Hemostasis

1° platelet (weak plug)

2° Coagulation Cascade (cements it)

Step 1: Vasoconstriction (endothelin release)

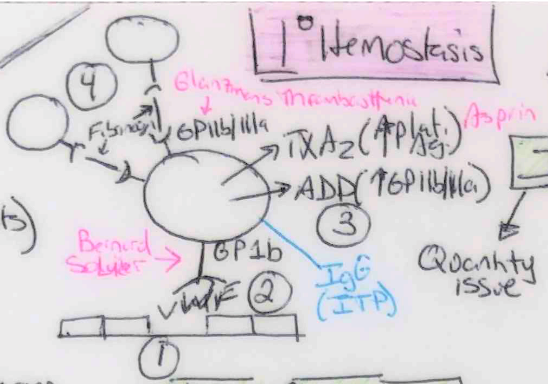
Step 2: Platelet adhesion
- VWF binds exposed collagen
VWF ⟷ GP1b

Step 3: Platelet degranulation
- ADP released (↑GP IIb/IIIa)
- TXA_2 (from COX) - promotes platelet aggregation

Step 4 Platelet Aggregation (weak)

Fibrinogen, GP IIb/IIIa

1° Hemostasis



If Platelet Disorder (nml 150-400K/uL)
(SS_x: mucosal & skin bleeding)

1 Platelet Quality issue
- Bernard-Soulier (GP1b def) impaired platelet adhesion
- Glanzmann's - Thrombasthenia genetic GP IIb/IIIa def
- Aspirin / ↓COX
- Uremia (↓platelet Fxn)

Quantity issue

Immune Thrombocytopenia Purpura (ITP) - MCC thrombocytopenia

Quantity issue

IgG against platelet (GP IIb/IIIa)

IgG, macrophage in spleen

Acute	Chronic
children post viral inf.	women/SLE

LABS: ↓Platelet (<50K), nml PT/PTT, ↑Megakaryocyte.

Tx: corticosteroid (children), IVIG (tricks body), Splenectomy (chronic)

Microangiopathic Hemolytic anemia

RBC - anemia with shistocytes

- pathologic formation of platelet microthrombin in small vessels.

(TTP) Thrombotic Thrombocytopenic Purpura (↓ADAMSTS13 - cleaves VWF into smaller pieces) (think CNS vessels of brain)

(HUS) Hemolytic Uremic Syndrome. E. coli damage endothelium (Think Kidney mostly)

LABS: ↑bleeding, Thrombocytopenia, nml PT/PTT, Anemia w/ Schistocytes, ↑Megakaryocytes.

Tx: plasmapheresis and corticosteroids

2° Hemostasis

thrombin → Fibrinogen → Fibrin

- Stabilizes weak platelet plug via Coagulation Cascade (makes Thrombin)

activated Subendothelial collagen: 12, 11, 9, 8 — X — 7 ← activated Tissue Thromboplastin
PTT intrinsic HEParin; PT coumadin
X → 5 → 2 → 1

Hypercoagulable

Protein C,S def. (A.D) (normally will inactivate Factor V, VIII) - shorter half life than II, VII, IX, X ∴ risk skin necrosis

Factor V Leiden (mutated Factor V) ∴ not deactivated by Protein C,S. "can't be shut off"

Fibrinolysis (removes thrombus)
plasminogen ⊖ aminocaproic acid; ↓tPa
plasmin (cleaves fibrin and serum fibrinogen)
- destroys coagulation factors
- blocks platelet aggregation

* Note: α2-antiplasmin (inactivates plasmin)

Cirrhosis of Liver = ↓α2-antiplasmin

Disorders of fibrinolysis
Labs (Cirrhosis, Radical prostatectomy)
- ↑PT/PTT (↓coag. factors)
- ↑bleeding w/ nml pt. count
∴ low D-dimer

XS cleaving of serum fibrinogen (not fibrin)

Tx: Aminocaproic acid (blocks activation of plasminogen)

Hemophilia A - Factor VIII def.
- X-linked recessive or de Novo
- Deep tissue bleeding

LABS: ↑PTT, nml PT, ↓F VIII, nml plt / bleeding

Note: PTT corrects w/ Mixing nml Blood.

Tx: recombinant F VIII

Hemophilia B - Factor IX def.

Coagulation factor def.
acquired antibody against coag factor (MC FVIII)
(PTT does not correct upon mixing nml plasma w/ Pts.)

ATIII def.
↓protective effect of Hep. like molecules ↑risk thrombus

Note: Heparin like molecules normally activate ATIII, which inactivate thrombin and coagulation factors.
- PTT does not rise with Heparin dosing

Note: nml Heparin works by Binding to ATIII

Oral Contraceptives
↑production of Coagulation Factors

Von Willebrand Dz - MC inherited Disorder
- Autosomal dominant
- mild bleeding

Labs: ↑bleeding, ↑PTT / nml PT
VWF normally stabilizes FVIII (no deep bleeding)
- Abnormal Ristocetin Test - will normal help VWF bind to GP1b.

Tx: Desmopressin (ADH analog) (↑VWF release from WP bodies)

Vit. K. def - activated by epoxide reductase (Liver) II, VII, IX, X, protein C protein S
def. in newborns, long term antibiotics, Malabsorption

OTHER: Liver Failure (follow w/ PT) can't activate epoxide reductase

OTHER DISORDERS

Heparin Induced Thrombocytopenia (HIT)
Hep - (Platelet Factor 4) - Platelet
IgG antibody formed
- destroyed platelets may lead to thrombosis

DIC
- Pathologic activation of coagulation cascade.
- widespread microthrombi
- consumption of platelets and factors leads to bleeding.

why? obstetric (Tissue Thromboplastin activation)
- Sepsis
- Adenocarcinoma
- Acute Promyelocytic Leukemia
- Rattlesnake

LABS: ↓platelet ct., ↑PT/PTT, ↓Fibrinogen, Microangiopathic hemolytic anemia, ↑split products (D-dimer) (from splitting of fibrin) (not fibrinogen)

Tx: Tx cause and give blood products / Cryoprecipitate

Thrombosis

Pathologic formation of Intravascular clot.

risk factors:
1) disruption of blood flow (keeps platelets inactive)
2) endothelial cell damage
3) hypercoagulable state

Disrupts protective features.

tPA, NO, PGI_2, Hep like molecules

nml protectors:
- PGI_2 - ↓plat. agg.
- NO - vasodilation, inhibits plat. agg. (Nitrous Oxide)
- Hep like - augments anti-III (inactivates thrombin and coag. factors)
- tPA (see above)
- Thrombomodulin - activate protein C (inactivates Factors V, VIII)

secretes Thrombomodulin

Homocysteine injures endothelium (ie. atherosclerosis, vasculitis)

Red Blood cell Disorders

Anemia

- ↓ circulating RBC mass (Measured by Hb, Hct, RBC count)

SS_x: Weakness, fatigue, ~Hypoxia

Hb = heme + globin (Decrease in any of these ↓ Hb)

Iron Protophoryin

Microcytic (<80) "extra division"

absorbed Duodenum

Hb = heme + globin

Iron Protophoryin

Iron across w/ Ferroportin → in Blood via Transferrin, stored intracellularly to Ferritin (prevents free Radical formation)

enterocyte

M.Cs

- Infants: poor breast feed
- Children - poor diet
- Adults (20-50) - Peptic ulcer - D_x Male; menorrhagia XX
- Elderly - Polyps (Western World)
- Hookworm (Ancylostoma duodenale, Necatur Americanus)
- Gastrectomy - no acid

labs: ↑RDW, ↓Ferritin, ↓serum iron, ↓%sat, ↑FEP

Iron def / Anemia of chronic Dx

acute phase reactant "Hepcidin" from liver sequesters iron by
1) store in Macrophage Fe
2) suppress EPO

labs: ↑ferritin, ↓TIBC, ↓serum Iron, ↓%sat.

* ↑ Free erythrocyte Protophoryin

Sideroblastic Anemia

congenital or acquired

defective Protophoryin synthesis

Succinyl CoA —B6→ ALA —ALA dehydratase→ porphobilinogen

ALA synthase (congenital)

alcohol, lead, B6 def. (INH)

if deficient, iron is trapped in Mitochondria. Iron trapped around nucleus (in Mitochondria) (ringed Sideroblast)

Lab: ↑Ferritin, ↓TIBC, ↑Serum iron, ↑%sat.

Thallassemia

↓ synthesis of globin chains

protection: Plasmodium Falciparum.

HbF (α_2, γ_2)
HbA ($\alpha_2 \beta_2$)
HbA_2 (α_2, δ_2)

α-Thallassemia = usually gene deletion

β-Thallassemia = usually gene mutation (point mutation)

- minor: ↓HbA, ↑HbA_2, "Target Cells"
- major: severe anemia months after birth; ineffective erythropoiesis, extravascular hemolysis; "extramedullary hematopoesis" - Skull; risk of parvo B19 crisis; "Target Cells w/ nucleated RBC"

Lab: HbA_2 and HbF with little or no HbA.

Hyperkalemia

C BIG K Drop

- Calcium gluconate
- Bagonist
- Bicarbonate (if acidosis)
- Insulin
- Glucose
- Kayexelate
- Diuretic
- Dialysis

Calcium Chloride

Cardioprotection

Renal Tubular Acidosis

I, II, IV

- I - H^+ problem (systemic Acidosis) (can't excrete H^+ urine alkalosis) >5.5
- II "bi" - bicarbonate problem. can't reabsorb bicarb
- IV | K High K^+ - Due to low ALD (hold 4 fingers) or ALD insensitivity

Lung Volumes (mM)

6L

- IRV
- TV (what we breathe)
- ERV
- RV

0

I.C.

FRC

small m = Vital Capacity

Big M = Total Lung Capacity

Divide big M in ½
- residual is at bottom (FRC)
- upper ½ is Inspiratory Capacity

Normocytic Anemia

MCV 80-100

↓ due to:
- peripheral Destruction
- underproduction

Need Reticulocyte count

nml RC 1-2% (120 days, 1-2% renewal)

RC falsely elevated in anemia, so must correct

$RC \cdot \frac{HCT}{45 (nml)} = \square$

>3% good response

<3% poor response.

Peripheral Destruction

Extravascular

(RETICULO-endothelial) macrophages of spleen, liver, lymph.

∴ Globin released (amino acids)

Heme → broken Down

Protophoryin → unconjugated bilirubin (bound to albumin) to liver.

SS_x: splenomegaly, Jaundice (uncon. bili)

Intravascular

(w/in vessel)

- Hemosiderinuria.
- ↓Haptoglobin

Hereditary Spherocytosis

ankyrin, spectrin

- spherocytes w/ no central pallor
- ↑RDW, |↑MCHC| *
- splenomegaly, jaundice (uncon.)

↓ osmotic fragility Test.

T_x: splenectomy

Howell-Jolly Bodies (nuclear remnants)

Sickle Cell

glutamic acid changed w/ Valine

>90% HbS (polymerizes)

forms needle like when deoxygenated.

HbF is protective

T_x: Hydroxyurea (↑HbF)

Lab: 90% HbS, 8% HbS, 2% HbA_2, no HbA.

If no spleen at risk: Strep Pneumo, Haemophilus, - Salmonella (osteomyelitis), - Howell Jolly bodies on smear

Sickle Cell Trait

< 50% HbS

only SS_x microscopic Hematuria and eventual ↓ ability to conc urine

Lab: 55% HbA, 43% HbS, 2% HbA_2

Immune Hemolytic Anemia

IgG or IgM

- IgG (extravascular): Warm temp. of inner body; a/w SLE, CLL, drugs PCN.
- IgM (Intravascular): Cold Temp. a/w mycoplasma Pneumonia, Infectious mono.

T_x: Stop Drug. Steroids, IVIG, splenectomy.

D_x IMA w/ Coombs

G6PD def

- X-linked.
- oxidative stress.

nml: G6PD → NADPH → Glutathione (nml will protect against H_2O_2)

If ↓ → ↓ ↓Glutathione

Oxidative stress caused by: Primaquine, Sulfa Drugs, Dapsone, Fava beans

HEINZ BODIES SEEN

Intravascular Hemolysis ∴ Hemoglobinuria, Back Pain

Microangiopathic Hemolytic Anemia

RBC's destroyed a/w TTP-HUS, DIC, Prosthetic Valves

Malaria

Infection of RBC and Liver by Plasmodium transmitted by female Anopheles mosquito

RBC's rupture as result of Plasmodium life cycle.

- Falciparum - Daily fever
- Vivax / ovale - Every other day

UNDERPRODUCTION CAUSES

ParvoB19

infects progenitor cell and stops erythropoiesis

Aplastic Anemia

Damage to hematopoietic Stem cell. (Pancytopenia)

Cause: Drugs, Viral, autoIm.

T_x: Marrow Stimulating Drugs (erythropoietin, GM-CSF, G-CSF) or Immunosuppression (if cause was abnormal T-cell.

Macrocytic Anemia > 100

Folate | or | B12 (Ileum)

Folate (Jejunum)

months

Diet, cancer, Methotrexate.

labs: Hypersegmented, Glossitis, ↓Folate, ↑Serum Homocysteine, nml methylmalonic Acid

DNA precursor ②

THF → VB_{12} ③

Homocysteine → Methionine

(M) ···> (M) Transfer ①

Methyl groups

If ↓ impaired division (no material for nucleus)

- alcohol
- liver
- Drugs (5FU)

Other

B12

animal based

↓ amylase liberates B_{12}

binds to R-binder (thru stomach)

↓ Pancreatic proteases cleave.

Small bowel (Ileum) absorbed by Intrinsic Factor gastric parietal cell

- Pernicious anemia: MC autoimmune destruction of Parietal Cell.
- Chrons (Ileum)
- Fish Tapeworm (Diphyllobothrium Latum)

Labs: Macro, Hypersegmented
- Glossitis
- Subacute Combined deg. of spinal cord (↑ methylmalonic acid in cord)

lab: ↓B12, ↑Serum Homocysteine, ↑methylmalonic Acid

Intravascular

1) Paroxysmal Nocturnal Hemoglobinuria (PNH)

absent GPI (attaches Decay accelerating Factor)

if no DAF then cell is susceptible to complement mediated damage. (acidosis at night) RBC's, WBC's lyzed.

Hemoglobinemia, Hemoglobinuria

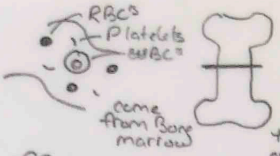
D_x with Flow cytometry lack of CD55

MC cause of death from PNH is thrombosis from destroyed platelets

a/w Iron def. and AML (10%)

Leukemia

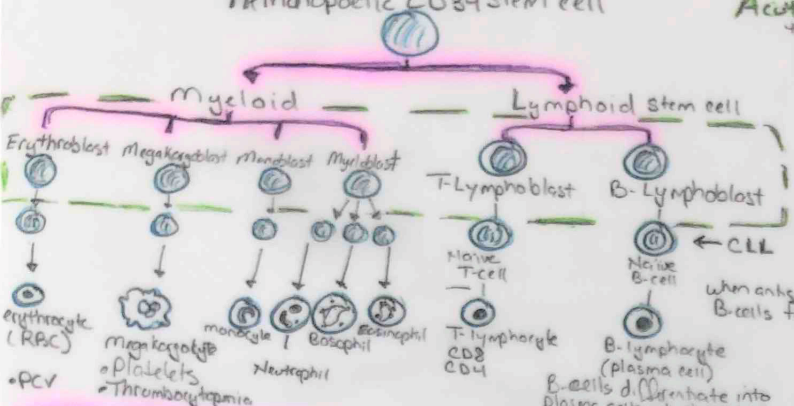
unregulated growth of leukocytes in Bone marrow
"cancer of blood cells"



In Leukemia the cells RBC, Platelets or WBC can replicate so rapidly and use up all the growth factors and nutrients. NML cells "don't have a chance." The "new cells" dont serve a purpose and only take up space and resources.

SSx:
↓RBCs: Pale SOB fatigue
↓platelets: bruising prolonge bleeding
↓WBC ↑infections
weakness, weight loss
2/2 excess energy.
Eventually the ↑↑ cells pushes its way into bone wall ∴ painful.

Hematopoetic CD34 Stem cell



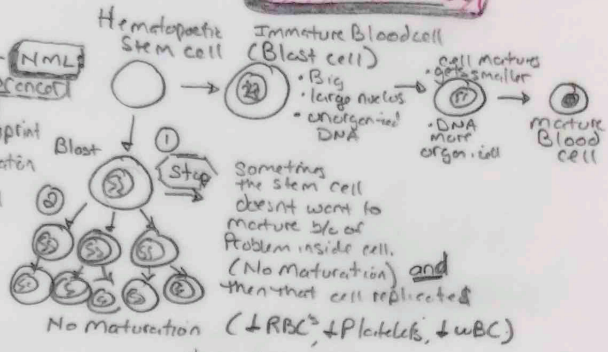
•PCV
•Thrombocytopenia

When antigen is encountered B-cells turn into plasma cells

B-cells differentiate into plasma cells, which produce large amounts of antibodies specific to a particular antigen

Acute Leukemias = from the most immature cells. Either myeloid or Lymphoid

Pathophysiology



Sometimes the stem cell doesn't want to mature b/c of problem inside cell. (No maturation) and then that cell replicates

(↓RBCs, ↓Platelets, ↓WBC)

How does a cell become mutated?
1. exposure to radiation
2. exposure to carcinogens
3. Translocation (error in cell Division)

Acute Lymphoblastic Leukemia aka ALL

>20% lymphoblast in Bone Marrow

Lymphoid Stem cell
T-Lymph
B-Lymph

Markers: TdT⊕ CALLA⊕
preB (CD19, CD10)
preT (CD1, CD2, CD5)

Tx: Intrathecal Methotrexate

Also Kids most (<15yoa)
Also Downs Syndrome

Q: How can we look at something and determine it is a lymphoblast cell?
A: Lymphoblast have TdT in their nucleus unique to lymphoblast. (stain TdT⊕)

Q: How can we determine if T or B lymphocyte?
A: We look at markers and we should know that B-cell ALL is Also Translocations:
t(12;21) → Kids (good prognosis b/c these cells respond better to Tx)
t(9;22) → Adults

In T-cell ALL (when bone marrow release T-cells they go to thymus to mature)
∴ If mass amounts of T-cells in blood → Thymus enlarges (mass)
(also Teenagers)

AML

2 items also cancer
1. Bad Blueprint
2. replication out of control

Acute Myeloid Leukemias

accumulation of >20% immature myeloid cells in bone marrow.

Since there are a bunch of Acute Myeloid cells you can have multiple Types of AML:
M3 → Acute Myeloblastic
gums → Acute Monoblastic
Also Downs → Acute Megakaryoblastic (Down also)
Acute Erythroblastic (so rare)

•characterized by ⊕ cytoplasmic staining of **Myeloperoxidase (MPO)**
Myeloperoxidase — can be thought of as → Auer Rods

M3 also t(15;17) which is retinoic acid receptor on chromosome 17, blocks maturation

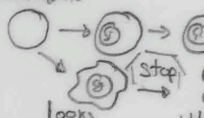
M3 → ↑risk of DIC after Tx of AML M3 due to release of Auer rods.

"Bleeding from IV site"
Median is 60 yoa

Tx: Chemo: Daunorubicin and cytosine arabinoside
If M3 → ATRA
So, Tx with All-Trans retinoic Acid (Vit A) will bind to faulty receptor and allow maturation to occur.

Myelodysplastic Syndrome

neutrophils
Basophils
Eosinophils
abnormal



recall: 2 items also cancer but there is No excessive replication
also Myelodysplastic

even if nml cells get made, they will die off quicker.

Or 1° problem in Myelodysplastic Syndrome is ↓# myeloid cells.

In nml Bone Marrow on 2-3% of cells are blasts
In cancer >20% but w/o replication <20% blasts
However, if these cells did develop a mutation where they did replicate uncontrollably, then it turns into AML (only if it gets the 2nd mutation)

Chronic Leukemias

Chronic Lymphoid Leukemia CLL

CLL is a "B-cell" Leukemia
• CLL cell looks like a mature B-cell but not as structurally strong as a mature cell.
∴ if you put that fragile cell on a slide you would "smudge" the cell.

nml B-cells would usually go to ① Lymph node and mature.
② Liver
③ Spleen

so, CLL cells go to same areas.
∴ those organs get "bigger"

S/S lymph nodes → enlarged, lymphadenopathy

Now, normally, B-cells make antibodies but CLL cells fall short ∴ ↓hypogammaglobulinemia results so, and the antibodies they can make are not good and they actually attack our own RBC's (autoimmune hemolytic Anemia)

Small lymphocytic lymphoma (small mass of CLL cells)
• once in the lymph nodes, they get more mutations and become more "sticky" and mass grows

Small lymphocytic Lymphoma → Richter Transformation (from small to diffuse) → Diffuse B-cell lymphoma (one lymph node in particular gets "big")

Chronic Myeloid Leukemia

WBC (50-200k)
Age 30-60
Age >60 yoa

Tx is based on staging

Stage	
0	↑WBC
1	enlarged lymph
2	Spleen enlarged
3	Anemia
4	low platelets

no Tx
Tx: Fludarabine ± Rituximab (CD20)

BCR (ch 22) + Abl (ch 9) → BCR-Abl (Tyrosine Kinase is constantly "ON")
t(9;22) Philadelphia chromosome
FISH stains (DDx also CML)
SSx: abdominal fullness (excess platelets) ↑liver, ↑spleen
Fever (due to ↑WBC's)
↑Basal metabolism
Bleeding (platelets not working) ecchymoses (bruising)
Bone Pain (↑Myeloblasts)
↑Basophils
* Tx: Imatinib (blocks Tyrosine Kinase activity)

* CML DDx vs Leukemoid Rx:
① CML has ⊖ Leukocyte Alk phos (LAP) (Rx for infection)
② ↑Basophils (absent in Leukemoid)
③ t(9,22)

Hairy Cell Leukemia

≈50 yoa Adult mature B-cell tumor
• massive splenomegaly
• Pancytopenia

Stains TRAP (Tartrate resistant acid phosphatase ⊕)

Tx: Cladribine (resistant to degradation by adenosine deaminase ∴ good to go into CNS)

Adult T-cell Leukemia

proliferation of adult CD4⊕ t-cells

S/S skin rash, lymphadenopathy hepatosplenomegaly
* lytic (punched out) Bone lesions *

Mycosis Fungoides

proliferation of CD4⊕ T-cells
• infiltrate to skin
• can spread to blood causing Sezary-Syndrome

Leukemoid Rx often confused w/ Leukemia. ↑WBC count w/ left shift ↑LAP, usually due to infection (vs. CML ↑WBC, L shift ↓LAP)