
- Ferritin
% transferrin saturation

Macrocytic Anemias: (MCV >100)

Megaloblastic Anemia:
-impaired DNA synthesis → maturation of nucleus precursor cells is delayed in comparison to maturation of cytoplasm
-Hypersegmented PMNs
-Causes: Folate def, B12, Meds (Hydroxyurea, phenytoin, MTX, sulfa drugs)

1. Folate Deficiency:
-causes = Malnutrition (Alcoholism), Malabsorption, Drugs (MTX, Trimethoprim, Phenytoin), increased requirement (Pregnancy, Hemolytic Anemia)
- **Homocysteine, Normal Methylmalonic acid**
-No Neurologic sxs (vs. B12)

2. Vitamin B12 (Cobalamin) Def.:
-causes = Pernicious Anemia, Malabsorption (Crohns), Pancreatic Insufficiency, Gastrectomy, Insufficient intake (Veganism), Diphyllobotrhrium Latum (Fish tapeworm)
- **Homocysteine, Methylmalonic acid**
-Neurologic Sxs***
- Reversible dementia
- Subacute combined degeneration (b12 needed for Fatty acid synth + myelin production) = Spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction

-Folate supplementation can correct anemia but worsens neurological sxs
-DDx = Schilling test (insuff vs. malabsorption)
-Anemia from insufficient intake, takes years (liver can store plenty) vs. Folate (depleted within weeks)

3. Orotic Aciduria:
-Inability to convert orotic acid to UMP (de novo PYRimidine Synth)
-defect in UMP Synthase
-Autosomal recessive
-"Children who fail to thrive", developmental delays, megaloblastic anemia refractory to folate + B12 supps
-No Hyperammonemia (vs. ornithine transcarbamylase def → orotic acid w/ hyperammonemia)
-Orotic Acid seen in urine
-Tx = Uridine Monophosphate (UMP) or Uridine Triacetate to bypass defective enzyme

Non-Megaloblastic Anemia:
-macrocytic anemia BUT DNA synthesis is normal
-RBC macrocytosis w/o Hypersegmented PMNs
-Causes = Liver dx, alcoholism

1. Diamond-Blackfan Anemia:
-congenital form of Pure red cell aplasia (vs. Fanconi anemia, which causes pancytopenia)
-Rapid-onset anemia within 1st year of life due to defect in Erythroid Progenitor Cells
- % HbF (but total Hb)
-Short stature, craniofacial abnormalities, upper extremity malformations (Triphalangeal thumbs)

Normocytic: (MVC 80-100)

Normocytic, Normochromic:
-classified as either nonhemolytic or hemolytic (intrinsic vs. extrinsic)
-Hemolysis = LDH, reticulocytes, unconjugated Bili, pigmented gallstones, urobilinogen in urine

Intravascular Hemolysis:
- haptoglobin, schistocytes on blood smear
-hemoglobinuria, hemosiderinuria, urobilinogen in urine
-Causes = Mechanical hemolysis (prosthetic valves), Paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias

Extravascular Hemolysis:
-Mech = macrophages in **spleen** clear RBCs
-spherocytes in peripheral smear (commonly due to hereditary spherocytosis, and autoimmune hemolytic anemia), **No Hemoglobinuria/hemosiderinuria**
-can still have urobilinogen in urine

Nonhemolytic, Normocytic:

1. Anemia of Chronic Dx:
-inflammation (IL-6) → Hepcidin (released from liver, binds ferroportin on intestinal mucosal cells + macrophages, inhibiting iron transport)
- release of iron from macrophages + iron absorption from gut
-Conditions = Chronic Infxn, Neoplastic Disorders, CKD, SLE, RA
- **iron, TIBC, Ferritin**
-Normocytic but can become microcytic
-Tx = fix underlying dx, consider blood transfusions,

2. Aplastic Anemia:
-Failure/destruction of hematopoietic stem cells
-"Reducing Volume From Inside Diaphysis"
1. Radiation
2. Viral agents (EBV, HIV, Hepatitis)
3. Fanconi Anemia (Auto Recessive DNA repair defect → bone marrow failure)
4. Idiopathic (immune mediated, primary stem cell defect)
5. Drugs (Benzene, Chloramphenicol, Alkylating agents, Antimetabolites)

- **Reticulocyte count, EPO**
-Pancytopenia w/ anemia, leukopenia, thrombocytopenia (NOT the same as aplastic crisis which ONLY causes anemias)
-Normal cell morphology, but hypocellular bone marrow w/ **fatty infiltration (looks like fat lipid deposits in bone marrow)**
-sxs = fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection
-Tx = stop drugs, bone marrow allograft, RBC/platelet transfusion, Bone marrow stimulation (GM-CSF)

Hemolytic (Intrinsic):

1. Hereditary Spherocytosis:
-Autosomal dominant
-defect in proteins interacting w/ RBC membrane skeleton + plasma membrane (Ankyrin, Band 3 Protein 4.2, Spectrin)
-Small, round RBCs w/ less SA and no central pallor (MCHC)
-leads to premature removal by spleen (Extravascular Hemolysis)
-Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 Infxn)
Labs:
- fluorescence of RBCs in Eosin 5-maleimide (EMA) binding test
fragility in osmotic fragility test
-normal/ MCV w/ abundance of RBCs
-Tx = Splenectomy

2. G6PD Def:
-X-linked recessive
-G6PD defect → NADPH → Glutathione → RBC susceptibility to Oxidative Stress (ROS) → Hemolysis
-Drugs (**Sulfas, Antimalarials, Fava Beans**)
-Extravascular + Intravascular Hemolysis
-**Back pain, Hemoglobinuria** (a few days later)
-**Heinz Bodies + Bite Cells**

3. Pyruvate Kinase Def.
-Autosomal recessive
-Pyruvate Kinase Defect → ATP → rigid RBCs → extravascular hemolysis
- levels of 2,3-BPG → hemoglobin affinity for O2
-Hemolytic Anemia in a Newborn
-Blood smear w/ **Burr Cells** (Echinocytes - uniform blebs)

4. Paroxysmal Nocturnal Hemoglobinuria:
-Hematopoietic stem cell mutation → complement-mediated intravascular hemolysis (especially at Night)
-**PIGA mutation** → impaired GPI anchor synthesis for decay-accelerating factor (DAF/**CD55**) + Membrane inhibitor of reactive lysis (MIRL/**CD59**) = both normally protect RBC membrane from Hemolysis
-Triad:
1. (-) Hemolytic Anemia
2. Pancytopenia
3. Venous Thrombosis (Budd-Chiari Syndrome)

-Pink/Red urine in morning
-Associated w/ Aplastic Anemias + Acute Leukemias
-CD55/CD59 (-) RBCs on Flow Cytometry
-Tx = Eculizumab (targets terminal complement protein C5)

5. HbC Disease:
-Glutamic Acid-to-Lysine Point Mutation in B-globin
-Causes Extravascular hemolysis
-pts w/ PbSC (1 of each mutant Gene) have milder dx than HbSS pts
-Blood smear in homozygotes = Hemoglobin Crystals inside RBCs (Target Cells)

EPO for CKD

6. Sickle Cell Anemia:
-B-globin Gene point mutation (single AA switch from Glutamic Acid → Val)
-Mutant HbA becomes HbS
-Causes Extravascular + Intravascular Hemolysis
-Low O2, High Altitude, Acidosis = triggers sickling (deoxygenated HbS polymerizes) → Anemia + VOC
-Asymptomatic Newborns (b/c of HbF for short time)
-Heterozygotes have resistance to Malaria
-Most common autosomal recessive dx in Black population
-Sickle Cells are Crescent Shaped RBCs
-"Crew-Cut" on Skull X-ray due to marrow expansion from erythropoiesis (seen in thalassemia too)
-Complications:
1. Aplastic Crisis (transient arrest of Erythropoiesis due to Parvovirus B19)
2. Autosplenectomy (**Howell-Jolly Bodies**) → infxn w/ encapsulated organisms (Strep pneumo, Neisseria)
3. Splenic Infarct/Sequestration Crisis
4. Salmonella Osteomyelitis
5. VOC: dactylitis (painful swelling of hands/feet), Priapism, Acute Chest syndrome (pulm infiltrates on CXR, common cause of mortality), Avascular Necrosis, Stroke
6. Renal Papillary Necrosis (sickling in renal medulla); PO2 → hematuria

- **HbA, HbF, HbS**
-Tx = Hydroxyurea (HbF), Hydration

Hemolytic (Extrinsic):

1. Autoimmune Hemolytic Anemia (AIHA):
-often Idiopathic + Coombs (+)
-Spherocytes + Agglutinated RBCs on peripheral smear
Warm AIHA:
-chronic anemia
-**IgG** causing extravascular hemolysis
-SLE, CLL, B-lactams, a-methyldopa
Cold AIHA:
-acute anemia
-**IgM** + **Complement** causing RBC agglutination and extravascular hemolysis upon exposure to cold
-Cold, Painful blue fingers/toes

2. Microangiopathic Hemolytic Anemia:
-RBCs damaged when passing through obstructed/narrowed vessels
-causes intravascular hemolysis
-DIC, TTP/HUS, SLE, HELLP syndrome, Hypertensive Emergency
-**Schistocytes** (helmet cells) seen in peripheral smear "Split RBCs"

3. Macroangiopathic Hemolytic Anemia:
-Prosthetic hear valves + aortic stenosis
-mechanical destruction of RBCs
-Schistocytes on peripheral blood smear (same as above)

4. Hemolytic Anemia due to Infxn:
- destruction of RBCs (Malaria, Babesia)

Leukopenias:

1. Neutropenia:
-ANC < 1500 (< 500 indicates severe infxn)
-Causes = Sepsis, Drugs (chemo), Aplastic anemia, SLE, radiation

2. Lymphopenia:
-Absolute Lymphocyte Count < 1500 (< 3000 in children)
-HIV, DiGeorge, SCID, SLE, Steroids, Radiation, Sepsis, Post-Op

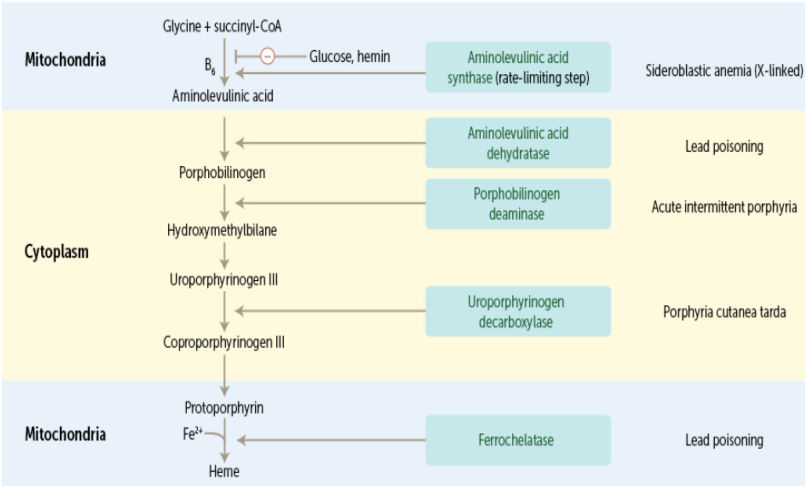
3. Eosinopenia:
-Absolute Eos Count < 30
-Cushing Syndrome, Steroids

Steroids cause Neutrophilia (PMNs) despite causing Eosinopenia/Lymphpenia b/c they activation of PMNs adhesion molecules → impairing migration to sites of infxn

-CLL, **Mycoplasma** pneumoniae infxns, **Mono**nucleosis

Heme Synthesis Disorders/Toxins

	Enzyme Affected	Accumulated Precursors	Sxs
Lead Poisoning	1. **Ferrochelatase** (last step in Heme synth - Mitochondrial side) 2. **ALA Dehydratase** (Cytoplasm)	-Protoporphyrin -ALA (Aminolevulinic Acid)	-Microcytic Anemia (basophilic stippling - blood, Ringed Sideroblasts -marrow), GI, Kidney Dx -Children = exposure to lead paint → mental deterioration -Adults = Environmental exposure (Batteries/Ammunition) → HA, Memory Loss, Demyelination (Peripheral Neuropathy)
Acute Intermittent Porphyria	1. **Porphobilinogen Deaminase** (Cytoplasm)	-Porphobilinogen -ALA	-5 P's 1. Painful abd 2. Port wine - colored pee 3. Polyneuropathy 4. Psychological disturbances 5. Precipitated by factors that ALA Synthase (CYP Inducers, Alcohol, Starvation) -Tx = Hemin + Glc
Porphyria Cutanea Tarda	1. **Uroporphyrinogen Decarboxylase** (Cytoplasm)	-Uroporphyrin (Tea-Colored Urine)	-Blistering cutaneous photosensitivity + Hyperpigmentation -MOST COMMON PORPHYRIA -exacerbated w/ Alcohol Consumption -Causes = Familial, Hepatitis C -Tx = Phlebotomy, Sun avoidance, antimalarials (Hydroxychloroquine)



Acute Iron Poisoning:
-High mortality (accidental child ingestion)
-cell death due to formation of Free Radical + Peroxidation of membrane lipids
-Abd pain, vomiting, GI bleeding
-Severe = Anion Gap metabolic acidosis + organ failure
-Sequelae = scarring + GI obstruction
-Radioopaque pill seen on x-ray
-Tx = Chelation (Deferoxamine, Deferasirox), Gastric Lavage:

Chronic Iron Poisoning: "Hemochromatosis"
-seen in pts w/ hereditary or acquired (chronic transfusions for thalassemias/Sickle Cell)
-Arthropathy, cirrhosis, cardiomyopathy, DM, Skin pigmentation (Bronze Diabetes), Hypogonadism
-Tx = Phlebotomy (pts w/o anemia) or Chelation

Coagulation Disorders:

-**PT** = tests function of common + **Extrinsic** pathway (Factors I, II, V, VII, X) “Play Tennis Outside”
-**INR** = patient PT/control PT (Warfarin prolongs INR > 1
-**PTT** = tests function of **Intrinsic Pathway** (all factors except VII, XIII) “Play Table Tennis Inside”

1. Hemophilia A, B, or C:
-No change PT
- **PTT**
-Intrinsic Pathway Coagulation:
A = **def VIII** (8) “hemophilia eight ~A”
B= def IX (9)
C = def XI (11)
-Hemarthroses (bleeding into joints), easy bruising
-Tx = Desmopressin, Factor VIII concentrate, Emicizumab (A); Factor IX (B), Factor XI concentrates (C)

2. Vitamin K Def:
- PT
- PTT
-General coagulation defect (Bleeding time is normal)
- activity of factors 2, 7, 9, 10, protein C, protein S

Platelet Disorders:

-All platelet disorders have an Bleeding Time (BT), Mucous membrane bleeding, and Microhemorrhages (Petechiae, Epistaxis)
-Platelet count (PC) may be low, or normal (qualitative issues instead - dysfunctional, but count ok)

1. Bernard-Soulier:
- /- PC
- BT
-Autosomal recessive
-defect in Adhesion
- GpIb → platelet-to-vWF adhesion
-Abnormal Ristocetin test, Large Platelets

2. Glanzmann Thrombasthenia:
- PC normal
- BT
-autosomal recessive
-defect in aggregation
- GpIIb/IIIa (integrin) → platelet-to-platelet aggregation +

3. Immune Thrombocytopenia:
- PC
- BT
-destruction of platelets in spleen
-Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets
-idiopathic or secondary to autoimmune disorders (SLE), Viral illness (HIV, HCV), Malignancy (CLL), or drug rxns
- Megakaryocytes in bone marrow biopsy, PC
-Tx = Steroids, IVIG, Rituximab, TPO receptor agonists (Eltrombopag, Romiplostim), splenectomy

Thrombotic Microangiopathies:

1. Thrombotic Thrombocytopenic Purpura (TTP):
-females
-inhibition/def of **ADAMTS13** (vWF metalloprotease) → degradation of vWF → large vWF multimers → platelet adhesion + aggregation (Microthrombi formation)
-Triad:
- Thrombocytopenia (platelets)
- Microangiopathic hemolytic anemia (Hb, schistocytes, LDH)
- AKI (SCr)

-Unique sxs = **Fever + Neurologic sxs**
-**Normal PT, and PTT** (helps distinguish TTP and HUS from DIC), Coagulation pathway is NOT activated in TTP/HUS but is w/ DIC
-Tx = plasma exchange, steroids, rituximab

2. Hemolytic Uremic Syndrome (HUS):
-Children
-**Shiga Toxin-Producing E.coli (STEC)** Infxn (serotype O157:H7)
-Triad (same as above)
-Unique Sxs = **Bloody Diarrhea**
-Normal PT and PTT (same as above)
-Tx = Supportive care

Mixed Platelet and Coag Disorders:

1. Von Willebrand Disease (VWD):
-PC normal
- BT
-PT normal
- PTT/normal
-Intrinsic pathway coagulation defect:
vWF → PTT (vWF carries/protects Factor VIII)
-defect in platelet plug formation: vWF → defect in platelet-to-vWF adhesion
-Autosomal dominant
-MOST COMMON Inherited Bleeding Disorder (sxs are mild)
-No platelet aggregation w/ Ristocetin Cofactor Assay
-Tx = Desmopressin (releases vWF stored in endothelium)

2. Disseminated Intravascular Coagulation (DIC):
- PC
- BT
- PT
- PTT
-Widespread clotting factor activation → def in clotting factors → bleeding state (blood oozing from puncture sites)
-Causes = “SSTOP Making New Thrombi”
1. Snake bites
2. Sepsis (Grm (-))
3. Trauma
4. Obstetric Complications
5. Pancreatitis (Acute)
6. Malignancy
7. Nephrotic Syndrome
8. Transfusions

-(+) Schistocytes
- fibrin degradation products (D-dimers)
- Fibrinogen
- Factors V and VIII

defective platelet plug formation
-No platelet clumping observed in peripheral blood smear

Hereditary Thrombophilias:

-All autosomal dominant
-leads to HYPERCOAGULABLE STATE (clots!)

1. Antithrombin Def:
-no direct effect on PT, PTT, or Thrombin time
-decreases the increase in PTT after getting Heparin
-Most inherited some acquired (Renal Failure/Nephrotic Syndrome→AT3 loss in urine→ **inhibition of Factors IIa, Xa**

2. Factor V Leiden:
-production of mutant factor V (**guanine → adenine DNA point mutation**) → **Arg506Gln** mutation near cleavage site
-**Factor V is resistant to degradation by activated Protein C**
-Complications = DVT, cerebral vein thrombosis, recurrent pregnancy loss

3. Protein C or S def:
- **ability to inactivate factors Va and VIIIa**
- risk of Warfarin-Induced Skin Necrosis

4. Prothrombin G20210A Mutation:
-point mutation in 3' untranslated region → **production of prothrombin** → plasma levels + venous clots

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Blood Transfusion Therapy:
-Risks: infxn transmission, transfusion rxns, iron overload (hemochromatosis), hypocalcemia (Ca2+ chelators in products), Hyperkalemia (RBCs lysed in old blood products)

1. Packed RBCs:
- Hb and O2 carrying capacity
-acute blood loss, severe anemia

2. Platelets:
-stops significant bleeding

3. Fresh Frozen Plasma (FFP)/Prothrombin Complex Concentrate (PCC):
- coag factor levels; FFP contains all coag factors/plasma proteins, PCC has 2, 7, 9, 10, C, S
-immediate anticoag reversal

4. Cryoprecipitate:
-fibrinogen, factor VIII, factor XIII, vWF, fibronectin

Leukemia and Lymphomas:

-Leukemia = Lymphoid or myeloid neoplasm w/ widespread involvement of bone marrow (Tumor cells usually found in peripheral blood)
-Lymphoma = discrete tumor mass arising from lymph nodes, Variable clinical presentation

Both Hodgkin + Non-Hodgkin:
-Both present w/ Constitutional (B) sxs:
1. Low-grade fever
2. Night sweats
3. Weight loss

Hodgkin Lymphoma:
-localized, single group of nodes w/ contiguous spread
-Stage is strongest predictor of prognosis
-Better prognosis overall
-**Bimodal distribution** (Young Adult + Old (>55yo))
-Males > Females (except nodular sclerosing subtype)
-Associated w/ EBV

Non-Hodgkin Lymphoma:
-MULTIPLE Lymph nodes involved; extranodal involvement common
-"Non-contiguous Spread"
-Worse prognosis
-Most involve B-cells, some T-cells
-Children + adults
-Autoimmune + viral associations (HIV, EBV, HTLV)

Hodgkin Lymphoma:

-Reed-Sternberg Cells = "Owl Eyes"
-CD15+ and CD30+
1. Nodular Sclerosis: (Most Common)

2. Lymphocyte Rich:
-Best Prognosis

3. Mixed Cellularity:
-Eosinophilia; seen in immunocompromised

4. Lymphocyte Depleted:
-Worst prognosis
-immunocompromised pts

Non-Hodgkin Lymphoma:

Neoplasms of Mature B-Cells:

1. Burkitt Lymphoma:
-Adolescents, young adults
-**t(8;14)** - translocation of ***c-myc*** (8) and Heavy-Chain Ig (14)
-"Starry Sky" lymphocyte sheets + "tingible body" macrophages dispersed
-EBV association
-Jaw Lesions in Africa

2. Diffuse Large B-cell Lymphoma (DLBCL):
-older adults (some young children)
-**BCL-2, BCL-6** mutations
-MOST COMMON type of Non-Hodgkin's Lymphoma in adults

3. Follicular Lymphoma:
-adults
-**t(14;18) -** translocation of heavy chain Ig (14) and BCL-2 (18)
-indolent course w/ painless "waxing and waning" lymphadenopathy
-BCL-2 normally inhibits apoptosis

4. MANtle Cell Lymphoma:
-Adult MALES > > > > females
-**t(11;14)** - translocation of Cyclin D1 (11) and Heavy chain Ig (14)
-CD5+
-very aggressive, often late stage at ddx

5. Marginal Zone Lymphoma [MALT]:
-adults
-**t(11;18)**
-associated w/ Chronic Inflammation (Sjogren's Syndrome, Chronic Gastritis [MALT Lymphoma may regress w/ H. pylori eradication]

6. Primary Central Nervous System Lymphoma (PCNSL):
-EBV related, HIV related

-used for coag factor def involving fibrinogen and factor VIII

Neoplasms of Mature T-Cells:

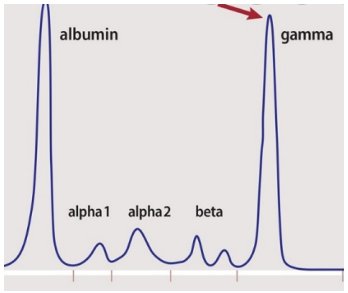
1. Adult T-cell Lymphoma:
-adults
-caused by HTLV (associated w/ IV drug use)
-Cutaneous lesions
-common in Japan, West Africa, Caribbean
-Lytic Bone Lesions, Hypercalcemia

2. Mycosis Fungoides/Sezary Syndrome:
-adults
-Mycosis fungoides = skin patches + plaques (Cutaneous T-cell Lymphoma)
- Atypical Cd4+ cells w/ "Cerebriform" nuclei + intraepidermal neoplastic cell aggregates (Pautrier Microabscess)

-Progression = Sezary Syndrome (T-cell Leukemia)

Plasma Cell Dyscrasias:

-monoclonal immunoglobulin (paraprotein) overproduction due to plasma cell disorder
-Serum protein electrophoresis (SPEP) for Free Light Chain (FLC) assay for tests (**M-Spike** on STEP = overproduction of monoclonal Ig Fragment)
-Urinalysis = 24-hr urine protein electro (UPEP) to detect light chain (No urine dipstick b/c only looks for albumin)
-Confirm w/ Bone Marrow Biopsy



1. Multiple Myeloma (MM):
-overproduction of **IgG** > IgA
-**CRAB**:
- **hyperCalcemia**
- **Renal involvement**
- **Anemia**
- **Bone Lytic Lesions** ("punched out on X-ray") → back pain

-**Rouleaux** Formation (RBCs stacked like poker chips)

2. Waldenstrom Macroglobulinemia:
-overproduction of **IgM** (Macroglobulinemia b/c IgM is the largest Ig)
-Features:
- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity Syndrome:
  - HA
  - Blurry Vision
  - Raynaud Phenomenon
  - Retinal Hemorrhages

-Bone Marrow = > 10% small lymphocytes w/ intranuclear pseudoinclusions containing IgM (lymphoplasmacytic Lymphoma)
-Complications = Thrombosis

3. Monoclonal Gammopathy of Undetermined Significance (MGUS):
-overproduction of ANY Ig Type
-usually asymptomatic
-No CRAB findings
-Bone marrow = < 10% monoclonal plasma cells
-Complication = 1-2% yearly risk of transitioning into Multiple Myeloma

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Myelodysplastic Syndromes (MDS):

-Stem cell disorders involving ineffective Hematopoiesis → defects in cell maturation of non lymphoid lineages
-Bone marrow blasts < 20% (vs. AML > 20%)
-Causes = de novo mutations or environmental exposure (rads, benzene, chemo)
-Risk of AML transformation
Pseudo-Pelger-Huet Anomaly;
-Neutrophils w/ Bilobed ("Duet") nuclei
-associated w/ MDS or Drugs (Immunosuppressants)

-"AIDS-defining Illness" = confusion, memory loss, seizures
-CNS mass (single, ring-enhancing lesion), may look like Toxo (except toxo is multiple)

Leukemias:

-unregulated growth/differentiation of WBCs in Bone marrow → marrow failure →
- anemia (RBCs)
- Infxns (mature WBCs)
- Hemorrhage (platelets)

- circulating WBCs (malignant leukocytes in blood)
-leukemic cell infiltration of Liver, spleen, LNs, and skin (Leukemia Cutis)

Lymphoid Neoplasms:

1. Acute Lymphoblastic Leukemia/Lymphoma (ALL):
-Children > > > > Adults (although worse prognosis)
-T-cell ALL = Mediastinal mass (often as SVC-like Syndrome)
-Associated w/ Down Syndrome
-Blood/Marrow = Lymphoblasts
-TdT+ (marker for pre-B and pre-T cells)
-CD10+ (pre-B cells)
-most responsive to therapy
-**t(12;21)** = better prognosis
-t(9;22) (**Philadelphia Chromosome)** = worse prognosis

2. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL):
- >60 yo
-Most COMMON adult leukemia
-CD20+, CD23+, CD5+ B-cell Neoplasm
-Asymptomatic w/ slow progression
-"**Smudge Cells"** in peripheral blood (Autoimmune hemolytic anemia)
-**Richter Transformation** = CLL/SLL transformation into aggressive lymphoma (often DLBCL)

3. Hairy Cell Leukemia:
-Adult Males (Mature B-cell Tumor)
Filamentous, hair-like projections on LM
-Uncommon to have Lymphadenopathy
-**Marrow Fibrosis** = dry tap on aspiration**
-**Massive splenomegaly + Pancytopenia**

-UA shows Ig Light Chains (Bence Jones Proteinuria) w/ (-) Urine Dipstick
-Bone marrow = > 10% monoclonal plasma cells w/ Clock-Face Chromatin + Intracytoplasmic inclusions containing IgG
-Increased risk of infxns + Amyloidosis

Myeloid Neoplasms:

1. Acute Myelogenous Leukemia (AML):
-65 yo
-**Auer Rods**; Myeloperoxidase (+) cytoplasmic inclusions seen mostly in APL
- circulating Myeloblasts
-RF:
- Alkylating Chemo Exposure
- Radiation
- Myeloproliferative disorders
- Down syndrome

-APL: t(15;17) = responds to **ATRA** (all-trans retinoic acid - vit A) or Arsenic Trioxide = triggers differentiation
-DIC is the most common presentation

2. Chronic Myelogenous Leukemia (CML):
-45-85 yo (64 mean)
-**Philadelphia Chromosome; t(9;22), BCR-ABL** + myeloid stem cell proliferation
-dysregulated production of mature and maturing granulocytes (PMNs, Metamyelocytes, Myelocytes, Basophils)
-Splenomegaly
-May accelerated and transform to AML or ALL ("Blast Crisis")
-Responds BCR-ABL TKIs (Imatinib)

Myeloproliferative Neoplasms:

-Malignant hematopoietic neoplasms w/ varying impacts on WBCs and Myeloid Cell lines

1. Polycythemia Vera:
-disorder of RBCs
-acquired **JAK2** mutation
-presents as intense itching after showering (aquagenic pruritus)
-Erythromelalgia = severe, burning pain + red-blue coloration due to blood clots in vessels of extremities
- **EPO** (something in marrow is causing excessive production outside of hormonal control)
-Tx = Phlebotomy, hydroxyurea, Ruxulitinib (JAK1/2 inhib)

2. Essential Thrombocythemia:
-massive proliferation of megakaryocytes + platelets
-bleeding + thrombosis

1. Polycythemia Vera:
   a. RBCs
   b. WBC
   c. Platelets
   d. (-) Philadelphia Chromosome
   e. (+) JAK2 mutation
2. Essential Thrombocythemia:
   a. Normal RBCs
   b. Normal WBCs
   c. Platelets
   d. (-) Philadelphia Chromosome
   e. (+) JAK2 (30-50%)
3. Myelofibrosis:
   a. RBCs
   b. Variable WBC
   c. Variable Platelets
   d. (-) Philadelphia Chromosome
   e. (+) JAK2 (30-50%)
4. CML:
   a. RBCs
   b. WBC
   c. Platelets
   d. (+) Philadelphia
   e. (-) JAK2

Polycythemia (cont.):

1. Relative Polycythemia:
- plasma volume (primary issue)
-normal RBC mass, O2 Sat, EPO levels
-Dehydration, Burns

2. Appropriate Absolute Polycythemia:
-normal plasma vol
- RBC mass
- O2 saturation (primary issue)
- EPO
-Lung Dx, Congenital heart dx, High altitude

3.Inappropriate Absolute Polycythemia:
-normal plasma vol
- RBC mass
-normal O2 sat
- EPO (Primary issue)

-(+)TRAP Stain = Tartrate-Resistant Acid Phosphatase)
-BRAF mutations
-Tx = Purine Analogs (Cladribine, Pentostatin)

Leukemoid Reaction:
- in WBC count that can mimic Leukemia
-Reactive neutrophilia (WBCs > 50,000)
-Toxic Granulation, Dohle Bodies, Cytoplasmic Vacuoles
- LAP Score (decreased in CML)
-Normal Eos, Basophils

High-Yield Mutations:
1. **t(8;14) = Burkitt Lymphoma (c-myc activation)**
2. **t(11;14) = Mantle Cell Lymphoma (Cyclin D1 activation)**
3. **t(11;18) = Marginal Zone (MALT)**
4. **t(14;18) = Follicular Lymphoma (BCL-2 Activation)**
5. **t(15;17) = APL (formally M3 AML)**
6. **t(9;22) = CML (BCR-ABL Hybrid), Philadelphia Chromosome,** ALL (less commonly)

-Ig Heavy Chain genes on Chr 14 are constitutively expressed…when other genes (c-myc, BCL-2) are translocated next to this heavy chain gene region, they get overexpressed**

Langerhans Cell Histiocytosis:
-collective group of proliferative disorders of Langerhans cells
-presents in children as Lytic Bone Lesions + skin rash OR recurrent otitis media w/ mass involving mastoid bone
-cells are functionally immature + do not effectively stimulate primary T cells via antigen presentation
-S-100 (+) and CD1a
-Birbeck Granules ("Tennis Racket") on EM

Tumor Lysis Syndrome:
-Oncologic Emergency due to massive tumor cell lysis

-+/- Erythromelalgia, crazy amount of platelets

3. Myelofibrosis:
-Megakaryocyte Hyperplasia→ TGF-B secretion→ fibroblast activity → obliteration of bone marrow (massive fibrosis)
-Splenomegaly + "tear drop" RBCs, Dry Bone Tap

-Exogenous EPO (blood doping), Malignancy (Epo)

4. Polycythemia Vera:
- plasma vol
- RBC mass (primary issue)

-normal O2 sat
- EPO levels (negative feedback on Renal EPO)

- K+, Ca2+, Phos, Uric Acid
-HyperPhos causes Ca2+ binding
-Muscle Weakness, Arrhythmias, Seizures, Tetany, **AKI**
-Tx = Massive Hydration, Allopurinol, Rasburicase

Heparin:
-Mech = activates AT (which action of IIa (Thrombin) + Xa)
-doesn't cross placenta (good for pregnancy)
-Antidotes = Protamine Sulfate
-Sxs = Excessive Bleeding, Heparin-induced Thrombocytopenia (HIT), Osteoporosis (chronic use),
-HIT Type 2:
- clinically significant hit w/ IgG antibodies against heparin bound PF4; characteristically 5-10 days after administration.
- Antibody-heparin-PF4 complex binds and activates platelets → removal by splenic macrophages + thrombosis → Platelet count

-Monitoring w/ PTT (Intrinsic Pathway)

LMWH: (Enoxaprin, Dalteparin) = act on Factor Xa, longer t1/2, renally cleared/adjusted
Fondaparinux = only on factor Xa

Warfarin:
-inhibits vitamin K epoxide reductase by competing w/ Vit K → prevents vit K-dependent gamma-carboxylation of clotting factors 2, 7, 9, 10, C and S
-VKORC1 gene polymorphisms impact activity/metabolism
-Acts on Extrinsic Pathway (PT)
-Long half-life, takes time to work (not used for acute setting)
-Teratogen (heparin is safe)
-DDIs common (CYP2C9)
-Initial risk of Hypercoagulation (Protein C has shorter half-life than Factors II and X → C depleting first → 1st couple days may see small vessel microthrombosis (Requires Heparin Bridging)
-Reversal = Vit K, FFP, PCC

Direct Coagulation Factor Inhibitors:
Bivalrudin, Argatroban, Dabigatran:
-Direct Thrombin Inhibitors (IIa)
-VTE, Afib, HIT when Heparin contraindicated
-Idarucizumab = reverses Dabigatran (PO)

Apixaban, Edoxaban, Rivaroxaban:

Antiplatelets:
ASA:
-irreversibly blocks COX → TXA2 release
-sxs = gastric ulcers, tinnitus, allergic rxns, renal

Clopidogrel, Prasugrel, Ticagrelor, Ticlopidine:
-Block ADP (P2Y12) receptor → ADP-induced expression of Gp IIb/IIIa

Abciximab, Eptifibatide, Tirofiban:
-blocks Gp IIb/IIIa (Fibrinogen receptor) on activated platelets
-sxs = bleeding, thrombocytopenia

Cilostazol, Dipyridamole:
-Blocks phosphodiesterase → cAMP in platelets
-sxs = nausea, HA, facial flushing, hypotension, abdominal pain

Thrombolytics: **Alteplase (tPa), Reteplase, Streptokinase, Tenecteplase**
-directly/indirectly aids conversion of Plasminogen to Plasmin → cleaving thrombin and fibrin clots
- PT, PTT, no change in platelet count

-Contraindicated in pts w/ active bleeding, hx of Intracranial bleeding, recent surgery, severe HTN
-Reversal = Aminocaproic Acid, Tranexamic Acid, Platelet transfusions, factor corrections (FFP, PCC, Cryoprecipitate)

Cancer Therapy Targets:
-Nucleotide Synth (1) → DNA (2) → RNA (3) → Protein (4)→ Cellular Division (5)

(1):
-MTX, 5-FU = Thymidine Synthesis
-Thiopurines = de novo purine synth
-Hydroxyurea = inhibits ribonucleotide reductase

(2):
-Alkylating Agents/Platinums = Cross-link DNA

Cell-Cycle Independent:
-Platinum compounds
-Alkylating Agents: (Anthracyclines, Busulfan, Dactinomycin, Nitrogen Mustards, Nitrosoureas, Procarbazine)

Antimetabolites; Myelosuppression is a class effect
1.Thiopurines (AZA, 6-MP):
- de novo purine synthesis

-myelosuppression, GI, Liver tox
- tox if given w/ Allopurinol (Xanthine Oxidase dependent metabolism)

2. Cladribine, Pentostatin = purine analog
3. Cytarabine = pyrimidine analog
4. 5-FU = Pyrimidine analog
-bioactivated to 5-FdUMP → thymidylate synthase inhibition → DNA synth
-Effects enhanced if given w/ Leucovorin
-Hand-Foot Syndrome (Palmar-plantar erythrodysesthesia)
5. Hydroxyurea:
-inhibits Ribonucleotide reductase → DNA synth
6. MTX:
-folic acid analog → competetively inhibits dihydrofolate reductase (DHFR) → dTMP → DNA synth
-Myelosuppression (reversible w/ Leucovorin)
-Hepatotoxicity, Mucositis (mouth ulcers), Teratogenic, Folate def.

Alkylating Agents; Really Toxic
1. Busulfan
2. Nitrogen Mustards (Cyclophosphamide, Ifosfamide) - Ifos causes Fanconi Syndrome, Hemorrhagic Cystitis w/ Cyclo (prevent w/ Mesna)
3. Carmustine, Lomustine - Glioblastoma
4. Procarbazine

-direct Factor Xa Inhibitors
-Andexanet Alfa = Apixaban reversal
-minimal lab monitoring (also Dabigatran)

Microtubule Inhibitors:
-Taxanes (Docetaxel, Paclitaxel) = Hyper Stabilize (neuropathy, myelouspp, hypersensitivity) ("Taxes Stabilize society")
-Vinca Alkaloids (Vincristine, Vinblastine) = prevent formation
Vincristine = Crisps the nerves (Neuropathy)
Vinblastine = Blasts the marrow (myelosupp)

Topoisomerase Inhibitors; Myelosuppression
1. Irinotecan, Topotecan = Topo I (I run to the can - Diarrhea)
2. Etoposide, Teniposide = Topo II

Tamoxifen:
-SERM = Antagonist in Breast, Partial Agonist in Endometrium/Bone, Blockers estrogen binding in ER+ BC
-Hot flashes, DVT/PE/VTE, Endometrial cancer slightly

Anticancer Monoclonal Antibodies:
1. Alemtuzumab = CD52
2. Bevacizumab = VEGF (BV formation inhibitor)
3. Cetuximab, Panitumumab = EGFR inhib
4. Rituximab = CD20 Inhib ("B-Cell Bomb")
5. Trastuzumab = HER2 (risk of Dilated Cardiomyopathy)
6. Pembrolizumab, Nivolumab, Cemiplimab = PD-1
7. Atezolizumab, Durvalumab, Avelumab = PD-L1
8. Ipilimumab = CTLA-4

-Bleomycin = DNA strand breaks (G2/M phase)
-Anthracyclines, Dactinomycin = DNA intercalators
-Etoposide/Teniposide = Inhibit Topoisomerase II
-Irinotecan/Topotecan = Inhibit Topoisomerase I

(5):
-Vinca Alkaloids = Inhibit Microtubule FORMATION
-Taxanes = Inhibit microtubule DISASSEMBLY

Small Molecule Anti-Cancers:
1. **Alectinib = ALK**
2. **Erlotinib, Gefitinib, Afatinib = EGFR** (Rash)
3. **Imatinib, Dasatinib, Nilotinib = BCR-ABL**
4. **Ruxolitinib = JAK1/2**
5. **Bortezomib, Ixazomib, Carfilzomib = Proteasome** (inducing arrest at G2-M phase → Apoptosis)
6. **Vemurafenib, Encorafenib, Dabrafenib = BRAF**
7. **Palbociclib = Cyclin-dependent Kinase 4/6** (inducing arrest at G1-S phase → apoptosis)
8. **Olaparib = Poly(ADP-Ribose) Polymerase** (DNA repair)

High Yield Drug Toxicity:
1. Cisplatin/Carboplatin = Oto + Nephrotoxic
2. Vincristine = peripheral neuropathy
3. Bleomycin, Busulfan = pulmonary fibrosis
4. Doxorubicin, daunorubicin = Cardiotoxic
5. Trastuzumab = cardiotoxic
6. Cyclophosphamide = hemorrhagic cystitis

Platinum Compounds: **Cisplatin, Carboplatin, Oxaliplatin**
-Cross-link DNA
-Nephrotoxic (fanconi Syndrome - prevent w/ Amifostine)
-Peripheral neuropathy + Ototoxicity
-Highly Emetogenic (CINV)

Cancer Therapy Reprieve:
1. **Amifostine:**
   a. Free radical scavenger
   b. Protect kidney from platinum nephrotoxicity
2. **Dexrazoxane:**
   a. Iron chelator
   b. Protect heart from cardiotoxic anthracyclines
3. **Leucovorin (Folinic Acid)**
   a. Tetrahydrofolate precursor
   b. Enhances 5-FU effects
   c. Rescues MTX myelosuppression
4. **Mesna:**
   a. Binds Acrolein (toxic metabolite of Cyclophosphamide)
   b. Prevents hemorrhagic Cystitis
5. **Rasburicase:**
   a. Uricase - catalyzing metabolism of uric acid to soluble Allantoin
   b. Protect from Tumor lysis syndrome
6. **Ondansetron/Granisetron**
   a. 5HT3 antag
7. **Prochlorperazine, Metoclopramide**
   a. D2 receptor antag
8. **Aprepitant, Foasaprepitant**
   a. NK1 receptor antag
   b. Ideal for Delayed N/V
9. **Filgrastim, Sargramostim**
   a. Recombinant G-CSF
   b. Tx Neutropenia
10. **Epoetin Alfa**:
   a. Synthetic EPO
   b. Tx Anemia

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