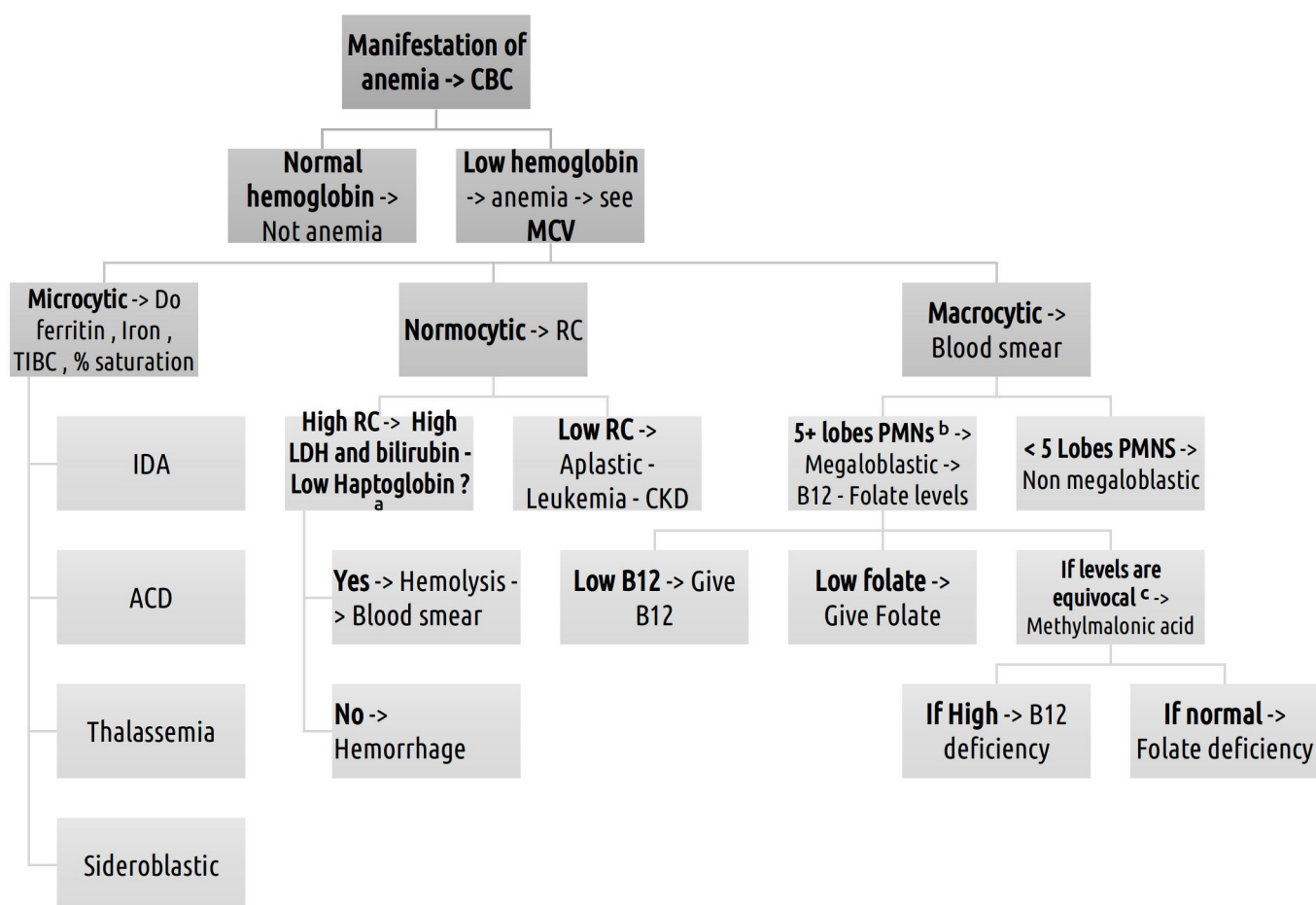


Hematology & Oncology

Anemia

Symptomatology of anemia depend on

Level of Hemoglobin	The lower the level , the more severe the symptoms -> Asymptomatic -> then Malaise and fatigue -> then Dyspnea of exertion and presyncope -> then MI , CVA , HOHF	
Acuity of anemia	The faster the rate of development of anemia , the more severe the symptoms	
Cardiovascular reserve	Delivered O ₂ = CO × Hemoglobin × %Saturation	
	CO	%Saturation
	Athlete	↑ 100 %
	CHF - MI - COPD	↓ ↓
Thus in Athletes more drop in hemoglobin is required for symptoms to appear while in patients with ↓ cardiac reserve little drop in hemoglobin can cause symptoms		



MI -> Myocardial infarction
CO -> Cardiac output
IDA -> Iron deficiency anemia
LDH -> Lactate dehydrogenase

CVA -> Cerebrovascular accident
MCV -> Mean corpuscular volume
ACD -> Anemia of chronic disease
CKD -> Chronic kidney disease

HOHF -> High output heart failure
TIBC -> Total iron binding capacity
RC -> Reticulocytic count
PMNs -> Polymorph nuclear cells

a	You aren't going to use labs to differentiate between Hemorrhage and hemolysis -> you will see them bleeding if it's hemorrhage -> But labs are used to confirm that the anemia is hemolytic
b	PMNs having more than 5 nuclear lobes
c	Both are at the lower end of normal

Macrocytic Anemia

Megaloblastic

Folate deficiency

B12 deficiency

Etiology	<ul style="list-style-type: none"> ■ Dietary deficiency ^a -> Tea and Toast diet - Alcoholics ■ ↑ Requirement -> Pregnancy - Hemolytic anemia ■ Drugs -> Methotrexate - Trimethoprim - Phenytoin 	<ul style="list-style-type: none"> ■ Dietary deficiency ^b -> Strict uneducated vegan ■ ↓ Intrinsic factor ^c -> Pernicious anemia ^d - Gastric bypass ■ ↓ Absorption -> Terminal ileum disease (e.g. Crohn's) or resection ■ Diphyllobothrium
Dx	As before	As before + Schilling test ^e
Tx	Folic acid -> 1mg orally	B12 -> <ul style="list-style-type: none"> ■ Orally -> If the etiology is nutritional deficiency ■ IM -> If the etiology is ↓ B12 absorption

Non Megaloblastic

- **Liver disease** -> Cirrhosis
- **Alcohol** -> even in absence of cirrhosis
- **Drugs** -> 5-Fluorouracil - HAART (AZT)
- **Metabolic** -> Lesch Nyhan syndrome

IM -> Intramuscular

HAART -> highly active antiretroviral therapy

AZT -> azidothymidine aka zidovudine

a	<ul style="list-style-type: none"> ■ Folate is present in leafy vegetables ■ Body stores of Folate can be depleted in 3-4 weeks without Folate intake ■ Alcohol abuse is the most common nutritional cause of folate deficiency in the United States
b	<ul style="list-style-type: none"> ■ B12 is present in Animal products ■ Body stores of B12 can be depleted in 3-10 years without B12 intake
c	Intrinsic factor binds B12 and the complex is absorbed in terminal ileum
d	<ul style="list-style-type: none"> ■ Auto antibody against Parietal cells -> ↓ Intrinsic factor ■ Most common cause of vitamin B12 deficiency ■ High risk of gastric cancer
e	<p>Schilling test isn't important for real life but for Exam -> Helps to decide whether B12 deficiency is due to nutritional deficiency or impaired absorption -> Steps</p> <ul style="list-style-type: none"> ■ Saturate Stores with IM B12 ■ Then give oral B12 ■ Then detect B12 in urine <ul style="list-style-type: none"> ● IF +ve -> this means it has been absorbed -> so the etiology was nutritional deficiency ● IF -ve -> this means it has not been absorbed -> so the etiology was Impaired absorption

Microcytic Anemia

		IDA	ACID	Thalassemia ^d	Sideroblastic
Etiology		<ul style="list-style-type: none"> ● Slow bleeding^a ● Children -> Premature - Lead - Cow milk <1 year 	Inflammation ^c	Globin	Reversible -> Drugs (Isoniazide) - Alcohol - Lead ^f Irreversible -> Deficient B6 - Myelodysplastic syndrome
Dx	Serum Iron	↓	↓	↑	↑
	Serum Ferritin	↓	↑	↑	↑
	TIBC	↑	↓	↓	
	Bone marrow	Not that useful			Ringed sideroblasts
	Hb Electrophoresis			Alpha ^d Beta ^e	
	DNA analysis			Alpha minor & minima ^d	
Tx		Iron -> 324 mg t.i.d Stool softener ^b	No intervention Severe -> EPO	Mild -> Asymptomatic -> No intervention (Reassurance) Severe -> Monthly Transfusion Iron chelation -> Deferoxamine	

t.i.d -> ter in die -> three times a day

EPO -> Erythropoietin

TIBC -> Total iron binding capacity

a	<ul style="list-style-type: none"> ■ Male > 50 years or postmenopausal female -> with +ve occult blood test ■ Female > 20 years with menometrorrhagia 																
b	As iron causes constipation																
c	In inflammation -> IL-6 is released -> ↑ Hcpidin -> ↓ Iron absorption from gut and ↓ iron release from macrophages -> ↓ iron and ↑ Ferritin (which is an inflammatory mediator)																
d	C/P depends on the number of genes affected <table> <tr> <th>Number of affected alleles</th><th>Beta thalassemia</th><th>Alpha thalassemia</th></tr> <tr> <td>1</td><td>Mild</td><td>Asymptomatic -> Minima -> Normal Electrophoresis</td></tr> <tr> <td>2</td><td>Severe</td><td>Mild -> Minor -> Normal Electrophoresis</td></tr> <tr> <td>3</td><td></td><td>Severe -> HbH on Electrophoresis</td></tr> <tr> <td>4</td><td></td><td>Hydrops fetalis -> Hb Barts on Electrophoresis</td></tr> </table>		Number of affected alleles	Beta thalassemia	Alpha thalassemia	1	Mild	Asymptomatic -> Minima -> Normal Electrophoresis	2	Severe	Mild -> Minor -> Normal Electrophoresis	3		Severe -> HbH on Electrophoresis	4		Hydrops fetalis -> Hb Barts on Electrophoresis
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3		Severe -> HbH on Electrophoresis															
4		Hydrops fetalis -> Hb Barts on Electrophoresis															
e	↓ HbA ₁ - ↑ HbA ₂ - ↑ HbF																
f	Lead poisoning Patho: Occupational exposure -> Lead paint - Batteries - Ammunition - Construction C/P: <ul style="list-style-type: none"> ■ GIT -> Pain - Constipation - Anorexia ■ Neurologic -> Cognitive deficits - Peripheral neuropathy ■ Hematologic -> Anemia ■ Other -> Black-blue lines on gums - Hyperuricemia Dx: <div style="text-align: center;"> History suggestive (e.g. old house) ↓ No -> No further testing Yes -> Venous lead level ↓ Undetectable -> No further testing 5-44 -> Repeat in 1 month - No medications 45 - 69 -> DMSA ≥70 -> BAL + EDTA </div>																

Hematology and Oncology

	Iron deficiency anemia	α -Thalassemia minor	β -Thalassemia minor
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBC	↓	Normal	Normal
Smear	Microcytosis	Target cells	Target cells
Iron	↓ Iron - ↓ Ferritin - ↑ TIBC	Normal / ↑ Iron and ferritin	Normal / ↑ Iron and ferritin
Response to iron	↑ Hemoglobin	No	No
Electrophoresis	Normal	Normal	↑ Hemoglobin A2

MCV -> Mean corpuscular volume

RDW -> Red cell distribution width

Notes

Normocytic anemia

Hemorrhage

Dx As before

Tx Plug the hole -> Give blood

Hemolysis

	Sickle cell	G6PD deficiency	HS	PNH
Patho	<ul style="list-style-type: none"> ■ AR ■ HbSS -> Disease ■ Acidosis , Hypoxemia , Dehydration -> Sickling 	<ul style="list-style-type: none"> ■ Oxidative stress Dapsone - TMP/SMX - Nitrofurantoin ■ African american 	<ul style="list-style-type: none"> Autosomal dominant ■ Ankyrin defect ■ Spectrin defect ■ Pallidin defect 	<ul style="list-style-type: none"> PIGA gene mutation -> ↓ synthesis of GPI anchor for DAF (CD55) and MIRL (CD59) -> Complement activation
C/P	<ul style="list-style-type: none"> Vaso-occlusive crisis ^a Aplastic crisis -> Parvo B19 infection Hyposthenuria ^b General C/P of anemia 	<ul style="list-style-type: none"> General C/P of anemia -> after Oxidative stress 	<ul style="list-style-type: none"> General C/P of anemia 	<ul style="list-style-type: none"> ■ Anemia ■ Pancytopenia ■ Thrombosis ^e
Dx	<ul style="list-style-type: none"> ■ 1st encounter -> Hb Electrophoresis ■ Confirmation -> Smear (Sickle cells -> indicative of acute crisis) 	<ul style="list-style-type: none"> ■ Smear -> Bite cells , Heinz bodies ■ G6PD level -> Best -> Not during the attack ^d 	<ul style="list-style-type: none"> ■ Smear -> Spherocytes ■ CBC -> ↑ MCHC ■ Osmotic fragility ■ EMA test ■ Flow cytometry 	<ul style="list-style-type: none"> ■ Flow cytometry -> -ve CD55 and CD59 RBCs ■ CBC -> Pancytopenia ■ Coombs -> Negative
General for hemolysis -> ↑ LDH - ↓ Haptoglobin - Indirect hyperbilirubinemia				
Tx	<ul style="list-style-type: none"> ■ Hydroxyurea -> ↑ HbF ■ Acute crisis -> IVF , O₂ , Analgesics ■ Exchange transfusion ^c ■ Transfusion (If Hb < 7) -> need Iron chelation 	<ul style="list-style-type: none"> ■ Supportive ■ Avoid stress 	<ul style="list-style-type: none"> ■ Splenectomy (Reduces the risk of pigment stones) ■ Folate ■ Iron ■ Blood transfusion 	<ul style="list-style-type: none"> ■ Supportive ■ Iron and folate ■ Bone marrow transplant ■ Allogenic stem cell transplant ■ Eculizumab -> Targets terminal complement protein C5

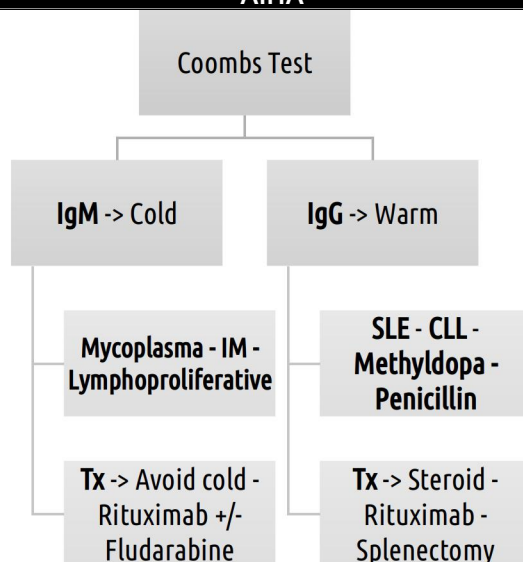
Exertional Hemoglobinuria(March Hemoglobinuria)

Patho Unknown, but thought to be due to mechanical (Intravascular) destruction of RBCs in the feet during strenuous exercise (e.g. Runners)

HS -> Hereditary spherocytosis AIHA -> Autoimmune hemolytic anemia PNH -> Paroxysmal nocturnal hemoglobinuria
 IM -> infectious mononucleosis SLE -> Systemic lupus erythematosus CLL -> Chronic lymphocytic leukemia
 MCHC -> Mean corpuscular hemoglobin concentration

- a ■ Acute chest (Myocardial infarction) - Acute brain (Cerebrovascular accident) - Priapism - Splenic infarction - Dactylitis - Avascular necrosis (Tx: Conservative (NSAID - Rest - Crutches) for 6 months then surgical)
- b Inability of the kidney to concentrate urine due to RBC sickling in the vasa rectae of the inner medulla, which impairs countercurrent exchange and free water absorption
- c ■ Indications -> Encephalopathy - Focal neurologic deficit - Chest pain - Noncardiogenic lung edema
- d ■ As it will be artificially normal during the attack -> As old cells with deficient G6PD will have hemolysed
 ■ So get the level at least 6 weeks after the attack
- e Due to vasoconstriction and platelet aggregation as a result of free hemoglobin (due to hemolysis) scavenging serum nitric oxide (a vasodilator) and, according to the prevalent hypothesis, activating the endothelial lining of blood vessels

AIHA



Notes ->

- Spherocytes on blood smear (Differentiated from hereditary spherocytosis by the fact that AIHA has +ve Coombs test)

Aplastic anemia

Patho	Radiation - Chemotherapy - Viral - Fanconi anemia (autosomal recessive DNA repair defect) - Idiopathic
C/P	<ul style="list-style-type: none"> ■ As Anemia -> May be with leukopenia and thrombocytopenia ■ Fanconi anemia -> Short - Microcephaly - Hypogonadism - Cafe au lait spots - Malformed forearm and/or thumbs - Strabismus - Low set ears - Deafness - High risk for leukemia
Dx	<ul style="list-style-type: none"> ■ Low reticulocytic count ■ High Erythropoietin
Tx	Accordingly

AIHA -> Autoimmune hemolytic anemia

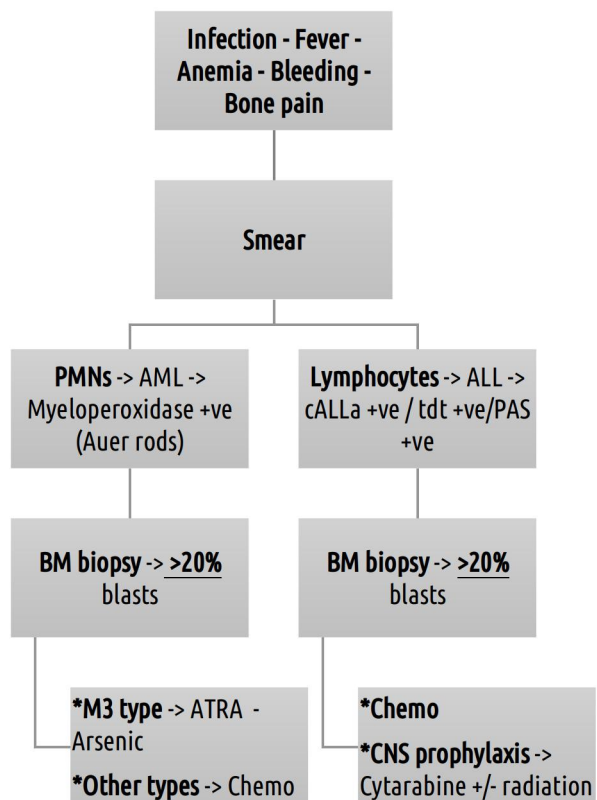
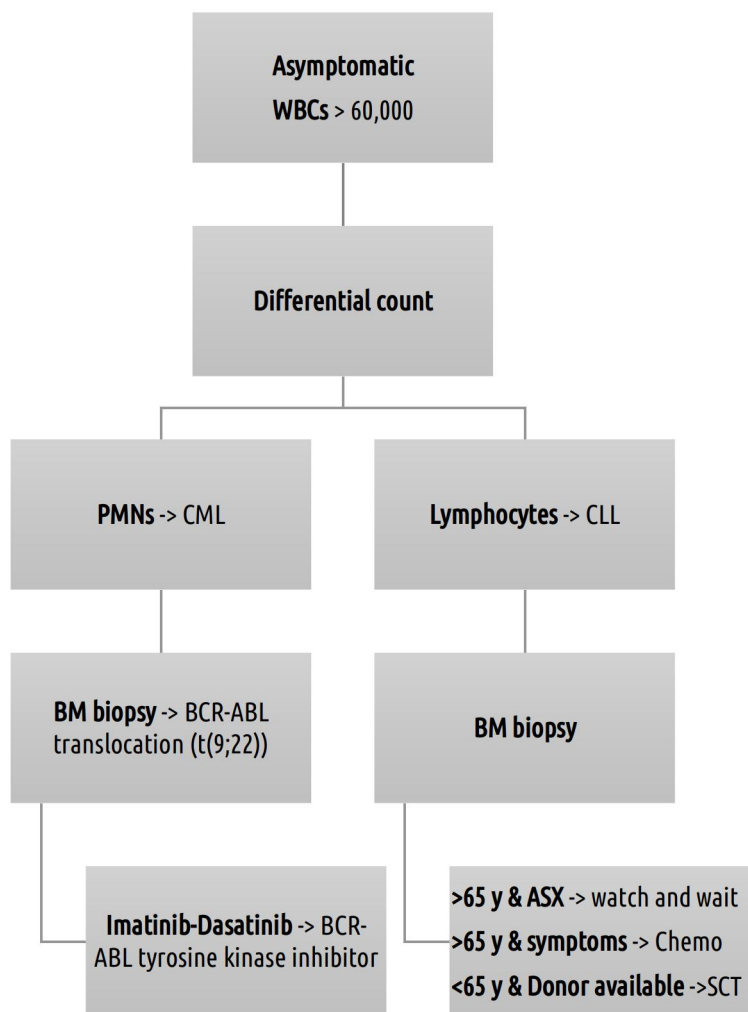
Notes

Polycythemia vera**Polycythemia vera**

Patho	JAK2 mutation
C/P	<ul style="list-style-type: none"> ■ ↑ Blood viscosity -> Hypertension - Erythromelalgia - Transient visual disturbances ■ ↑ Turnover -> Gouty arthritis ■ Aquagenic (e.g. after bathing) pruritis ■ Bleeding ■ Headache ■ Splenomegaly
Dx	<ul style="list-style-type: none"> ■ ↑ Hemoglobin ■ ↑ Leukocytes ■ ↑ Thrombocytes ■ Low Erythropoietin ■ Genetic assay
Tx	<ul style="list-style-type: none"> ■ Phlebotomy (Platelets less affected by phlebotomy so can give aspirin if needed) ■ Hydroxyurea -> if ↑ risk of thrombosis

Notes

Leukemia



	AML	ALL	CML	CLL
Median age in years	65	7	47	87
PMNs -> polymorphnuclear cells SCT -> Stem cell transplant		BM -> Bone marrow ATRA -> All-trans retinoic acid	y -> years M3 type -> Acute promyelocytic leukemia	ASX -> Asymptomatic

Hematology and Oncology

Hairy cell leukemia

Patho	<ul style="list-style-type: none"> ■ Clonal B cell neoplasm ■ BRAF mutation ■ Higher incidence -> Middle age or old adults
C/P	<ul style="list-style-type: none"> ■ Pancytopenia ■ Splenomegaly -> Early satiety ■ Hepatomegaly and lymphadenopathy -> Rare
Dx	<ul style="list-style-type: none"> ■ Blood smear -> Hairy cells ■ Bone marrow biopsy with flow cytometry
Tx	Chemotherapy -> For moderate to severe
F/U	Life expectancy is near normal

Leukamoid reaction

Chronic myeloid leukemia

Leucocytes	>50,000	>100,000
Cause	Severe infection - Medication - Hemorrhage	BCR-ABL fusion
LAP	High	Low
Neutrophil	More mature (Metamyelocytes > Myelocytes)	Less mature (Metamyelocytes < Myelocytes)
Absolute Basophilia	No	Yes

Chronic lymphocytic leukemia

C/P	Fatigue (Most common symptom) - Lymphadenopathy (In 80 %) - Hepatosplenomegaly (In 50 %) - Infection - Hemolysis
Dx	<ul style="list-style-type: none"> ■ CBC -> Lymphocytosis - Anemia - Thrombocytopenia ■ Smear -> Smudge cell ■ Flow cytometry (Diagnostic test of choice) ■ Lymph node biopsy ■ Bone marrow biopsy
Tx	<ul style="list-style-type: none"> ■ >65 y & ASX -> watch and wait ■ >65 y & symptoms -> Chemo ■ <65 y & Donor available -> Stem Cell Transplant
F/U	Poor prognosis with -> <ul style="list-style-type: none"> ■ Multiple chain lymphadenopathy ■ Hepatosplenomegaly ■ Anemia - Thrombocytopenia

Acute myeloid leukemia

Patho	Risk factors -> Alkylating chemo - Radiation - Myeloproliferative disorders - Down syndrome
C/P	<ul style="list-style-type: none"> ■ Most common adult leukemia ■ Median age -> 65 years ■ Symptoms -> Fatigue - Cytopenia - Hepatosplenomegaly/ Lymphadenopathy (rare) - DIC (in APL as Auer rods are thrombogenic)
Dx	<ul style="list-style-type: none"> ■ CBC -> Cytopenia (Leukocytes may be Normal - High - Low) ■ LDH -> High ■ Smear -> Myeloblasts with auer rods ■ Bone marrow biopsy -> Hypercellular with >20% myeloid blasts
Tx	<ul style="list-style-type: none"> ■ M3 type -> ATRA - Arsenic ■ Other types -> Chemo

Notes

- In chronic Leukemia -> WBCs look normal on smear -> Large nucleus with little cytoplasm
- In Acute Leukemia -> WBCs look abnormal on smear -> small nucleus with large cytoplasm
- T-ALL -> can present with mediastinal mass

LAP -> Leukocyte alkaline phosphatase

DIC -> Disseminated intravascular coagulation

ATRA -> All-trans retinoic acid

M3 type -> Acute promyelocytic leukemia

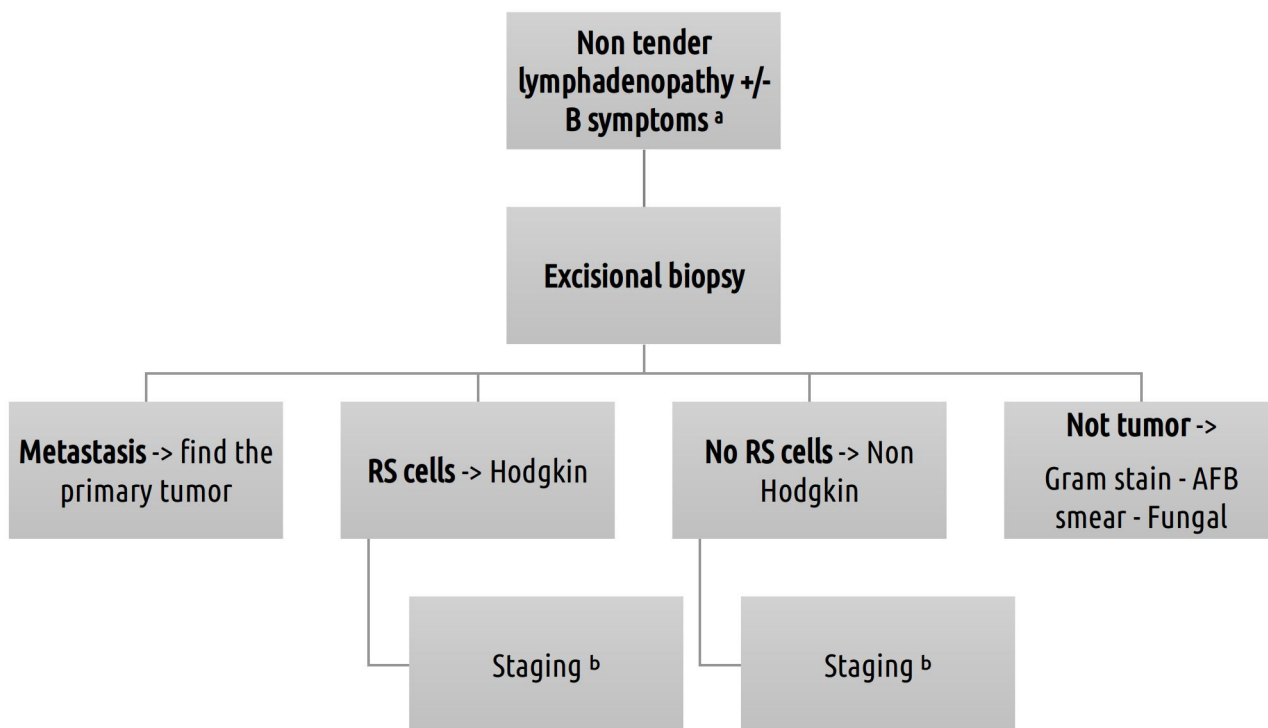
Hematology and Oncology

Acute lymphoblastic leukemia

Patho	<ul style="list-style-type: none">■ Most common childhood cancer■ Male > female■ Peak age -> 2-5 years
C/P	<ul style="list-style-type: none">■ Non-specific systemic symptoms■ Bone pain■ Lymphadenopathy■ Hepatomegaly■ Pallor■ Petechiae
Dx	<ul style="list-style-type: none">■ As before
Tx	<ul style="list-style-type: none">■ Chemo■ CNS prophylaxis -> Cytarabine +/- radiation

Notes

Lymphoma



	Hodgkin	Non Hodgkin
B symptoms	Both may present with B symptoms	
Stage	Usually IIa or better	Usually IIb or worse
Spread	Contiguous	Non contiguous -> Hematogenous
Other	<ul style="list-style-type: none"> ■ Pel ebstein fever ^c ■ Alcohol Lymph nodes ^d 	<ul style="list-style-type: none"> ■ Burkitt's lymphoma -> Starry sky pattern on histology ■ Extranodal disease
Tx	<ul style="list-style-type: none"> ■ Almost all Hodgkin -> ABVD ■ Really bad lymphoma (Really bulky) -> BEACOPP 	<ul style="list-style-type: none"> ■ R-CHOP -> R for Rituximab

Side effects of chemo

Vincristine/Vinblastine	Peripheral neuropathy
Doxorubicin - Daunorubicin	Dose dependent irreversible cardiomyopathy
Busulfan - Bleomycin	Pulmonary fibrosis
Cisplatin	Ototoxicity - Nephrotoxicity
Cyclophosphamide	Hemorrhagic cystitis

AFB -> Acid-Fast Bacilli

RS -> Reed Sternberg

- a**
- Night sweating , Low grade fever , Weight loss
 - Not necessarily present
 - Called B symptoms as it increases the grade from A to B if present

- b**
- Staging by ->**
- 1st -> CXR -> Not sensitive
 - 2nd -> CT
 - 3rd -> Bone marrow biopsy -> Result won't change the therapy that much
- Or by PET-CT**

Stage	Affected lymph nodes	Diaphragm
I	1	-----
II	≥2	Same side of diaphragm
III	≥2	Opposite sides of diaphragm
IV	Metastatic	

c Cyclical fevers that come and go randomly over weeks

d When consume alcohol -> the non tender lymphadenopathy becomes tender

Plasma cell disorders

Multiple myeloma (MM)

Patho	<p>Monoclonal expansion of plasma cells Producing -></p> <ul style="list-style-type: none"> ■ Incomplete Immunoglobulins mainly IgG -> Protein gap on LFTs and M Spike on SPEP ■ Bence jones proteins (Ig light chains) -> Deposit in kidneys -> Kidney injury -> M spike on UPEP ■ Osteoclast stimulating factors -> Lytic lesions in bones -> Leading to Pathologic fractures (Atraumatic fractures) -> Lesions can be identified by getting skeletal survey ^a <p>These abnormal plasma cells crowd out the marrow -> so good plasma cells can't do their job -> Recurrent infections</p>
C/P	<ul style="list-style-type: none"> ■ Age > 70 years ■ CRAB -> hyperCalcemia - Renal failure - Anemia - Bone lesions ■ ↑ Infection risk -> Due to Hypogammaglobulinemia ^b
Dx	<p>The following in order -></p> <ul style="list-style-type: none"> ■ Skeletal survey +ve ■ SPEP +ve ■ UPEP +ve ■ Bone marrow biopsy -> ≥ 10 % Plasma cells
Tx	<ul style="list-style-type: none"> ■ >70 years and no donor -> Chemo -> Melphalan + Steroid (Prednisone) + (Either Thalidomide or Bortezomib) ■ >70 years + Donor -> HSCT

Monoclonal gammopathy of undetermined significance (MGUS)

Patho	Early myeloma
C/P	<ul style="list-style-type: none"> ■ Age > 85 years ■ Asymptomatic
Dx	<ul style="list-style-type: none"> ■ SPEP +ve ■ UPEP -ve ■ Skeletal survey -ve ■ Bone marrow biopsy -> ≤ 10% Plasma cells
Tx	<ul style="list-style-type: none"> ■ Monitor for conversion to MM -> happens at a rate of 2%/year ■ If conversion to MM occurs -> treat MM

Waldenstrom's

Patho	Monoclonal expansion of plasma cells Producing -> Incomplete Immunoglobulins mainly IgM
C/P	<ul style="list-style-type: none"> ■ Hyperviscosity (because IgM is pentamer) ■ Constitutional symptoms -> Night sweating - Fever - Wight loss ■ Neuropathy ■ Bleeding ■ Hepatosplenomegaly ■ Lymphadenopathy
Dx	<ul style="list-style-type: none"> ■ Blood smear -> Rouleaux ■ Skeletal survey -ve ■ SPEP +ve ■ UPEP -ve usually ■ Bone marrow biopsy -> ≥10% Lymphoma -> lymphoplasmacytic lymphoma
Tx	<ul style="list-style-type: none"> ■ Rituximab based chemo ■ Hyperviscosity -> Plasmapheresis

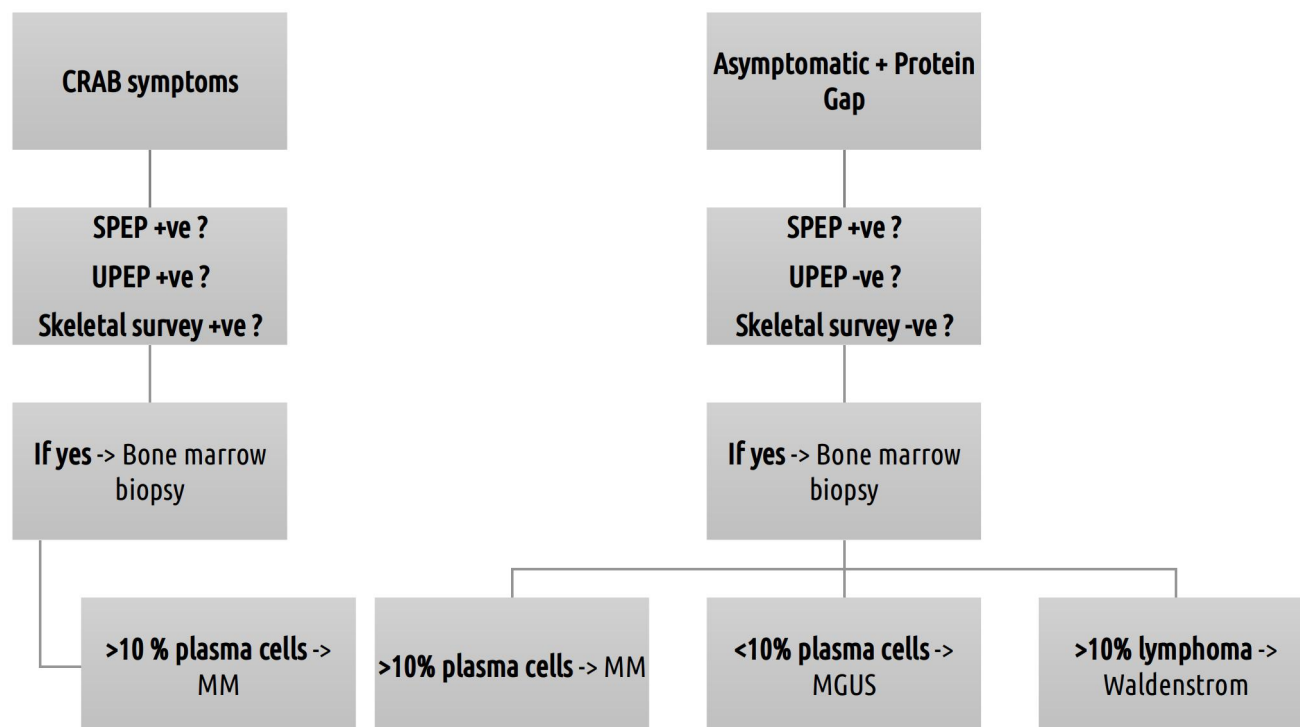
SPEP -> Serum protein electrophoresis

UPEP -> Urine protein electrophoresis

HSCT -> Hematopoietic stem cell transplant

a	<ul style="list-style-type: none"> ■ By getting serial X-Ray -> Detecting the lytic lesion ■ It's different from Bone scan /Nuclear medicine scan -> That detects metabolic activity (So used for detecting tumor)
b	Neoplastic infiltration of the bone marrow impairs normal lymphocyte population, resulting in ineffective antibody production

Hematology and Oncology



Langerhans cell histiocytosis

Patho	<ul style="list-style-type: none"> ■ Clonal proliferation of langerhans cells (Antigen-presenting cells) ■ I added it here with MM although not plasma cell disorder
C/P	<ul style="list-style-type: none"> ■ Osseous lesion -> Pain and/or swelling - Skull (Most common site) - Single or multiple ■ Systemic -> Rash - Lymphadenopathy - Bone marrow infiltration - Hypercalcemia
Dx	<p>X-ray -> Lytic lesions</p> <p>Biopsy -></p> <ul style="list-style-type: none"> ■ LM -> Polygonal cells with coffee bean nuclei - Eosinophilic cytoplasm ■ EM -> Birbeck granules ■ Marker -> CD1a

Notes

Primary myelofibrosis

Primary myelofibrosis

Patho	<ul style="list-style-type: none"> ■ Unknown -> JAK2 mutation in 50 % of patients ■ Peak incidence -> 60-70 years
C/P	<ul style="list-style-type: none"> ■ General -> Weakness - Fatigue - Weight loss ■ Splenomegaly -> Left upper quadrant abdominal pain ■ Hyperproliferative phase -> Thrombocytosis (Thromboembolism) - Leukocytosis ■ Pancytopenic phase -> Erythrocytopenia (Anemia) - Thrombocytopenia (Bleeding) - Leukopenia (Infection)
Dx	<ul style="list-style-type: none"> ■ Labs -> ↑ LAP - ↑ LDH - ↑ Uric acid ■ Blood smear -> Dacrocytes (Teardrop RBC) ■ Bone marrow aspiration -> Punctio sicca
Tx	<p>Allogenic stem cell transplant (Curative) -> For younger patients with available donor</p> <p>Supportive -></p> <ul style="list-style-type: none"> ■ <u>Hyperproliferative</u> -> <ul style="list-style-type: none"> ● Aspirin -> To prevent thromboembolism ● Hydroxyurea - Interferon α - Cladribine -> To control cell count ■ <u>Pancytopenic</u> -> <ul style="list-style-type: none"> ● JAK2 inhibitor (Ruxolitinib) ● Periodic transfusions ● Low dose thalidomide + Glucocorticoids

LAP -> Leukocyte alkaline phosphatase

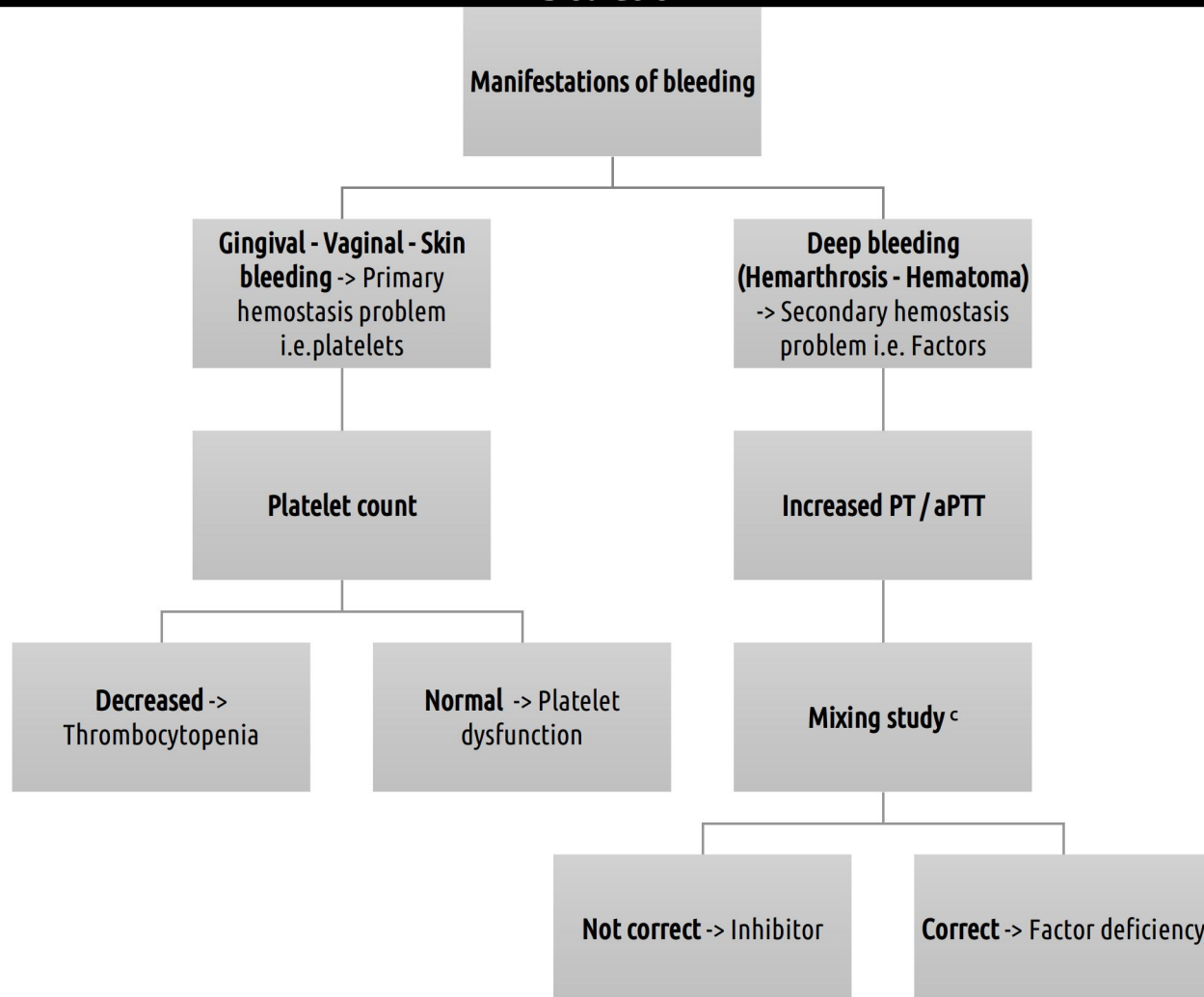
Notes

Bleeding

Hemostasis

Primary hemostasis	<ul style="list-style-type: none"> ■ Endothelial injury ■ Exposure of subendothelial collagen ■ vWF binds collagen ■ Adhesion -> Platelets bind vWF through Gp1b receptor at the site of injury only ■ Bound platelets release ADP, Ca^{+2} and TXA_2^a ■ Activation -> ADP binds $P2Y_{12}$ receptor -> \uparrow GpIIb/IIIa expression at platelet surface ■ Aggregation -> Fibrinogen binds GpIIb/IIIa receptors and links platelets ■ This results in a temporary plug that is unstable
Secondary hemostasis	Intrinsic or extrinsic pathway -> Activate X -> Activate V -> Activate II -> Activate I -> Clot -> broken down by plasmin ^b

Disorders



Gp -> Glycoprotein

PT -> Prothrombin time

PTT -> Partial thromboplastin time

a	<ul style="list-style-type: none"> ■ ADP -> helps platelets adhere to endothelium ■ Ca^{+2} -> Necessary for coagulation cascade
b	Plasmin is formed from plasminogen by the action of Tissue plasminogen activator tPA
c	<p>Normal plasma is mixed with patient's plasma -> then see if PT, PTT corrects</p> <p>Done to distinguish factor deficiencies from factor inhibitors (e.g. lupus anticoagulant, antibodies directed against factor VIII)</p> <ul style="list-style-type: none"> ■ If corrects -> Factor deficiency ■ If Not -> Inhibitor <p>Factor levels that are 50 percent of normal should give a normal PT or PTT</p>

Hematology and Oncology

Thrombocytopenia				
	TTP	DIC	HIT	ITP
Patho	Deficiency in ADAMTS13 -> ↓ Degradation of vWF multimers -> ↑ platelet adhesion and aggregation -> Hyaline clots ^a -> Affect CNS and Kidneys	Systemic activation of coagulation ^b -> Fibrin clot ^c	Antibodies to (Heparin-bound platelet factor 4) -> Antibody-Heparin-PF 4 complex activate platelets -> thrombosis -> Thrombocytopenia	Anti GpIIb/IIIa antibodies -> probably due to viral infection (EBV - HCV - HIV)
Patient	<ul style="list-style-type: none"> ■ Fever ■ Microangiopathic hemolytic anemia ■ Thrombocytopenia ■ Renal failure ■ Neurologic symptoms 	<ul style="list-style-type: none"> ■ Very sick ■ In ICU ■ In shock ■ Then -> Bleeding 	<ul style="list-style-type: none"> ■ In hospital ■ 7-14 days on heparin products ■ Low platelets ■ Thrombosis ■ Necrotic skin lesion 	<ul style="list-style-type: none"> ■ Woman with autoimmune disorder ■ Low platelets
Dx	<ul style="list-style-type: none"> ■ CBC -> ↓ Platelet count ■ Smear -> Schistocytes ■ PT - PTT -> Normal ■ Fibrinogen -> Normal ■ D-dimer -> Normal ■ Don't send out for ADAMTS13 	<ul style="list-style-type: none"> ■ CBC -> ↓ Platelet count ■ Smear -> Schistocytes ■ PT - PTT -> ↑ ■ Fibrinogen -> ↓ ■ D-dimer -> ↑ 	Serotonin release assay or HIT antibodies -> But will take long -> So start treatment immediately	<ul style="list-style-type: none"> ■ Dx of exclusion ■ Personal or family history of autoimmune disorder + low platelets ■ Test for HIV , HCV ^d
Tx	<ul style="list-style-type: none"> ■ Exchange transfusion -> to take out the bad blood and put the good blood ■ Platelet transfusion -> Never do it 	<ul style="list-style-type: none"> ■ Supportive -> Transfuse whatever is deficient ■ Fix the underlying disease 	<ul style="list-style-type: none"> ■ Stop Heparin ■ Argatroban -> For thrombosis ■ Bridge to warfarin 	<div>Children</div> <ul style="list-style-type: none"> ■ Skin only -> Observe ■ Bleeding -> IVIG or Steroids <div>Adults</div> <ul style="list-style-type: none"> ■ >30,000 & no bleeding -> Observe ■ <30,000 or bleeding -> IVIG or Steroids

DIC Types

	Bleeding type	Organ failure type	Consumptive type	Non-Symptomatic type
↓ Platelets	+	+	+	+
↑ D-Dimer	+	+	+	+
↑ PT and PTT	+	+	+	-
↓ Fibrinogen	+	-	+	-
↓ Antithrombin	-	+	-	-
↓ Hematocrite	-	-	+	-
Schistocytes	-	+	+	-

TTP -> Thrombotic thrombocytopenic purpura

HIT -> Heparin-induced thrombocytopenia

IVIG -> Intravenous immunoglobulins

PTT -> Partial thromboplastin time

DIC -> Disseminated intravascular coagulation

ITP -> Immune thrombocytopenic purpura

PT -> Prothrombin time

a	<ul style="list-style-type: none"> ■ Platelets will be consumed in hyaline clots -> Thrombocytopenia ■ No changes in Clotting Factors -> PT, PTT, Fibrinogen, D-dimer will be normal
b	Causes are -> Snake bites - Sepsis - Trauma - Obstetric complications - Pancreatitis - Malignancy - Nephrotic syndrome - Transfusion
c	<ul style="list-style-type: none"> ■ Platelets will be consumed in fibrin clots -> Thrombocytopenia ■ Clotting Factors will be consumed as well -> ↑ PT, ↑ PTT, ↓ Fibrinogen, ↑ D-dimer
d	As platelet counts can be affected by treating the underlying disease

Hematology and Oncology

Platelet dysfunction

Drugs	NSAIDS - Clopidogrel	
Metabolic	Uremia	
vWF deficiency	Patho	<ul style="list-style-type: none"> ■ AD ■ ↓ vWF ■ ↓ Factor VIII -> As vWF stabilizes factor VIII ■ Most common inherited bleeding disorder
	C/P	<ul style="list-style-type: none"> ■ Platelet bleeding -> Due to platelet dysfunction ■ Deep bleeding -> Due to factor VIII deficiency
	Dx	Normal PC - Normal PT - Normal or ↑ PTT - ↑ BT - vWF assay Not correct with ristocetin cofactor assay
	Tx	<ul style="list-style-type: none"> ■ DDAVP -> ↑ secretion of vWF ■ Factor VIII -> in times of acute hemorrhage
Bernard Soulier	Patho	Deficient GP1b - Autosomal recessive
	C/P	<ul style="list-style-type: none"> ■ Asymptomatic ■ Petechiae - Purpura - Epistaxis - Menorrhagia - Gingival bleeding
	Dx	<ul style="list-style-type: none"> ■ Smear -> Giant platelets - Thrombocytopenia (Or normal) ■ Normal PT, PTT, D-Dimer ■ ↑ Bleeding time ■ Abnormal Ristocetin test
Glanzmann thrombasthenia	Patho	Deficient GPIIb/IIIa - Autosomal recessive
	C/P	<ul style="list-style-type: none"> ■ Asymptomatic ■ Petechiae - Purpura - Epistaxis - Menorrhagia - Gingival bleeding
	Dx	<ul style="list-style-type: none"> ■ Smear -> Normal - No platelet clumping ■ Normal PT, PTT, D-Dimer ■ ↑ Bleeding time

Factor deficiency

Hemophilia	Patho	<ul style="list-style-type: none"> ■ A (VIII) and B (IX) -> XR ■ C (XI) -> AR
	Patient	Pediatric - Deep bleeding (e.g. joint or muscle) after minor trauma
	Dx	↑ PTT - Factor assay
	Tx	<ul style="list-style-type: none"> ■ Transfusions -> Develop inhibitors over time -> eventually becomes refractory ■ Factor concentrate -> Short lived -> So given when they bleed only ■ DDAVP -> Hemophilia A only
Vit K deficiency	Patho	↓ Factors II, IV, IX, X, protein C & S due to ↓ vitamin K in -> <ul style="list-style-type: none"> ■ ICU patient who have been NPO for a long time ■ Patients using Warfarin -> inhibits vitamin K epoxide reductase -> ↓ Vitamin K activation ■ Frequent antibiotic use ■ Fat malabsorption (Biliary atresia - Cystic fibrosis)
	Dx	Normal BT - ↑ PT - ↑ PTT

AD -> Autosomal dominant

PTT -> Partial thromboplastin time

XR -> X linked recessive

PC -> Platelet count

BT -> Bleeding time

AR -> Autosomal recessive

PT -> Prothrombin time

vWF -> Von willebrand factor

DDAVP -> D-amino D-arginine vasopressin

Hematology and Oncology

Hereditary telangiectasia (Osler-Weber-Rendu syndrome)

Patho	Autosomal dominant genetic mutations that result in an abnormal vasculature (e.g., AVMs)
C/P	<ul style="list-style-type: none">■ Epistaxis■ Red blanchable papules on the lips■ Digital clubbing■ Gastrointestinal telangiectasia■ Pulmonary AVMs -> Embolic stroke and cerebral abscess■ Cerebral AVMs -> Hemorrhagic stroke
Dx	<ul style="list-style-type: none">■ Clinical■ CBC -> Isolated polycythemia (Reactive due to chronic hypoxemia -> As it can produce arteriovenous malformations in the lungs -> Right-left shunt -> Hypoxemia)
Tx	Management is directed at the site of involvement -> e.g., nasal lubrication and laser treatment for epistaxis

AVM -> Arteriovenous malformation

Notes

Thrombophilia

Thrombophilia

	Factor V leiden	Prothrombin mutation	Protein C , S deficiencies	Antithrombin deficiency	Anti-phospholipid syndrome (APLA or APS)
Patho / CP	<ul style="list-style-type: none"> Genetic factor V mutation (Arg506Gln) -> DVT , Cerebral vein thrombosis , recurrent abortion Most common in Caucasian Mild 	Genetic 20210A mutation in 3' untranslated region -> ↑ Prothrombin production	After warfarin is started without heparin bridging -> Thrombotic skin necrosis and hemorrhage	Causes -> <ul style="list-style-type: none"> Inherited Acquired -> Nephrotic -> loss in urine Result -> ↓ inhibition of factors IIa and Xa	*Lupus anticoagulant ^d -> arterial and venous clots and recurrent abortion *Anti-cardiolipin *Anti β ₂ glycoprotein 1
Dx	Detect the mutation ^a	Detect the mutation ^a	Check level ^b	*Check level ^b *Not affect PT/PTT	*Russell viper venom assay *False +ve VDRL test but -ve FTA-ABS *High PTT
Tx	If the patient has Surgery / Trauma / Cancer -> <ul style="list-style-type: none"> Prophylaxis -> LMWH If develop a clot -> Treat it -> Heparin to warfarin bridge^c 				Warfarin -> Goal is INR 2-3

Antithrombin III deficiency

Patho / CP	Antithrombin III deficiency -> Decreased factor II and X inactivation -> Hypercoagulability
Tx	Higher doses of heparin -> due to heparin resistance (As heparin acts on Antithrombin III) so PTT remains normal after standard doses

Homocystinuria

CP	Thrombosis - Downward lens - Intellectual disability - Pale skin - Marfanoid habitus
Tx	Vitamin B6 and vitamin B12 supplementation

NB ->

- Having a trauma or surgery -> ↑ Venothromboembolism risk by 10 fold
- Having cancer -> ↑ Venothromboembolism risk by 20 fold
- Factor 5 leiden -> ↑ Venothromboembolism risk by 1.5 fold
- Warfarin -> given for life after ->
 - 1st clot -> in Antiphospholipid syndrome
 - 2nd clot -> in other causes of thrombophilia

LMWH -> Low molecular weight heparin

APLA -> Antiphospholipid antibody

APS -> Antiphospholipid syndrome

PTT -> Partial thromboplastin time

a	Chances are you aren't going to do it
b	You can't check a level while clotting , on heparin or on warfarin -> So never check the level
c	If the patient has metastatic cancer -> Give LMWH (Which is generally given for short-term) not (Heparin to warfarin bridge)-> because the chances are that he is going to die from cancer not from thrombosis
d	<ul style="list-style-type: none"> In vitro -> it anticoagulates (So PTT will not correct when mixed with normal plasma (mixing study); prolonged PTT is an in vitro artifact) In vivo -> it coagulates -> So causes arterial and venous clots in the body

Notes

Hematology and Oncology

Transfusion reactions

Febrile non-hemolytic reaction

Patho	Cytokine accumulation during blood storage
C/P	Fever - Chills -> Within 6 hours after transfusion
Dx	■ Clinical ■ Plasma free hemoglobin < 25 mg/dL
PPx	Leukoreduction

Acute hemolytic reaction

Patho	ABO incompatibility
C/P	Fever - Flank pain - Hemoglobinuria - Renal failure - DIC -> Within 1 hour after transfusion
Dx	■ Clinical ■ Coombs test -> +ve ■ Plasma free hemoglobin > 25 mg/dL

Delayed hemolytic reaction

Patho	Anamnestic antibody response
C/P	Mild fever and hemolysis -> 2-10 days after transfusion
Dx	■ Clinical ■ Coombs test -> +ve

Anaphylactic reaction

Patho	Recipient's Anti-IgA antibodies
C/P	Shock - Angioedema - Urticaria - Respiratory distress -> Seconds to minutes after transfusion
Dx	■ Clinical

Allergic reaction

Patho	Recipient's IgE
C/P	Flushing- Angioedema - Urticaria - Pruritis -> 2-3 hours after transfusion
Dx	■ Clinical

Transfusion-related acute lung injury

Patho	Donor anti-leukocyte antibodies
C/P	Respiratory distress (Signs of Non-Cardiogenic pulmonary edema) -> Within 6 hours of transfusion
Dx	■ Clinical ■ CXR ■ CT

Primary hypotension reaction

Patho	Bradykinin in blood products transfused to a patient on ACEI
C/P	Transient hypotension -> Start within minutes of transfusion

DIC -> Disseminated intravascular coagulation **ACEI** -> Angiotensin converting enzyme inhibitor

Notes

Specialized RBC treatment

Irradiated blood

Indications	<ul style="list-style-type: none"> ■ Bone marrow transplant recipients ■ Cellular immunodeficiency ■ Blood components donated by 1st or 2nd degree relative
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Leukoreduced blood

Indications	<ul style="list-style-type: none"> ■ Chronic transfusions ■ CMV at-risk patients who are seronegative (AIDS - Transplant) ■ Potential transplant patients ■ Previous febrile non-hemolytic reaction
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Washed blood

Indications	<ul style="list-style-type: none"> ■ IgA deficiency ■ Complement-Dependent autoimmune hemolytic anemia ■ Continued allergic reaction with RBC transfusion despite antihistamine treatment
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Notes

Hematology and Oncology

Graft-versus-host disease (GVHD)

	Acute	Chronic
Onset	<100 days after transplantation	>100 days after transplantation
Patho	Donor T lymphocytes react with recipient's antigens	Unknown
C/P	<ul style="list-style-type: none"> ■ Skin -> Maculopapular rash -> Pruritic ■ GIT -> Nausea - Vomiting - Diarrhea - Cramping pain ■ Liver -> Dysfunction - Jaundice 	<ul style="list-style-type: none"> ■ Skin -> Scleroderma-like changes ■ Sicca syndrome -> Dry pruritic skin - Dry mouth - Dry eye ■ GIT -> Chronic enteritis (Bloody diarrhea - Pain - Weight loss) ■ Liver -> Dysfunction - Jaundice ■ Lung -> Bronchiolitis Obliterans (Cough and dyspnea not responding to bronchodilators) ■ Skeletal muscle -> Polymyositis - Myasthenia
Dx	<ul style="list-style-type: none"> ■ CBC -> Pancytopenia ■ ALP -> ↑ ■ Biopsy -> Confirmation 	<ul style="list-style-type: none"> ■ Spirometry -> Obstructive lung disease ■ Biopsy -> Confirmation
Tx	Optimize GVHD prophylaxis (Cyclosporine level) Steroids -> <ul style="list-style-type: none"> ■ <50 % skin -> Topical steroid ■ >50 % skin or liver or GIT involvement -> Systemic steroid +/- Topical steroid 	<ul style="list-style-type: none"> ■ 1st line -> Steroids ■ 2nd line -> Cyclosporine and ↑ steroid dose
PPx	<ul style="list-style-type: none"> ■ Antithymocyte globulin ■ Cyclosporine + either methotrexate or Mycophenolate mofetil 	

ALP -> Alkaline phosphatase

Notes