# HEMATOLOGY REVIEW
# WEEK 9: ANEMIA

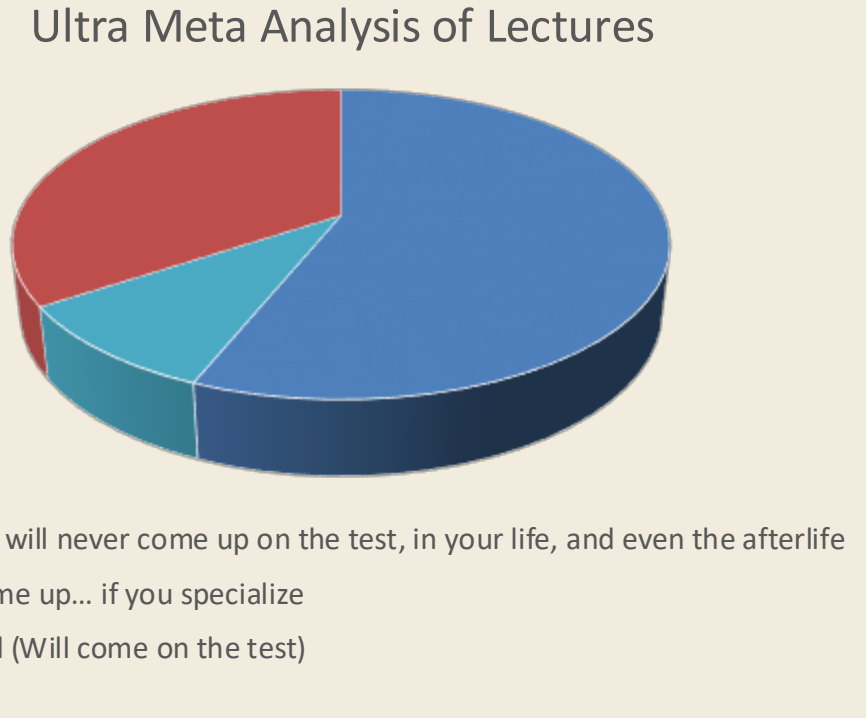
**Updated 2025!**

**Hamzah & Allison**

**Schulich Reviews**

# The Utility of these sessions

1. Goal: Excel on test + clerkship + Dr
2. Must prioritize High Yield (red)
3. How to know what's High yield?
4. That's where Schulich Reviews comes in! We guide your attention to the most important details




*** This is our disclaimer that we don't cover the entirety of lecture content. Don't sue us <3 ***

# SCHEDULE

| | |
|---|---|
| 6:00pm - 7:00pm | W9 - anemia |
| 7:00pm - 8:00pm | W10 - hemostasis |
| 8:00pm - 9:00pm | W11-12 - blood cancers, myeloid/lymphoid disorders |

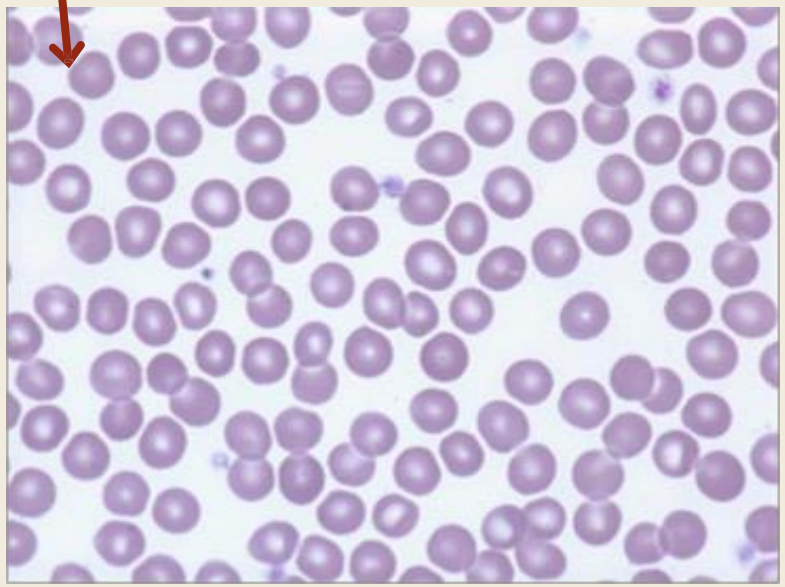
# RBC BASICS

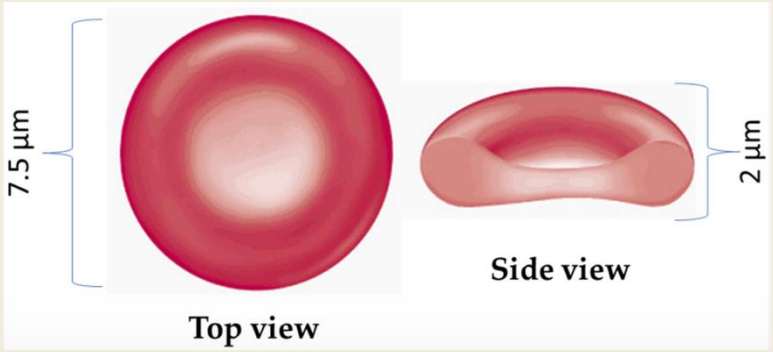
Morphology, development, components

# RED BLOOD CELLS

## Morphology

- Biconcave discs
- Pallor area (white part) in center due to the biconcave shape - 1/3 of the diameter of the RBC






## Components

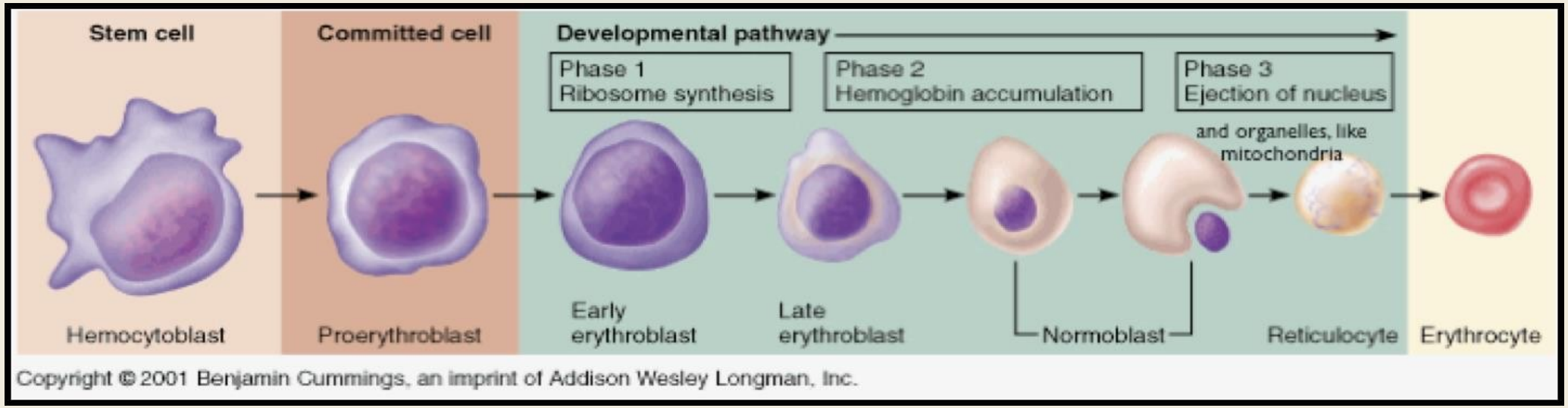
- Surface molecules (BLOOD GROUP!)
- Water, ions (Osmosis!)
- Hemoglobin (Oxygen!)
- Membrane
- Cytoskeletal proteins
- Cytoplasm
- Glycolytic enzymes

# ERYTHROPOESIS

## Steps

1. Early erythroid precursor
2. Erythroblast
3. Reticulocyte
4. Erythrocyte

- Lifespan of RBC is ~120 days (3 months)
- Damaged or senescent RBCs are filtered out from circulation by the spleen or removed by other tissues of the RES (i.e., liver, marrow, lungs)



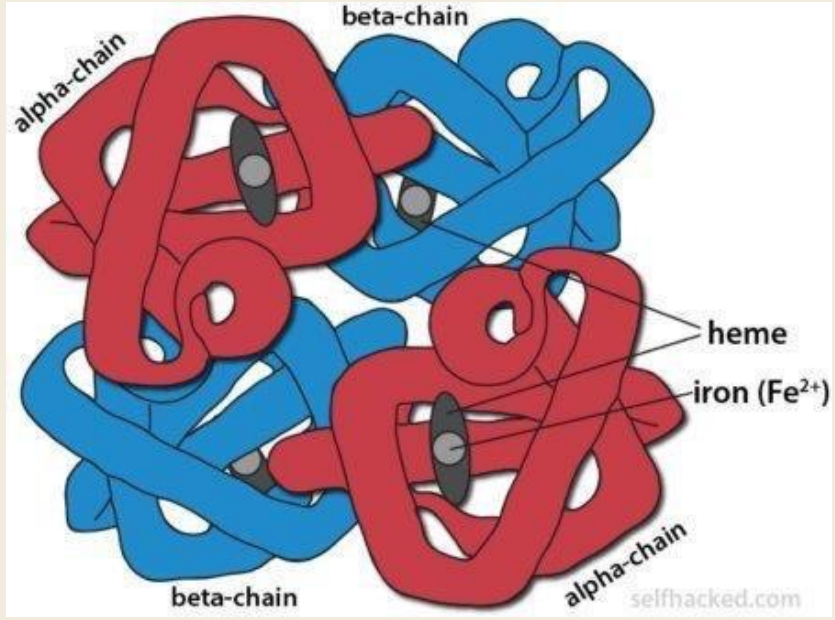
# HEMOGLOBIN (Hb) COMPONENTS

## 4 globin chains

- 2 alpha + 2 beta = Hb tetramer

- 2 alpha genes = total 4 alleles
- 1 beta gene = total 2 alleles

- Abnormal beta genes → sickle cell disease
- Mutations in beta or alpha → thalassemia



# HEMOGLOBIN (Hb) COMPONENTS

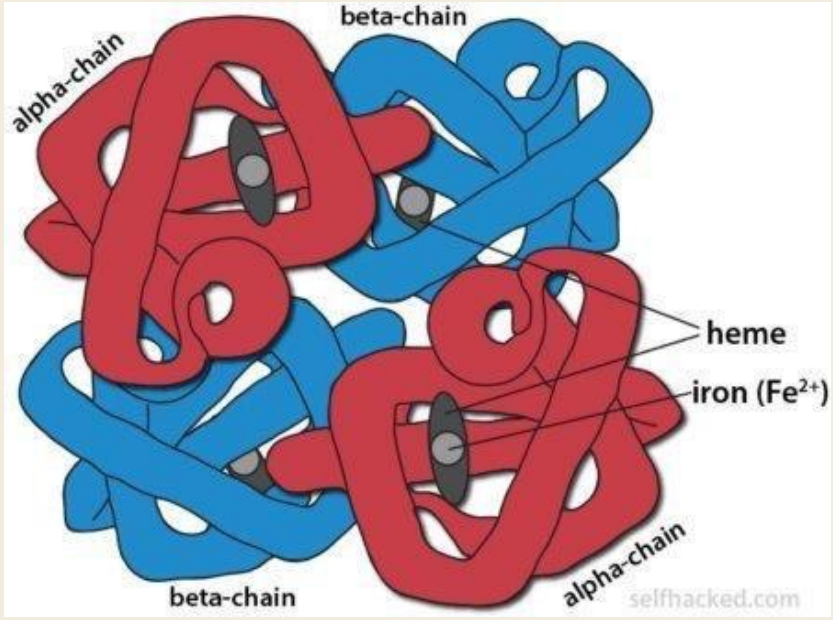
## 4 globin chains

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## 4 heme = 4 Oxygen



# TYPES OF HEMOGLOBIN

**During development proportions of Hb subunits change**

- **Alpha (α)** - alpha for always!
- **Gamma (γ) chains** – Gamma for gametes. Produced in fetus! Holds oxygen tighter!
- **Beta (β) chains** – Beta for birth. The adult chain! Produced after birth and replace the intrauterine gamma chains
- Delta (**δ**) chains – just a little random one

**Normal adult Hb consists of:**

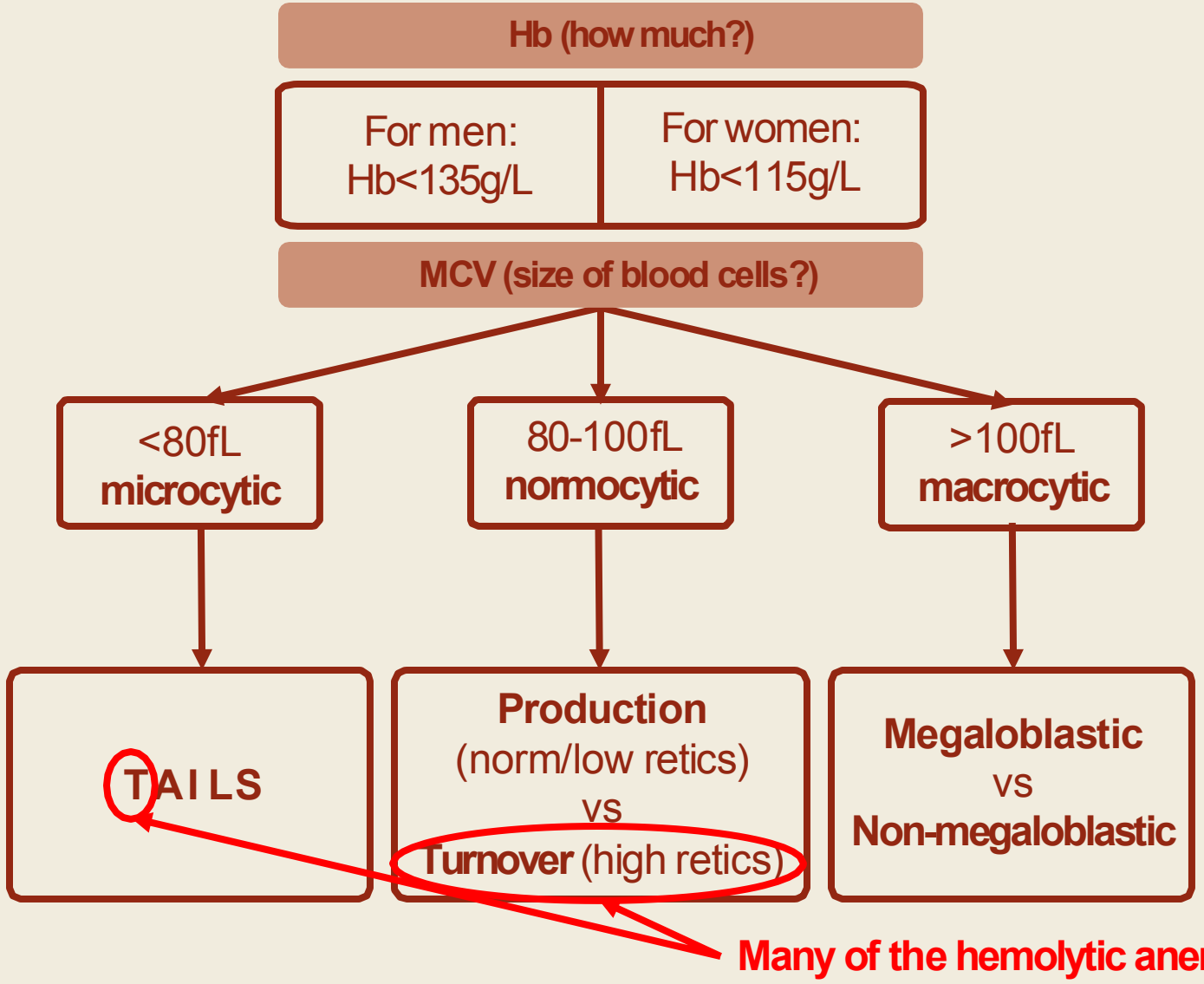
- 95% HbA ($\alpha 2\beta 2$)
- 3% HbA2 ($\alpha 2\delta 2$)
- <2% HbF (Fetal Hb - $\alpha 2\gamma 2$)

# ANEMIA

## Signs/Symptoms/Clues

- Fatigue, pallor
- Jaundice
- Brittle nails
- Pica
- SOB, chest pain
- Neurologic symptoms
- Hair loss
- Restless leg
- Leg swelling
- Glossitis
- Toxin exposure
- Demographics, family hx, exposures
- Etc. – presentation can be diverse

# OVERVIEW OF ANEMIA & CBC




| | | | | |
|---|---|---|---|---|
| WBC | 8.3 | | 4.0 - 11.0 | X E9/L |
| RBC | 3.51 | LO | 4.00 - 5.10 | X E12/L |
| HEMOGLOBIN | 93 | LO | 135 - 170 | g/L |
| HEMATOCRIT | 0.31 | LO | 0.350 – 0.450 | L/L |
| MCV | 73 | LO | 80 – 100 | Fl |
| RDW | 19.2 | HI | 11.5 -14.5 | % |
| PLATELET COUNT | 413 | HI | 150 – 400 | X E9/L |

# What's up with Iron?

- **Iron** – used to make hemoglobin

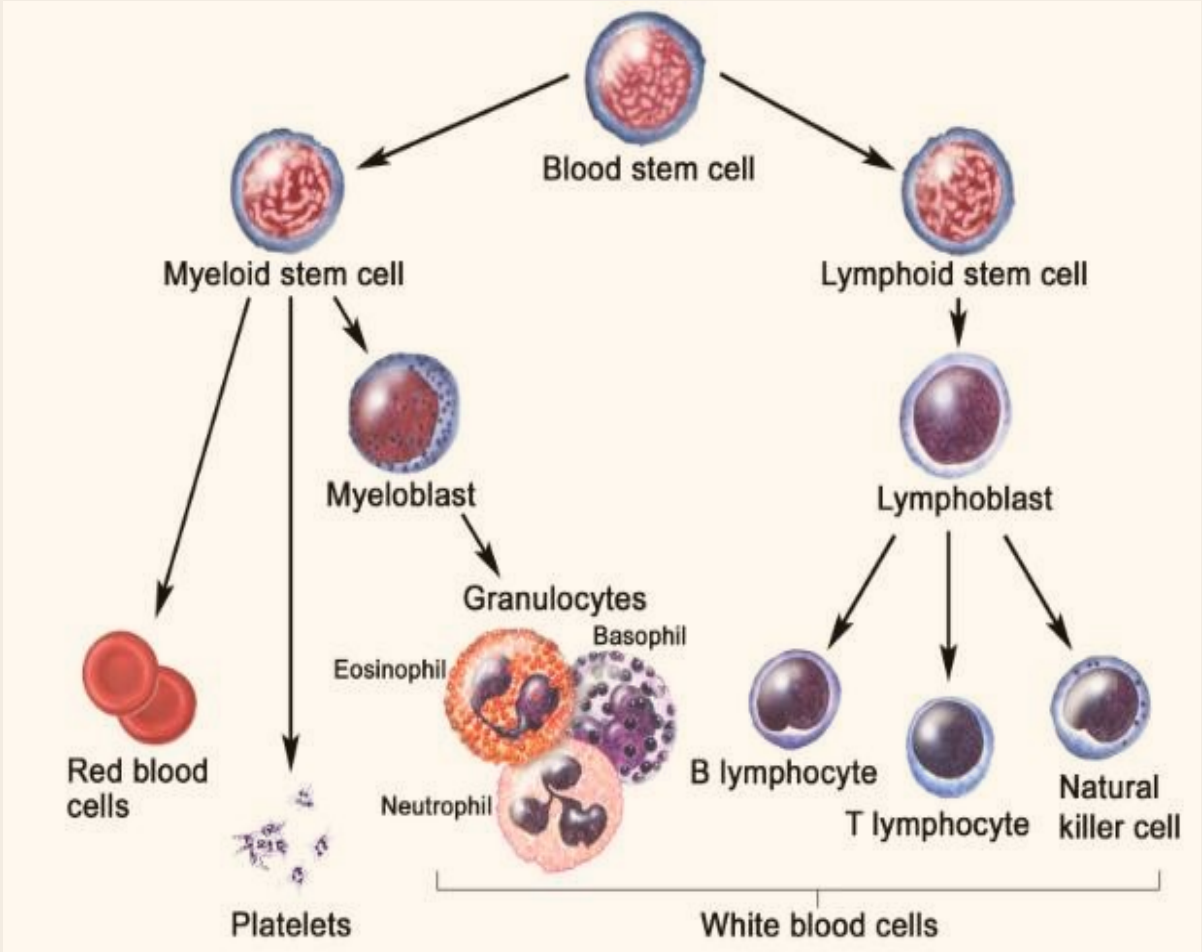
- **Hepcidin** – made in liver in response to high iron/inflammation. Blocks Ferroportin, trapping iron into cells, lowering blood iron, lowering Hb.

- **Ferritin** – Stores iron in cells to prevent oxidative damage & rises in inflammation. Low = iron deficiency.

- **Ferroportin** – iron exit channel from cells (macrophages, liver, enterocytes) and enter blood.

# Production?

- **MCV** – RBC size (micro, normal, macro)
- **RDW** – red cell distribution width, are the cells the same size? (High with production issues (B12/folate def = DNA issue (normal + large); IDA = iron issue (normal + small); Hemolysis (small + normal)
- **Platelets** – clotting cells
- **Reticulocytes** – new RBCs from bone marrow
- **Neutrophils** – segmentation.



# Other Labs

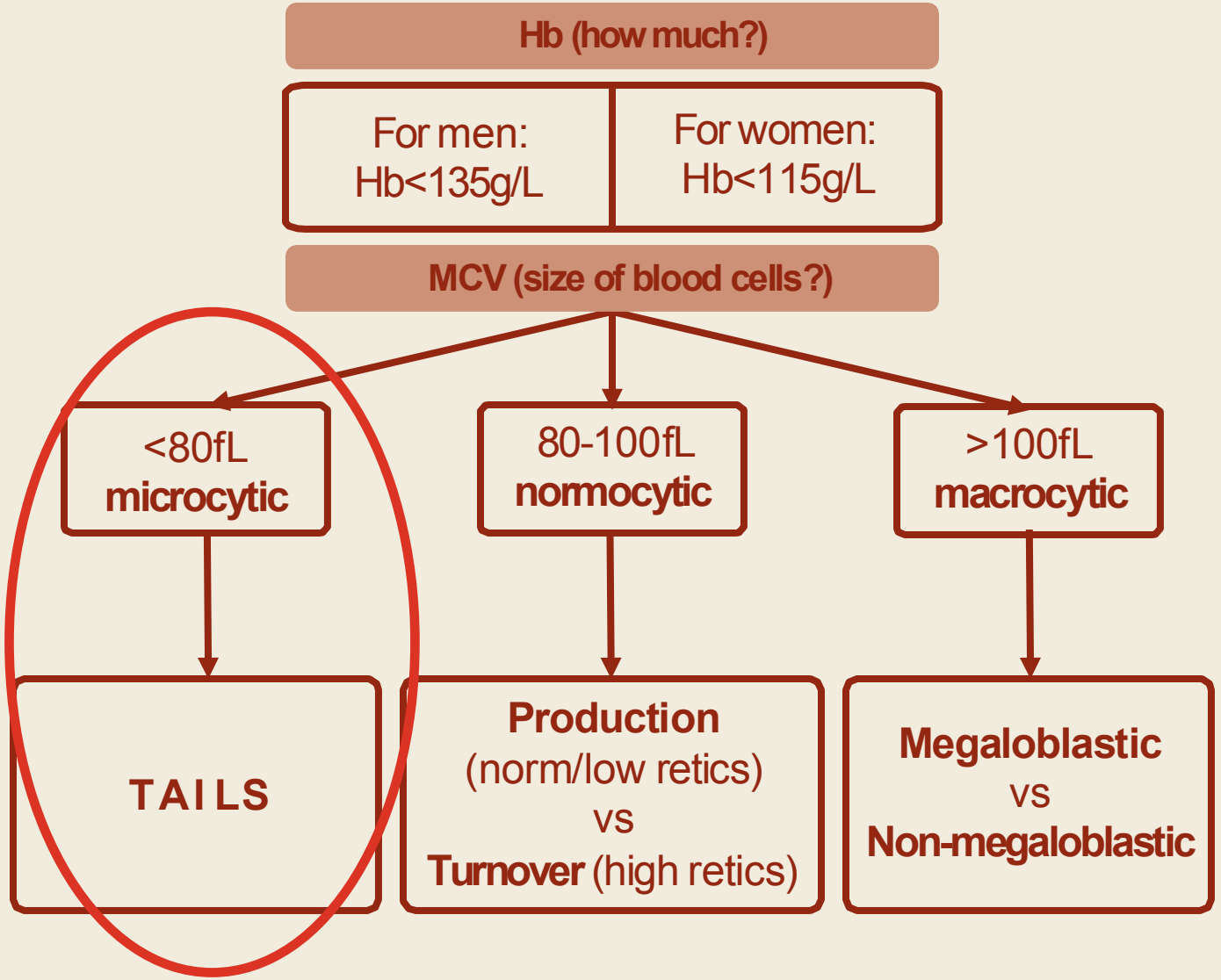
- **Hemoglobin (Hb)** – oxygen-carrying protein (anemic or not)
- **Hematocrit (Hct)** – % of blood that's RBCs (Low = destruction or low production; high = dehydrated, or high production (polycythemia))
- **LDH** – enzyme released when cells break down

# MICROCYTIC ANEMIA

**TALS**

**Globin problems (T) vs Heme problems (AILS)**

# OVERVIEW OF ANEMIA & CBC



# MICROCYTIC ANEMIA

## Definition

- MCV < 80 fL

## Mechanism

- Hb is low because of decreased Hb synthesis
- Decreased synthesis of Hb results in small RBCs
- Either decreased globin (Thalassemia) or decreased heme (AILS)

# DDx MICROCYTIC ANEMIA

- **T** Thalassemia
- **A** Anemia of Chronic Inflammation
- **I** Iron Deficiency Anemia (most common)
- **L** Lead Poisoning
- **S** Sideroblastic Anemia

**Decreased Globin Synthesis**

**Decreased Heme Synthesis**



# MICROCYTIC ANEMIA - REVIEW

| Iron Deficiency | Chronic Inflammation | Lead / Siderob | Thalassemia |
|---|---|---|---|
| **Bloodwork:**<br>• Low ferritin<br>• High RDW<br>• High Platelets<br><br>**Blood Film:**<br>• Hypochromia<br>• Anisocytosis<br>• Poikilocytosis<br>• Elliptocytosis<br>• Target cells | **Bloodwork:**<br>• Normal/high ferritin<br>• Inflammatory<br>• marker (ESR/CRP)<br><br>• Mild microcytosis (MCV rarely <75fL)<br>*can sometimes present as normocytic anemia* | **Bloodwork:**<br>• Normal/high ferritin<br><br>**BM Biopsy:**<br>• Ring sideroblasts<br>(can see rings around RBC precursors for lead poisoning) | **Bloodwork:**<br>• Everything normal except<br>• Normal ferritin, RDW, platelets<br>• Higher RBC than iron deficiency<br><br>**Blood Film:**<br>• Uniform cell size<br>• Target cells<br>• Basophilic stippling<br>• Hypochromasia |

# TAILS



# THALASSEMIA or should I say tha-LESS-emia

## Two types:

**α-thalassemia** –
mutation in the α gene → less production of α chains

**β-thalassemia** –
mutation in the β gene → less production of β chains

- Caused by globin gene mutations
- Results in less or absent globin chains which leads to less adult hemoglobin HbA ($\alpha_2\beta_2$)
- Mutations originate in South East Asia, Mediterranean and African areas



# THALASSEMIA

## Clinical Features

- **Short + Jaundice + Splenomegaly**
- Onset in neonatal period
- Family history, ethnicity
- Signs of hemolysis (to be discussed)

## Blood Film

- Microcytosis (duh)
- **Target cells** Reduced Hb causes cell membrane to fold inwards
- **NO variation in cell size (normal RDW)**
- Hypochromia
- **Basophilic stippling** - Decreased Hb synthesis slows ribosome breakdown and ribosomal RNA fragments are visible

* The 'T' in TAILS has 'Target' cells.






# THALASSEMIA

## α alpha

Presents immediately

Most prevalent in Asia and Africa

Alpha globin = 2 genes (4 alleles)

1. Silent carrier (1/4)
2. Minor/trait (2/4)
3. **Hemoglobin H (HbH) disease (3/4)**
4. Hydrops Fetalis (still birth) (4/4)

## β Beta

Presents a few months after birth

Most prevalent in Mediterranean

Beta globin = 1 gene (2 alleles)

1. Minor/trait (1/2)
2. Intermediate (1/2)
3. **Major (2/2)**

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3. **Major (2/2)**

## HbH Disease (3/4)

- Marked microcytic anemia +/- hemolysis
- Aggressive treatment with transfusion support and iron chelation

## βThalassemia Major

- Marked microcytic anemia +/- hemolysis
- Aggressive treatment with transfusion support and iron chelation

# THALASSEMIA & Hb ELECTROPHORESIS

## α alpha

- Silent carriers (1/4) & Thalassemia Minor (2/4) - **normal electrophoresis of HbA, HbA2** and **HbF**, diagnosed by Hb gene sequencing
- HbH disease (3/4) - excess $\gamma$ chains precipitate as **HbH ($\gamma_4$)** which can be detected on Hb electrophoresis

## β Beta

- Excess $\alpha$ chains combine with other family globin chains
- Higher amounts of **HbA2 ($\alpha_2\delta_2$)** and **HbF ($\alpha_2\gamma_2$)**
- **Hb Barts ($\alpha_4$)** may also form

# TAILS



# ANEMIA OF CHRONIC DISEASE

## Causes

- Infections
- **Inflammation (other inflammatory disorders, e.g. IBS)**
- Malignancies
- Other chronic disease (heart disease, liver disease)
- Idiopathic

## Pathophysiology mechanism

- Reduction in RBC production and shortened survival
- Poor marrow response to erythropoietin with relative deficiency
- **Hepcidin** upregulation → iron sequestration and relative deficiency



Inflammation ↑ IL6, liver makes more hepcidin, hepcidin binds ferroportin, iron cannot be released

# ANEMIA OF CHRONIC INFLAMMATION

## Clinical Feature

- Evidence of other medical conditions – infection, inflammation, malignancy

## Labs

- **Mild** anemia and microcytosis (MCV rarely <75fL), may also be normocytic
- **Ferritin** is slightly transiently increased (Inflammatory response)
- Elevated inflammatory markers **(ESR/CRP)**

## Management

- **Treat underlying disease**
- Rarely requires transfusion
- Erythropoietin in severe cases

# TAILS



# IRON DEFICIENCY ANEMIA

1. **Decreased intestinal absorption**
   - Iron is absorbed in the small intestine
   - Iron absorption depends on gastric acid and intact duodenum and jejunum
   - Celiac, gastritis, H, surgery (gastric bypass), food, medications

2. **Increased demand**
   - Pregnancy
   - Response to erythropoietin
3. **Increased loss (bleeding)**
   - Most common cause of iron deficiency
   - GI vs non-GI source of bleeding
4. **Decreased oral intake**

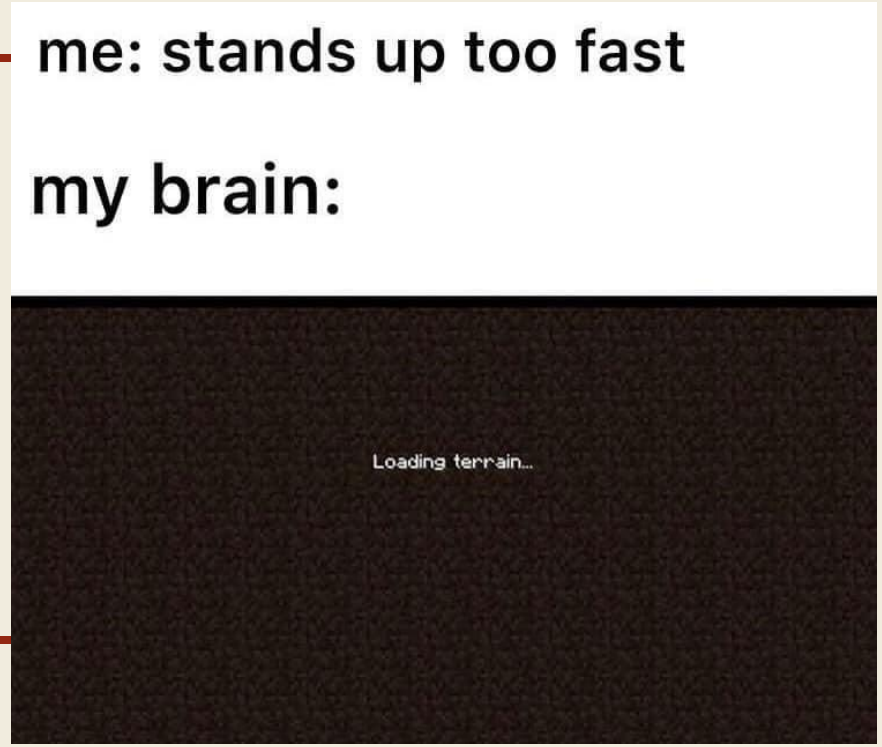


# IRON DEFICIENCY ANEMIA

## Clinical feautres

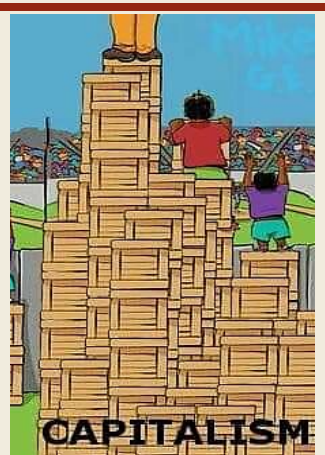
- Effects of Anemia
  - Fatigue, pallor, tachycardia

- **Effects of Iron Deficiency**
  - Brittle nails and hair, koilonychia (hollow nails), pica (desire to eat non-food items)




## Lab Results

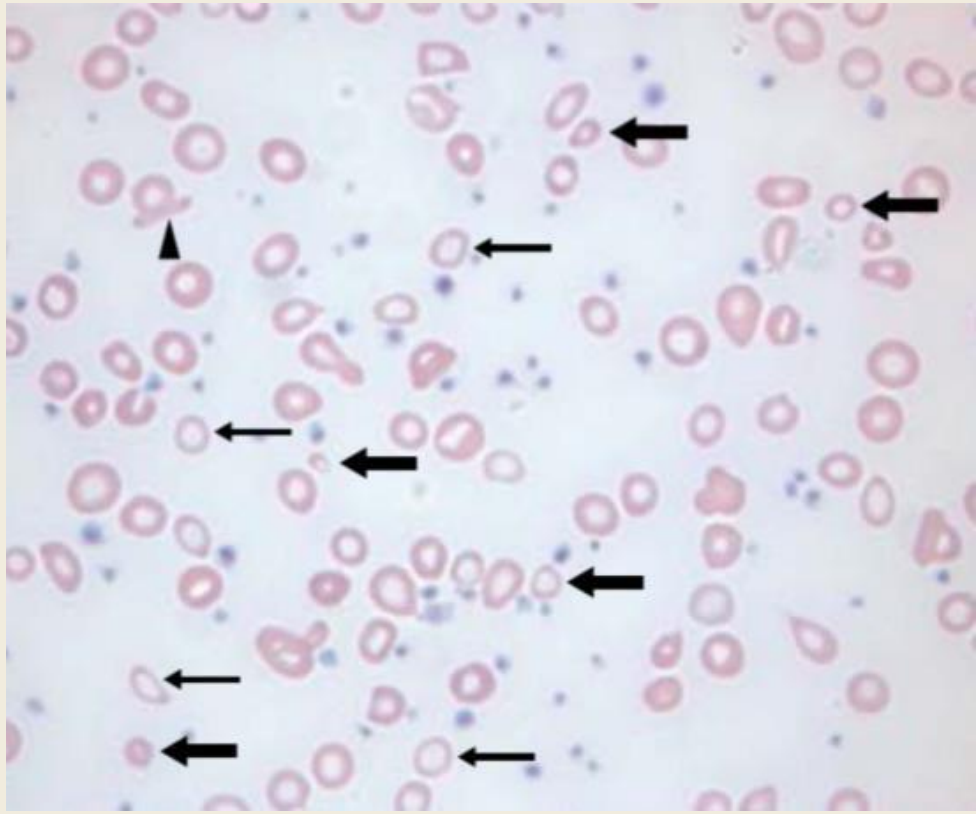
- **Low ferritin** - no stores
- **High RDW** - Normal than small
- **High platelets** → EPO ↑ b/c low $O_2$, ↑ bone marrow ↑ Plts > RBC (some myeloid line)



# IRON DEFICIENCY ANEMIA

## Blood Film

- **Anisocytosis (variety in cell size, high RDW)**
- Hypochromia (center pallor is >1/3 diameter)
- Poikilocytosis (abnormally shaped)
- **Elliptocytes (oval-shaped/elongated)**

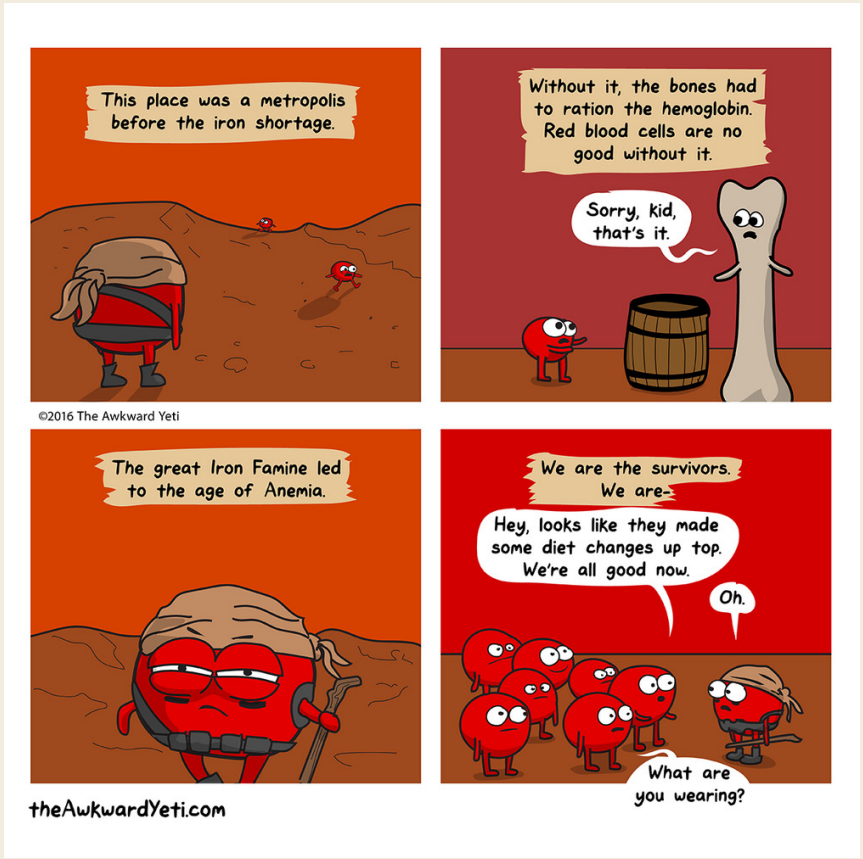


# IRON DEFICIENCY ANEMIA

reticulocytosis in 1 week...
but Hb adjusts in 1 month

## Management

- **Replace iron**
  - Oral supplements (**Gluconate 30** < Sulfonate 60 < fumarate 90)
  - IV Paranetral (if can't absorb
  - Transfusion if severe anemia
- **Search for and treat underlying cause**
  - Decrease absorption/intake
  - Increased demand
  - Increased loss – GI or non-GI bleed



# TAILS



# LEAD and SIDEROBLASTIC ANEMIA

## History

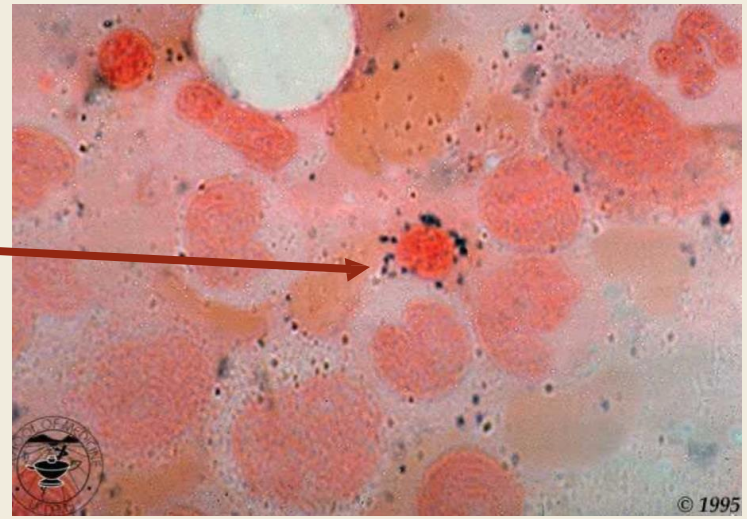
- Chronic lead poisoning – industrial exposure
- Ingestion of alcohol
- Drugs – anti-TB, prior alkylator chemotherapy
- Positive family history (in rare cases)
- Vitamin B6 deficiency (pyridoxine)



# LEAD and SIDEROBLASTIC ANEMIA

## Investigations

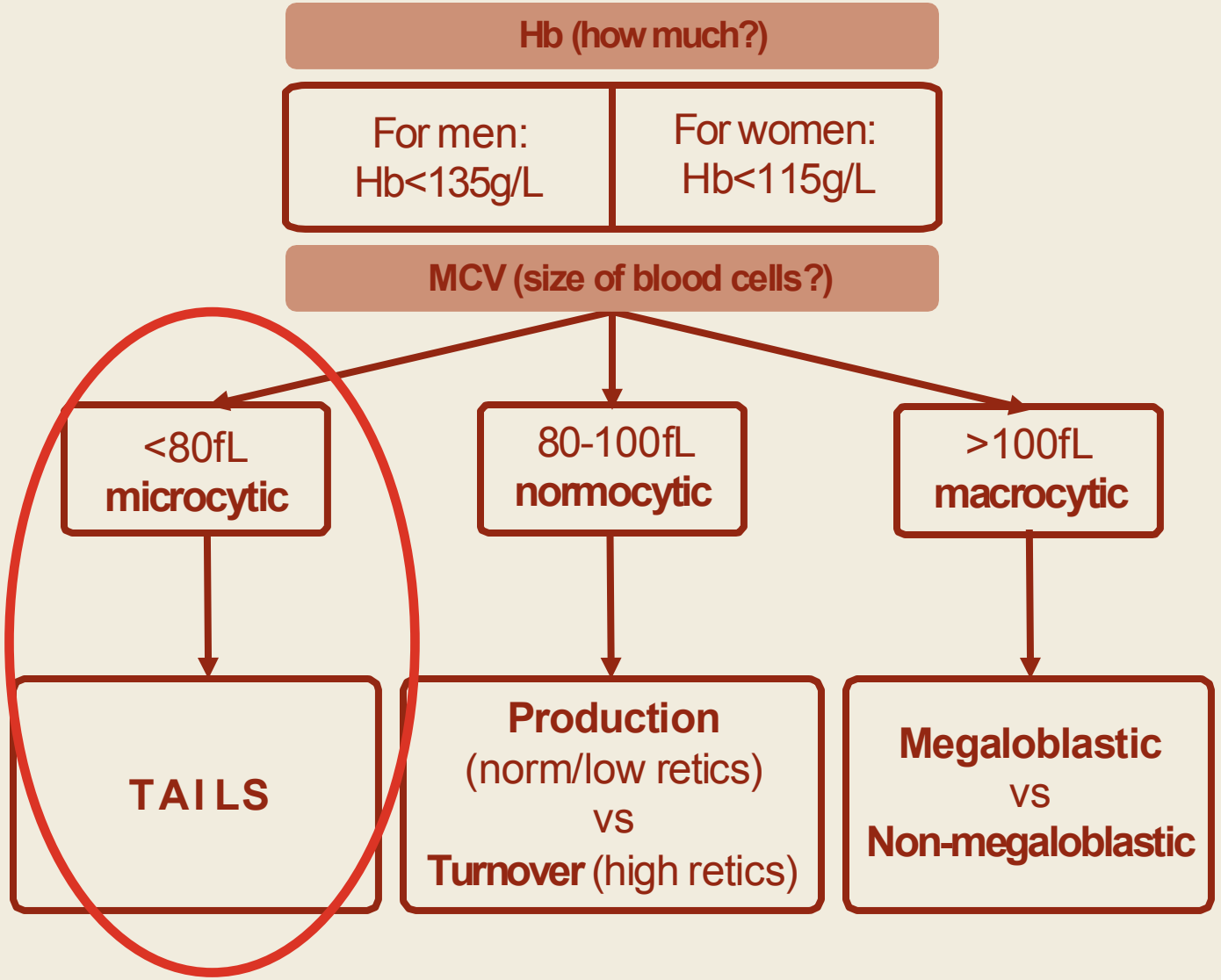
- Pathognomonic ring sideroblasts in the **marrow**



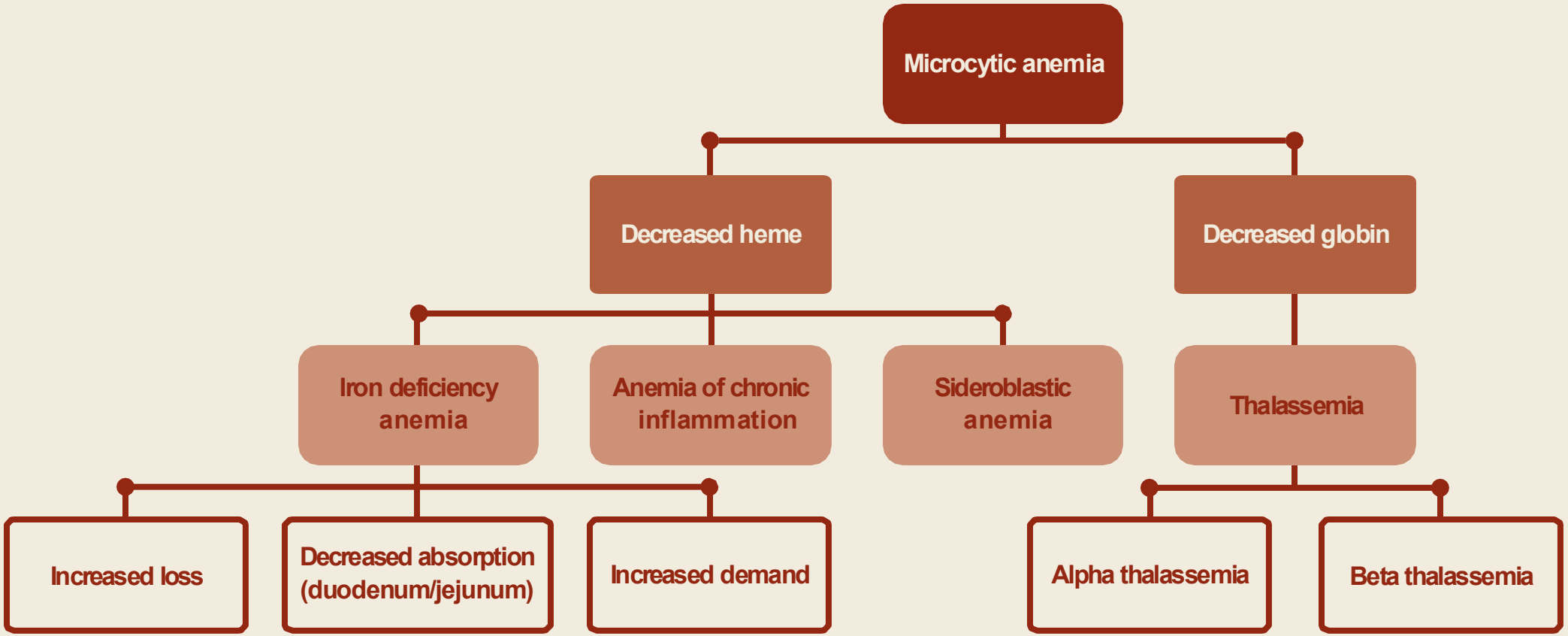

## Management

- **Removal of toxin – chelation therapy for lead, avoidance of chemicals**
- Pyroxidine useful infrequently
- Transfusion may be needed
- Bone marrow transplantation in rare cases

# OVERVIEW OF ANEMIA & CBC



# MICROCYTIC ANEMIA - REVIEW



# TAILS



# MICROCYTIC ANEMIA - REVIEW

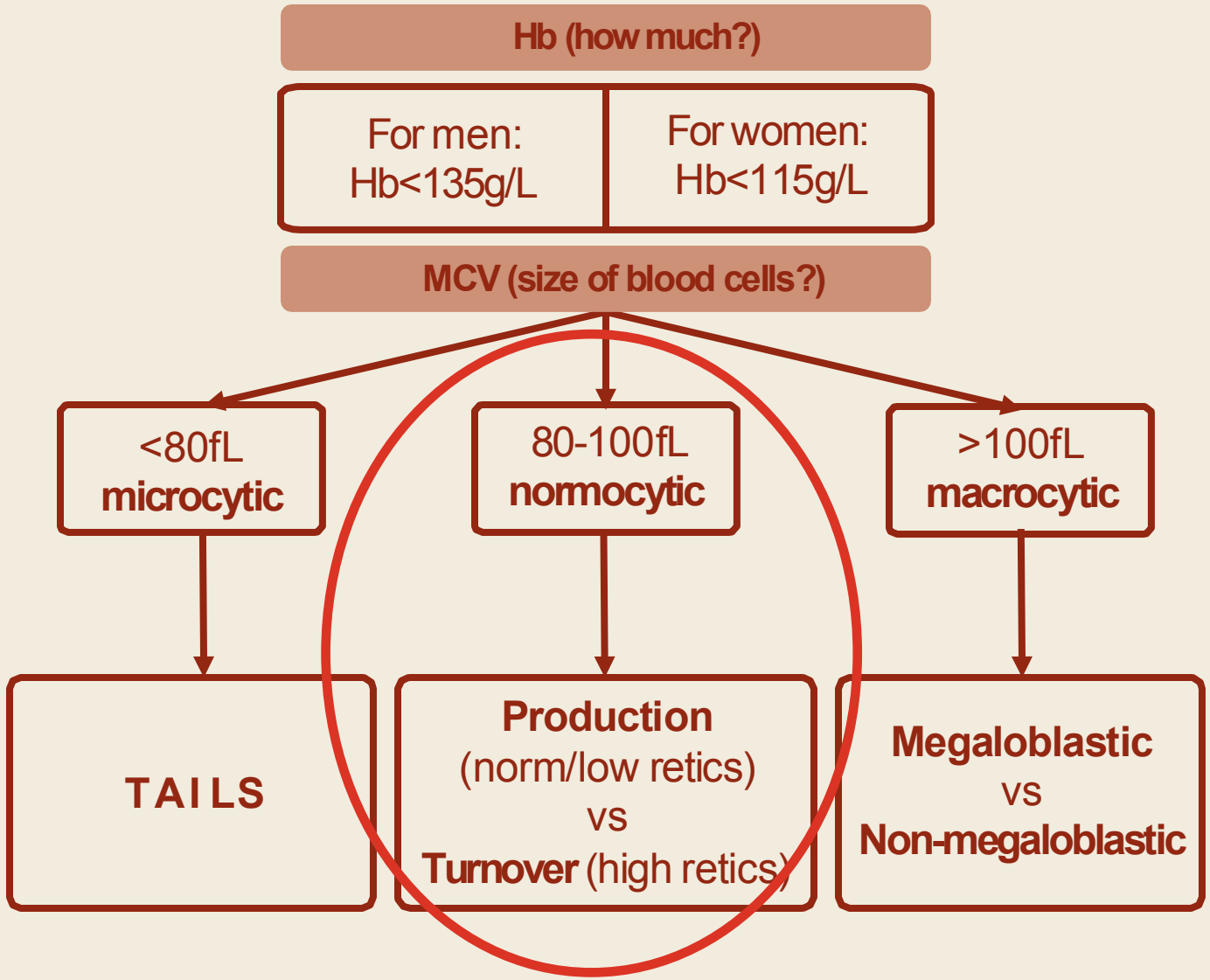
| Iron Deficiency | Chronic Inflammation | Lead / Siderob | Thalassemia |
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# NORMOCYTIC ANEMIA (MCV 80-100)

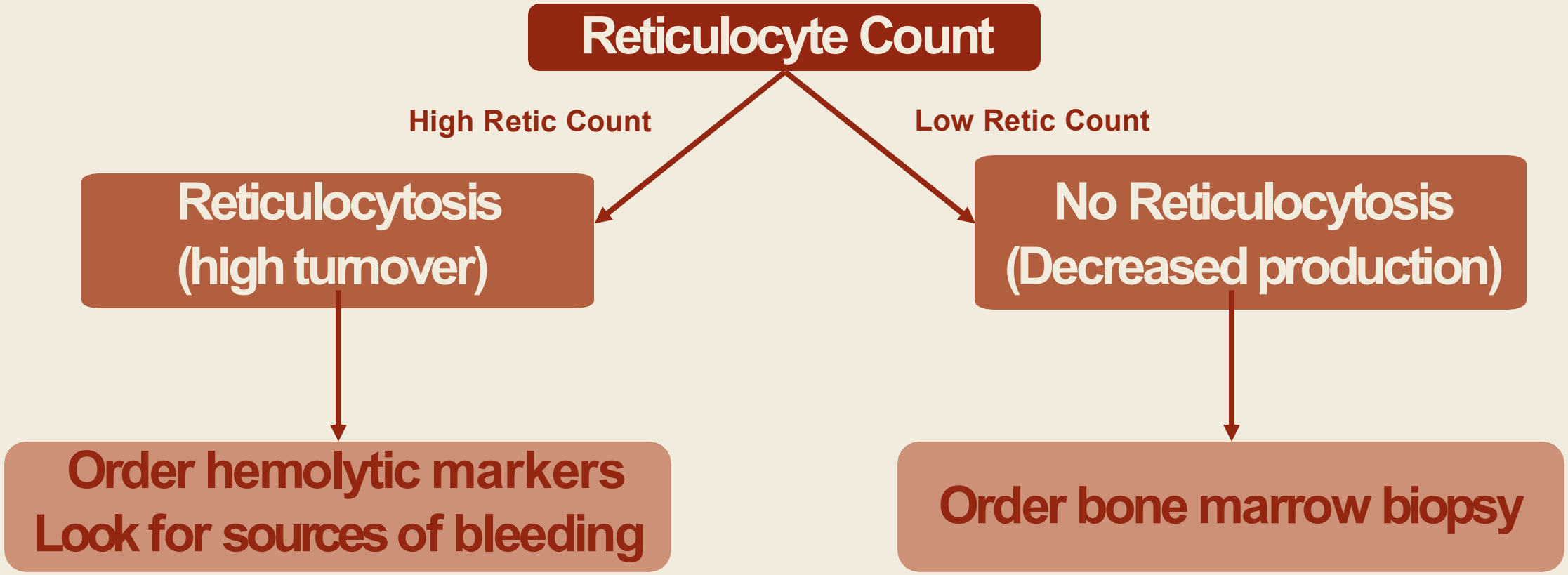
Normal Retic Count → Decreased production

High Retic Count → Increased Turnover

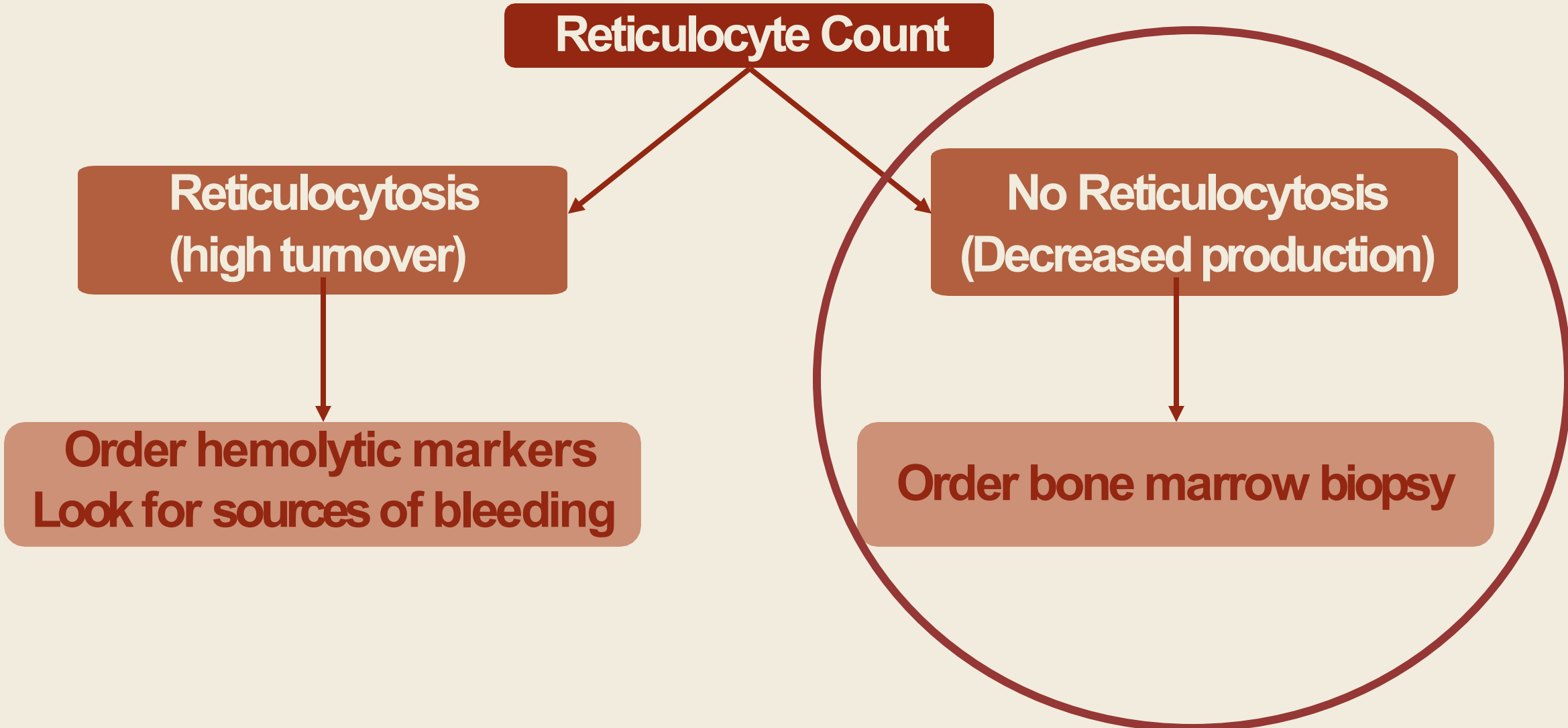
# OVERVIEW OF ANEMIA & CBC



# APPROACH TO NORMOCYTIC ANEMIA



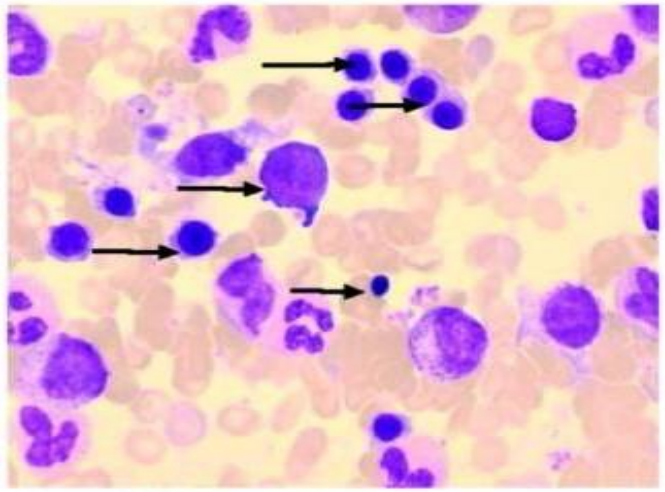
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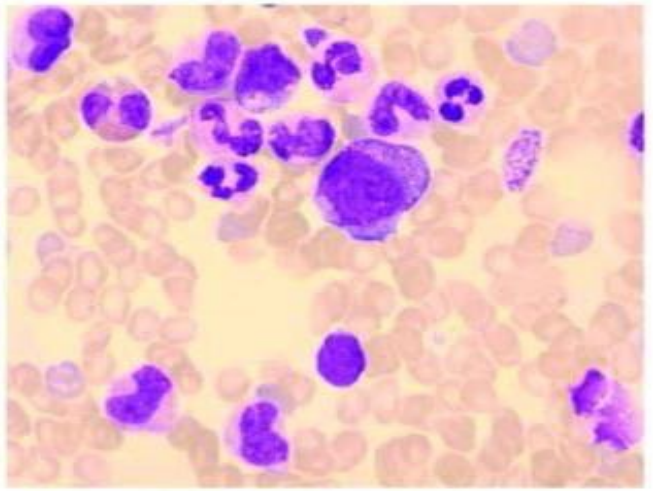
# EMPTY MARROW

## Pure Red Cell Aplasia (PRCA)

- Severe reticulocytopenia (retic count 0-2) and marked reduction or absence of erythroid precursor for bone marrow
- Causes: Congenital, primary acquired (autoimmune or myelodysplastic or secondary acquired (drugs, infection, tumor, pregnancy)



Normal BM containing polychromatophilic erythroblasts (arrows)



BM of a patient with Ab-mediated PRCA

understand this vs aplastic!

# EMPTY EMPTY MARROW

## Aplastic Anemia



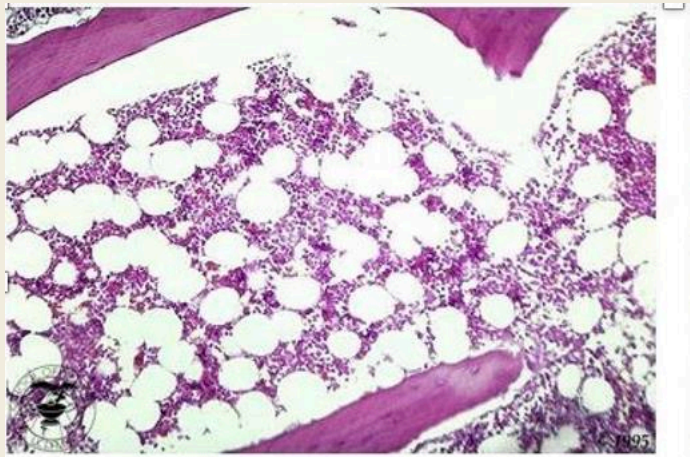

### Pathophysiology

Failure of all blood cells → **pancytopenia**

- Anemia (pallor, weak)
- Thrombocytopenia (Bruising)
- Leukopenia (recurrent infecitons)

### Treatment

- Blood products
- Antibiotics for neutropenic fever
- Bone marrow transplant if eligible
- Immunosuppression if autoimmune related



Normal Bone Marrow Biopsy
Cellularity = 100-age

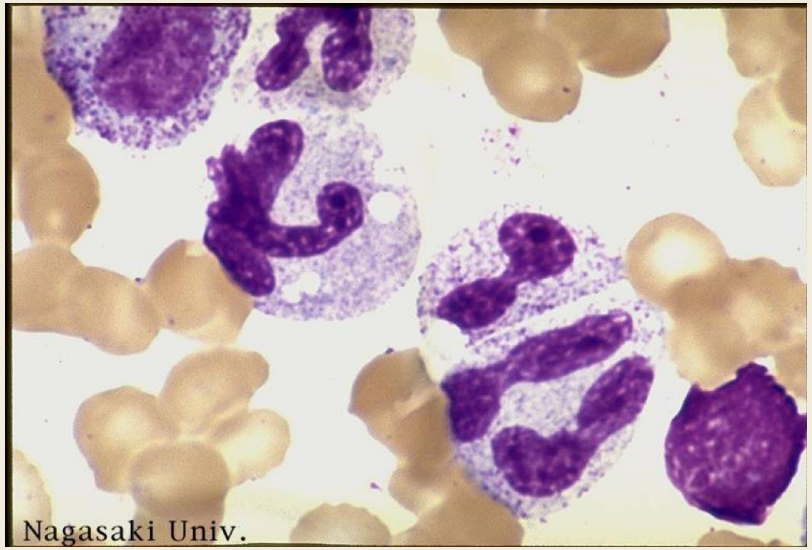



Aplastic Anemia
All fat

# ABNORMAL MARROW

## Myelodysplastic Syndrome (MDS)

- Group of disorders with reduced or ineffective hematopoiesis
- BM biopsy = dysplastic cells + **hyposegmented neutrophils (pseudopelgerhuet)**




Issue with cell maturation, neutrophils get stuck and do not fully segment

# ABNORMAL MARROW

## Myelodysplastic Syndrome (MDS)

### Features

- Often asymptomatic early on with *mild macrocytic anemia* and then progresses to **pancytopenia**
- Important exposure history – past radiation, toxin, chemotherapy

**Pancytopenia**: when all peripheral blood cells decrease
- RBC (anemia)
- Platelets (thrombocytopenia)
- WBC (neutropenia)

### Treatment

- Transfusion support, EPO
- BM transplant
- Chemotherapy (if high risk of progression to AML – more about this in cancer review)

# REPLACED MARROW

## Myelophthisis

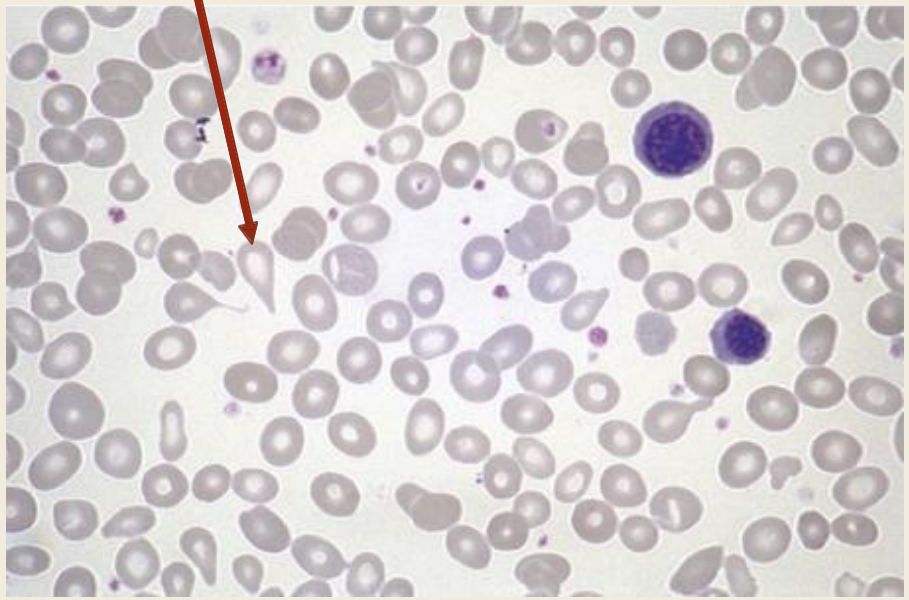



### Causes

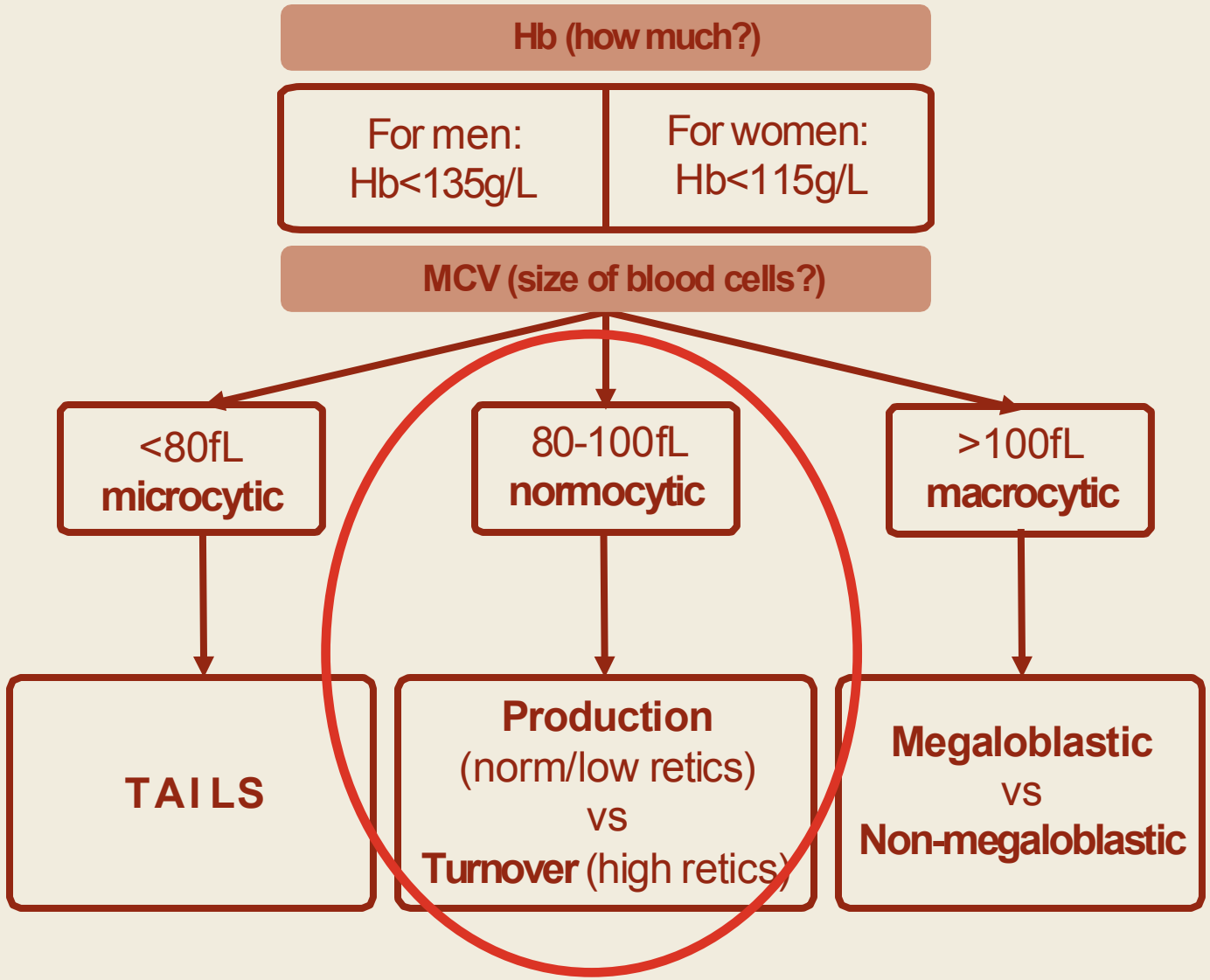
- **Myelofibrosis (scarring)**
- **Hematological Cancer – Lymphoma, Leukemia**
- **Metastatic Solid Cancer**

### Clinical Findings

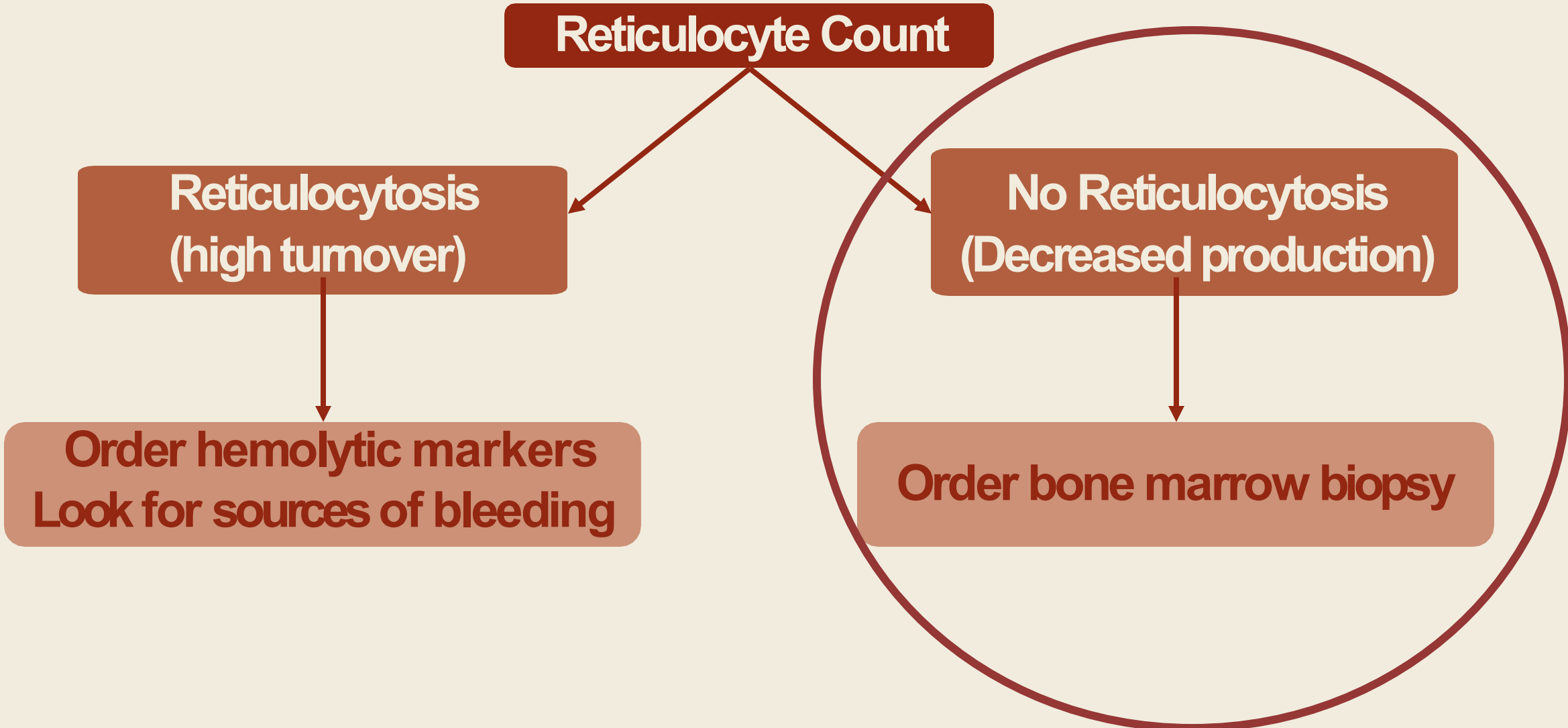
- Typically seen with **leucoerythroblastic picture** – immature WBCs and RBCS (nucleated) in peripheral smear
- **Tear drops on blood film** – cells getting squeezed out of marrow



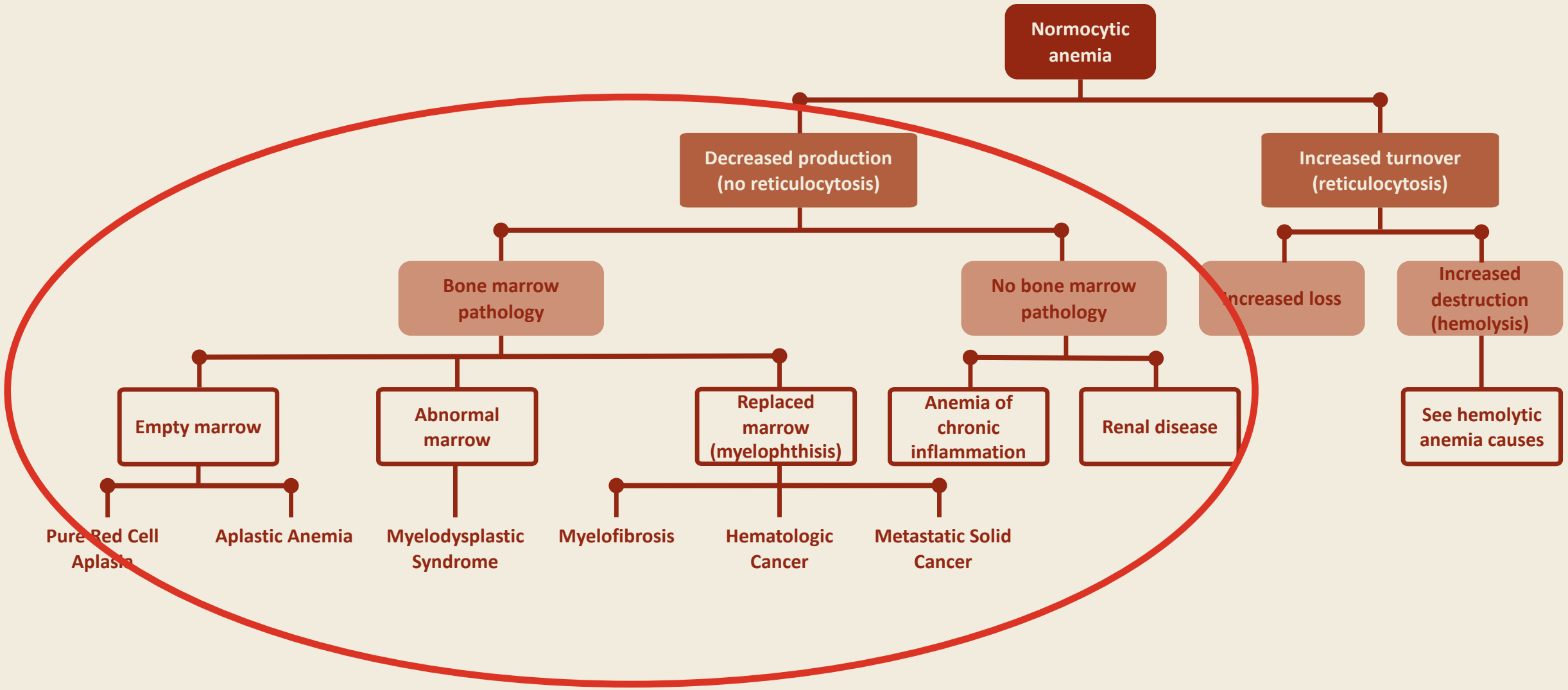
# OVERVIEW OF ANEMIA & CBC



# APPROACH TO NORMOCYTIC ANEMIA



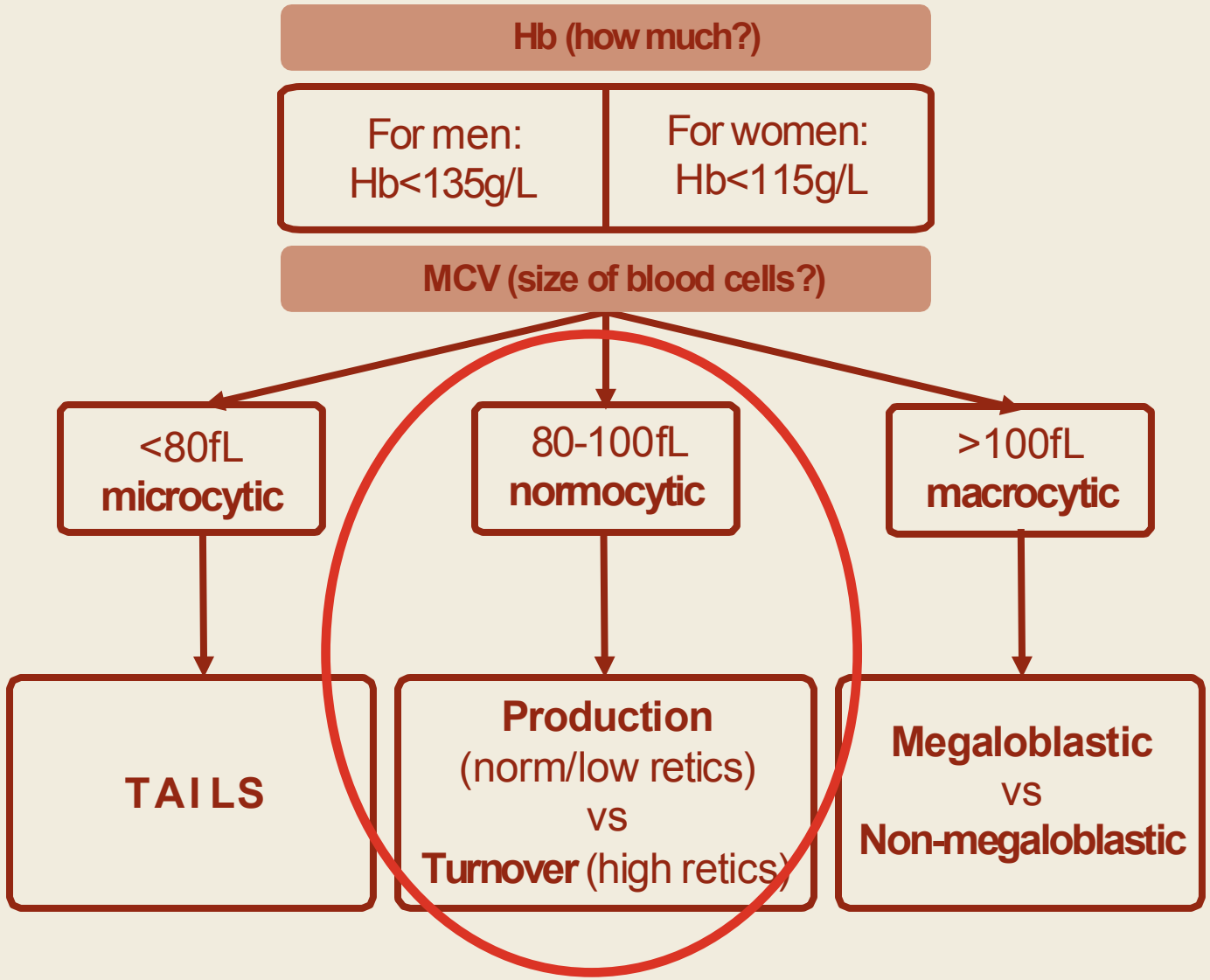
# NORMOCYTIC ANEMIA - REVIEW



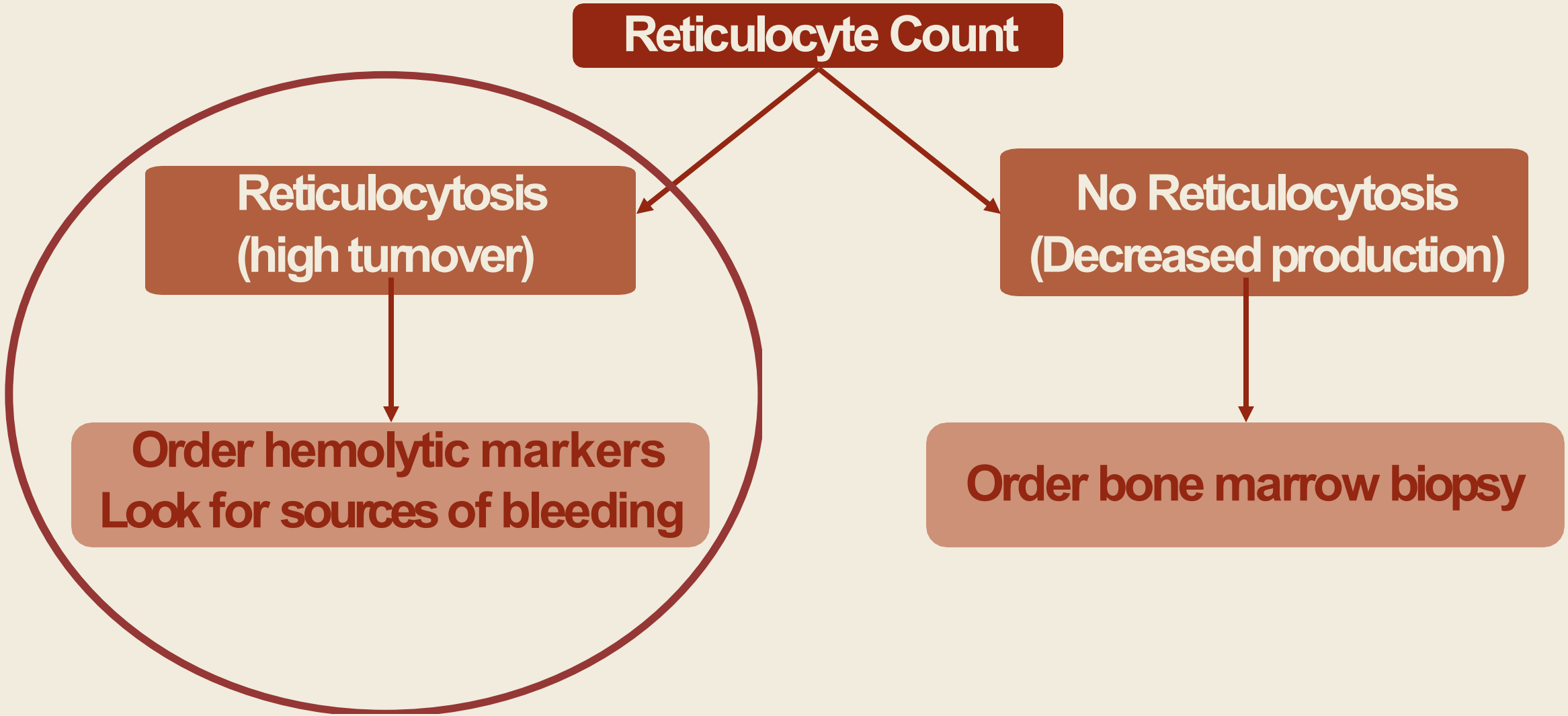
# HEMOLYTIC ANEMIA

Hereditary
Acquired

# OVERVIEW OF ANEMIA & CBC



# APPROACH TO NORMOCYTIC ANEMIA



# HEMOLYTIC ANEMIA

## Definition

- Lysis or breakdown of RBCs
- Releases heme, globin and iron

## Hemolytic Markers

- **LDH** – HIGH
- **Bilirubin** (**total** = direct + indirect) – HIGH
- **Bilirubin** (**indirect**) – HIGH
- **Haptoglobin** – LOW

Indirect increases bc when RBC break apart, heme is converted into indirect bilirubin and liver cannot process it quickly enough. Total increase bc indirect is increased.

## Most Important Test

- **Blood Film**

# HEMOLYTIC ANEMIA

## Hereditary Causes

### Membrane Defects

- Hereditary Spherocytosis
- Hereditary Elliptocytosis

### Enzyme Defects

- G6PD Deficiency

### Hemoglobin Defects

- Thalassemia
- Sickle Cell Disease



# HEMOLYTIC ANEMIA

## Acquired Causes

### Immune

- Infections
- Alloantibodies
- Autoantibodies

### Non-immune

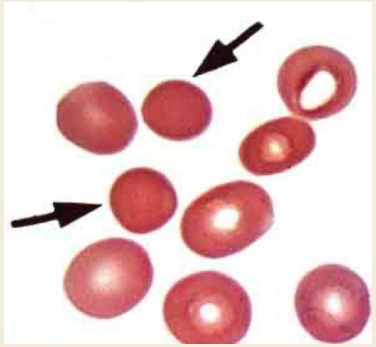
- Mechanical damage
- Physiochemical damage
- Membrane abnormalities

# HEMOLYTIC ANEMIA

## Spherocytes on Blood Film

### What could it be? – 2 options

- Hereditary Spherocytosis
- Autoimmune hemolytic anemia (AIHA)
  - Cold AIHA
  - Warm AIHA



### What are you going to order?

- **Direct Antibody Test (DAT)**
  - Positive – Cold/Warm AIHA
  - Negative – Hereditary Spherocytosis

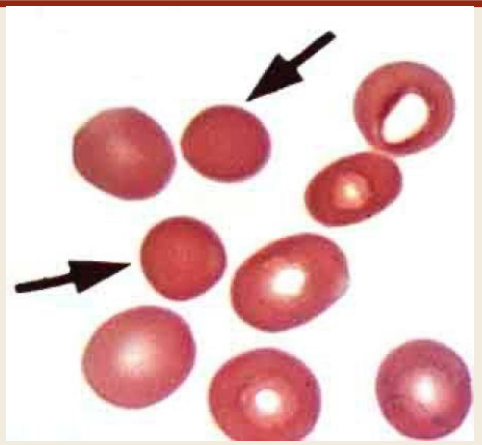


# HEMOLYTIC ANEMIA

## Hereditary Spherocytosis

### Mechanism

- Deficiency/defects in RBC membrane structural proteins → membrane fragments are lost
- Decreased membrane to volume ratio causes RBCs to become spherical instead of biconcave
- Spherical RBCs are more likely to get trapped and cleared by the spleen

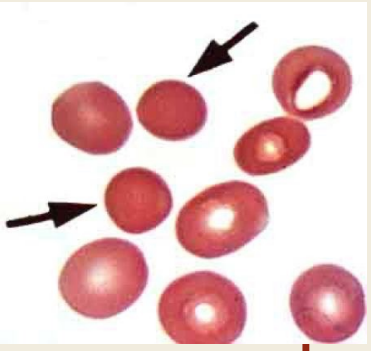


### Management

- **Confirm with flow cytometry for RBC membrane proteins** (looking for Band 3 protein, ankyrin and spectrin defects)
- Supportive – folate supplements
- Splenectomy in severe cases

# HEMOLYTIC ANEMIA

## Autoimmune Hemolytic Anemia (AIHA)



### Mechanism

- Antibodies are made to surface antigens on the body's own RBCs
- RBC membrane is removed by phagocytes
- Decreased membrane to volume ratio causes RBCs to become spherical instead of biconcave = **spherocytes**

### Warms vs. Cold AIHA

- **Warm** – IgG antibodies bind to RBC surface antigens at 37degC
- **Cold** – IgM antibodies bind to RBC surface antigens at 4-30degC, IgM fixes C3b, at 37degC IgM is released but C3b remains

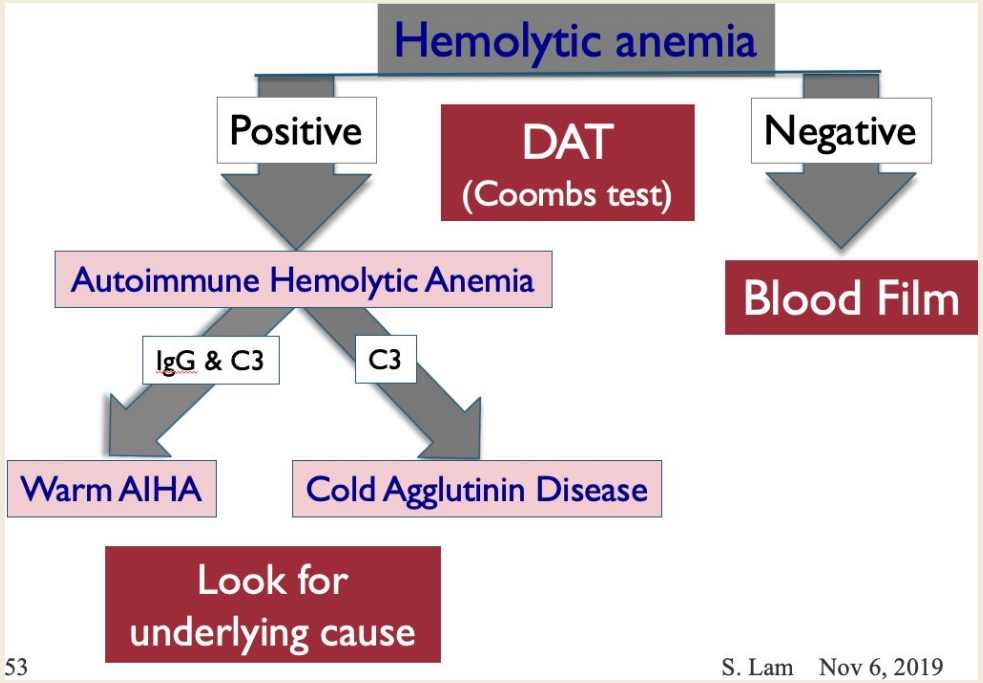
Warm → get grilling
Cold → get mittens

# HEMOLYTIC ANEMIA

## Autoimmune Hemolytic Anemia (AIHA)

### Diagnosis – DAT Positive

- Positive DAT shows agglutination
  - **Cold AIHA** – positive test with antibody to C3b alone
  - **Warm AIHA** – positive test only when antibody to IgG is also added in addition to C3



# HEMOLYTIC ANEMIA

## Autoimmune Hemolytic Anemia (AIHA) – Warm AIHA

### Primary Causes

- Idiopathic (most common cause – 60%)

### Secondary Causes

- The L's
  - Systemic **L**upus Erythematosus
  - Non-Hodgkin **L**ymphoma
  - Chronic Lymphocytic **L**eukemia
- Medications
  - Penicillin
  - Quinine
  - Alpha methyldopa

### Treatment

- First Line – steroids
- Second Line – splenectomy
- Third Line – other immunosuppressive agents



# HEMOLYTIC ANEMIA

## Autoimmune Hemolytic Anemia (AIHA) – Cold AIHA

### Causes

- Infections
  - Mycoplasma pneumoniae
  - Infectious mononucleosis
- B cell lymphoid malignancies

### Treatment

- Treat the underlying cause
- **Steroids, splenectomy and immunosuppressants are not effective**

# HEMOLYTIC ANEMIA

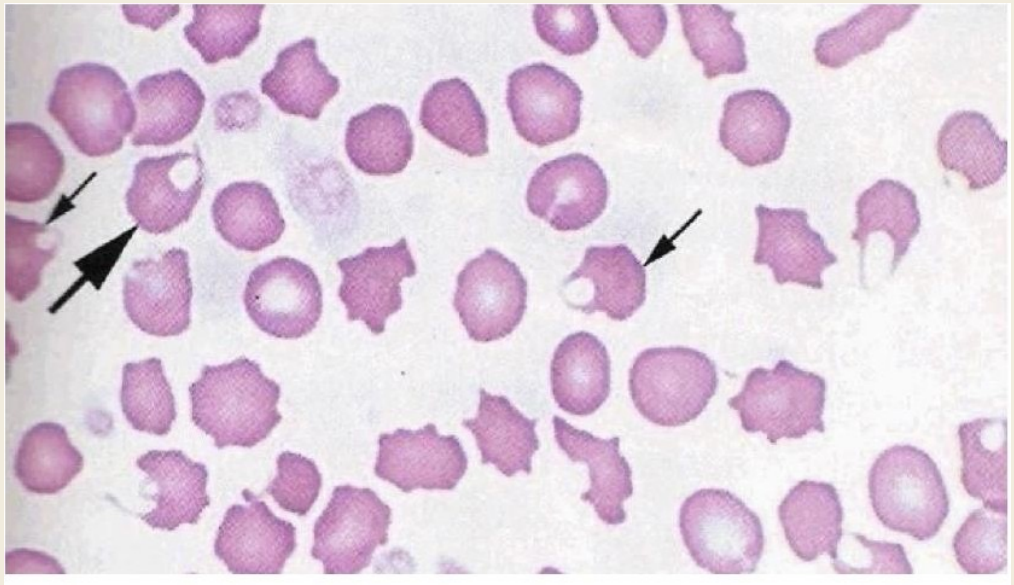
## Bite Cells on Blood Film

### What could it be? – 1 option

- G6PD Deficiency

### What are you going to order?

- G6PD Level

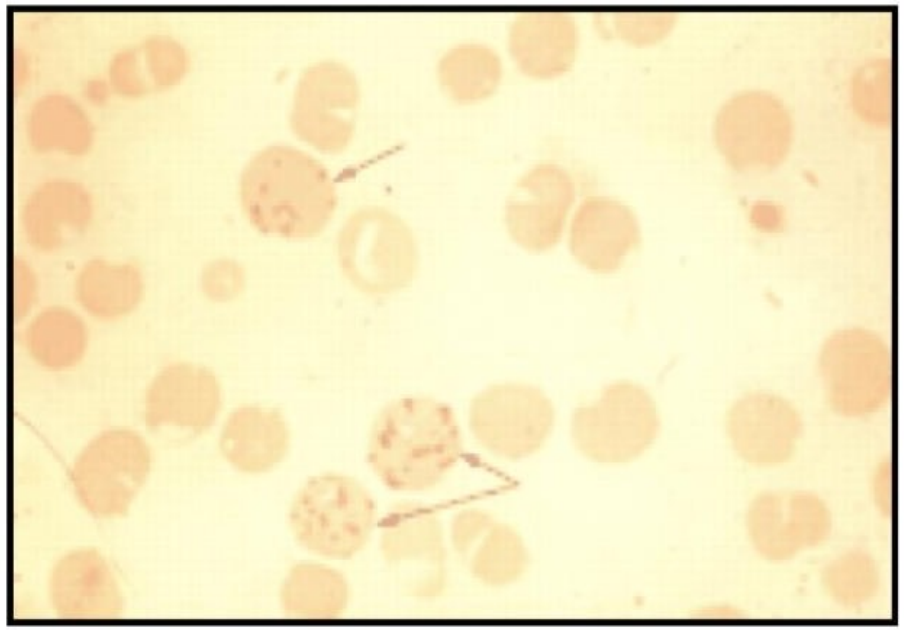


# HEMOLYTIC ANEMIA

## G6PD Deficiency

### Mechanism

- GP6D deficiency results in impaired GSH production
- GSH normally inactivates harmful endo/exogenous oxidants
- Without GSH, oxidative injury causes hemolysis



Heinz Bodies. Supravital staining with Methylene blue.

# HEMOLYTIC ANEMIA

## G6PD Deficiency

### Clinical Features

- Hemolysis is precipitated environmental factors:
  - Infections - cause increase in ROS
  - Drugs

### Diagnosis

- **G6PD Level**

### Treatment

- Avoid precipitants – **fava beans**
- Supportive - folate supplements
- Splenectomy in severe cases





# HEMOLYTIC ANEMIA

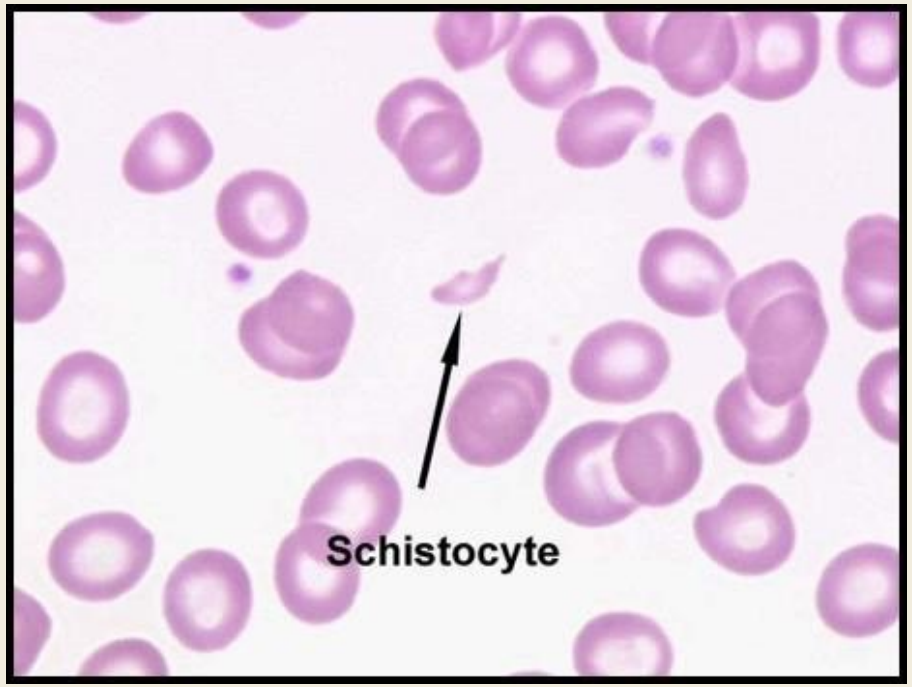
## Schistocytes on Blood Film

### What could it be?

- Mechanical heart valve
- Microangiopathic hemolytic anemia – DIC, TTP, HUS
- Repetitive mechanical trauma – marathon running, bongo drumming
- Endothelial cell injury

### What are you going to order?

- INR/PTT/Fibrinogen (more on this later)
- Renal function



# HEMOLYTIC ANEMIA

## Sickle Cells on Blood Film

### What could it be? – 1 option

- Sickle Cell Disease

### What are you going to order?

- **Hemoglobin Electrophoresis**



# HEMOLYTIC ANEMIA

## Sickle Cell Disease (SCD)

### Pathophysiology

- Autosomal recessive inherited disorders of the $\beta$ globulin gene
- Recall there are 2 alleles of the $\beta$ globulin gene
  - Individuals with sickle cell disease/trait have one copy of HbS = glutamate to valine mutation in the $\beta$ globulin gene
  - The type of sickle cell disease is determined by the other copy of the $\beta$ globulin gene
- **HbS polymerizes in low O2 → RBCs take on sickle shape → get stuck in blood vessels leading to complications**

# HEMOLYTIC ANEMIA

## Sickle Cell Disease (SCD)

| Sickle Cell Type | β gene 1 | β gene 2 |
|---|---|---|
| Carrier (Sickle Cell Trait) | HbS | Normal β gene |
| Sickle Cell SS | HbS | HbS |
| Sickle Cell SC | HbS | HbC |
| Sickle Cell $S\beta^{+}$thal | HbS | β Mutation causing low production |
| Sickle Cell $S\beta^{0}$thal | HbS | β Mutation causing no production |

**All forms of Sickle Cell Disease**

# HEMOLYTIC ANEMIA

## Sickle Cell Disease (SCD)

### Complications

- Splenic atrophy
- Veno-occlusive crisis (VOC)
- Acute chest syndrome (life-threatening)

### Treatment

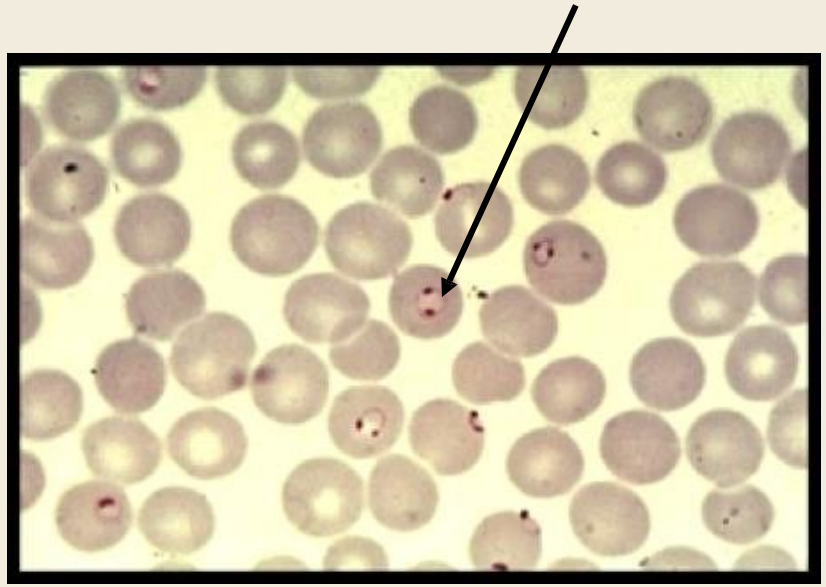
- **Hydroxyurea** (↑HbF which ≠ sickle)
- **Penicillin (from newborn to age 5)**

# HEMOLYTIC ANEMIA

## Infectious Causes of Hemolytic Anemia

### Malaria

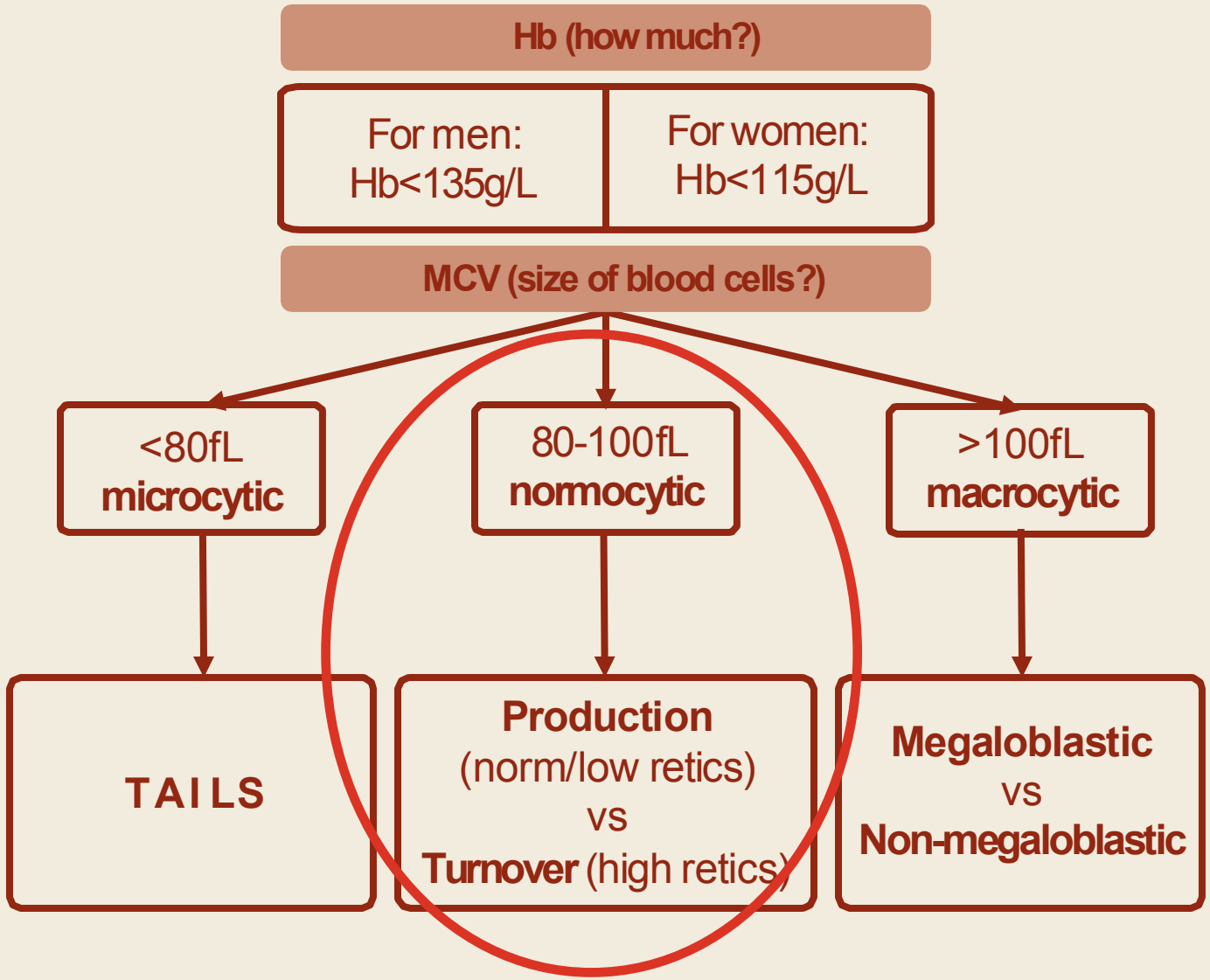
- Merozoites escape by lysing the RBCs and cause hemolytic anemia
- Patient will have fever, chills and shakes
- Hyperplasia of the RES leading to massive splenomegaly
- Ring structures on blood film



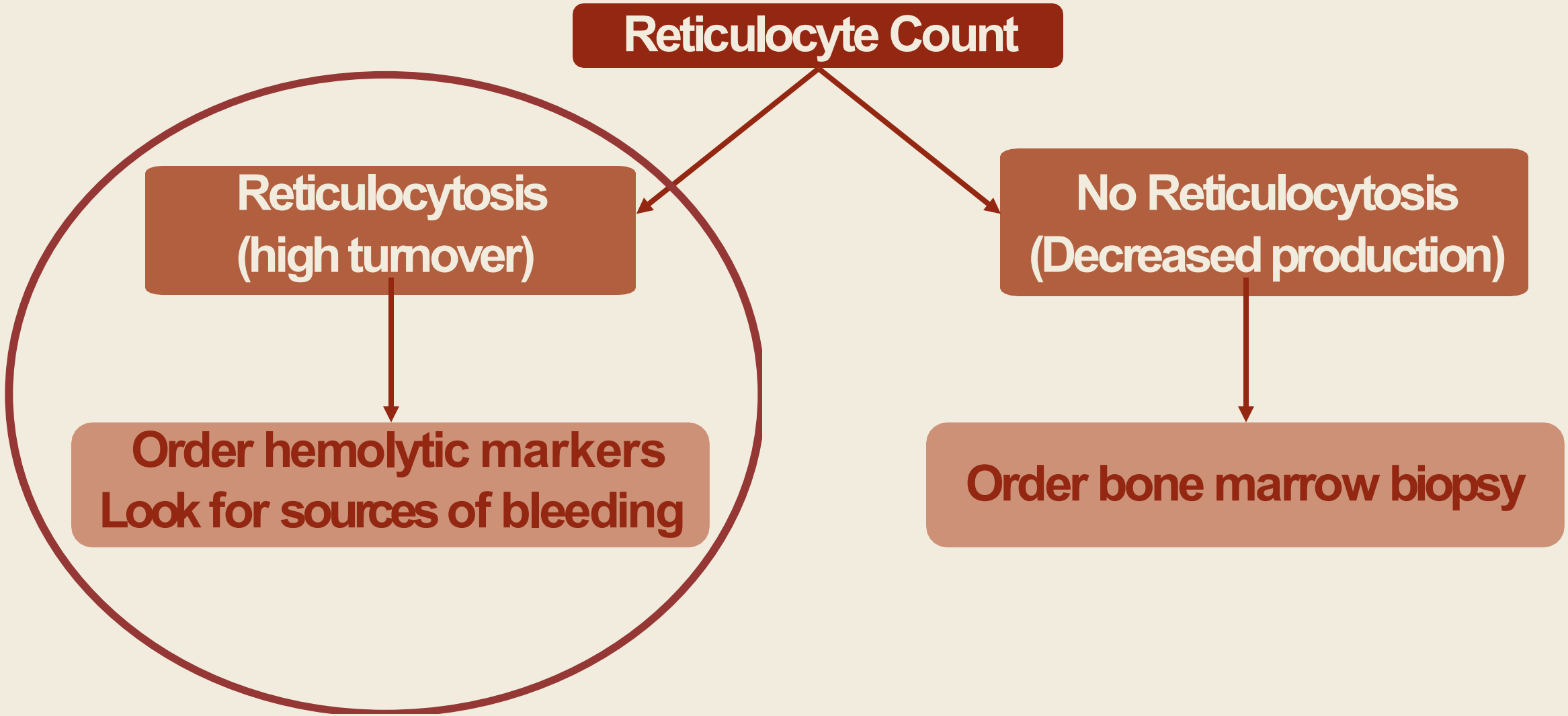
### Clostridial Sepsis

- Infection causes release of enzymes that degrade the phospholipids of the RBC membrane
- Microspherocytes on blood film

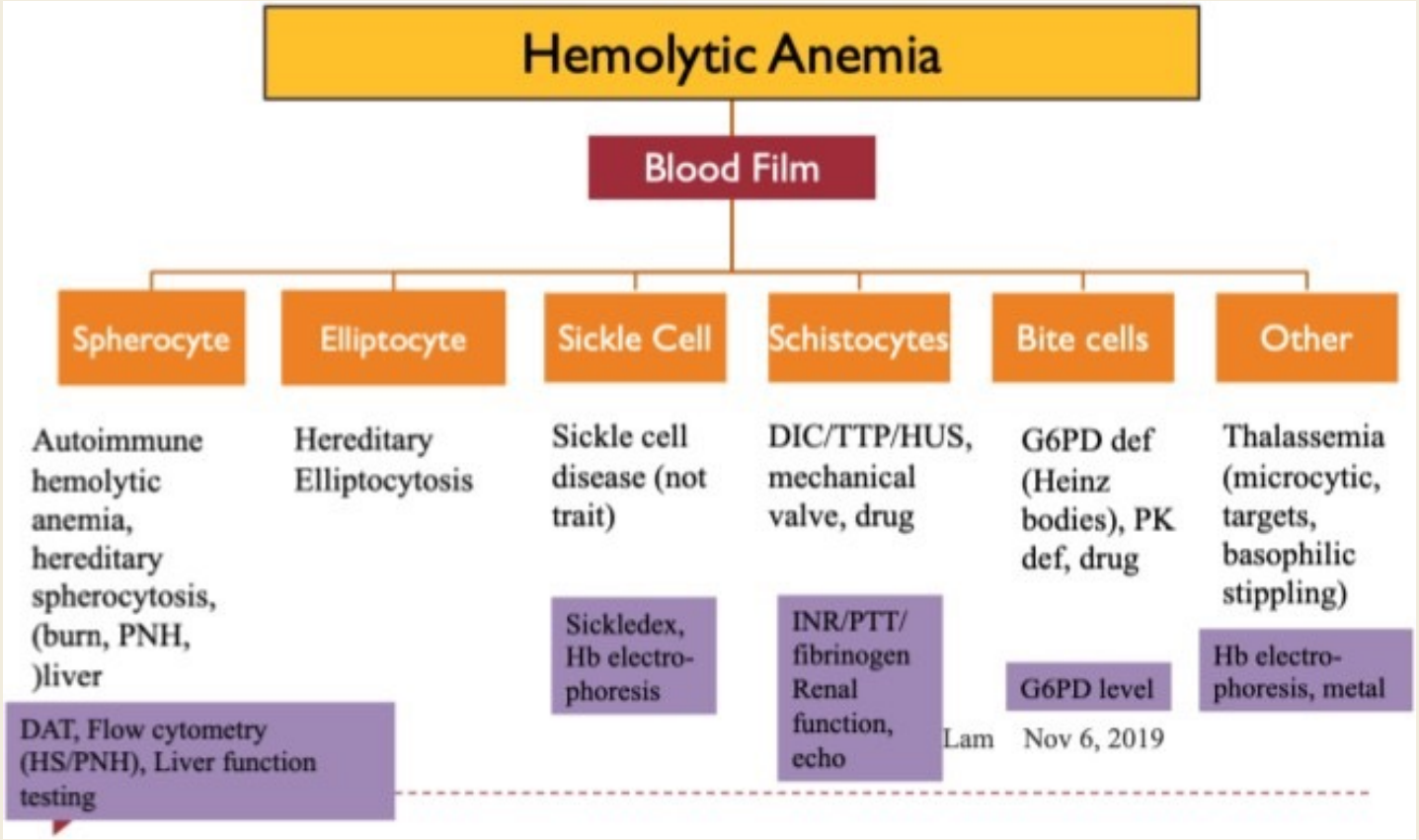
# OVERVIEW OF ANEMIA & CBC



# APPROACH TO NORMOCYTIC ANEMIA



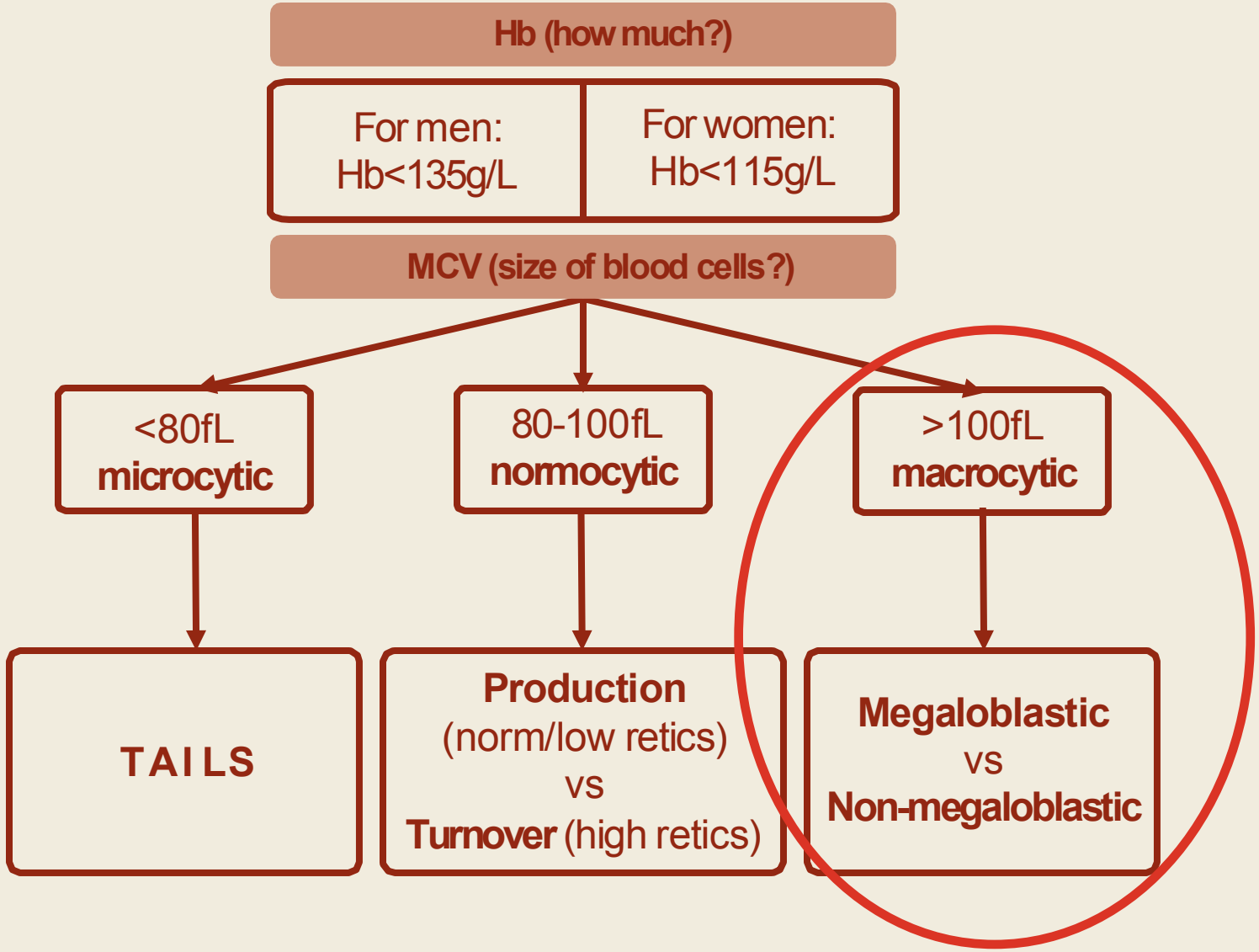
# HEMOLYTIC ANEMIA - REVIEW



# MACROCYTIC ANEMIA

Megaloblastic (drugs, deficiencies, MDS)
Non-megaloblastic (very heterogenous group)

# OVERVIEW OF ANEMIA & CBC



# MACROCYTIC ANEMIA

## Definition

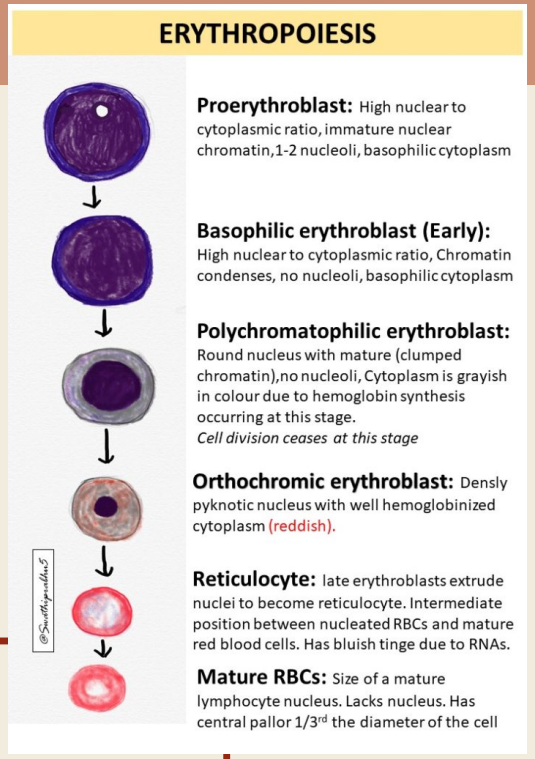
- MCV >100fL

## Two Main Groups

- **Megaloblastic**
  - Macrocytosis due to large immature RBCs in the peripheral blood
- **Non-Megaloblastic**
  - Macrocytosis due other causes (many different etiologies, history important)

## Important Tests

- Vitamin B12, folate, blood film, liver function testing, thyroid level, reticulocyte count



# MEGALOBLASTIC ANEMIA

## Mechanism

- Ineffective DNA synthesis → **nuclear-cytoplasmic dyssynchrony**

Not enough DNA, too much cytoplasm

## Causes

- Deficiencies
  - **Vitamin B12 Deficiency**
  - **Folate Deficiency**
  - Congenital deficiencies in Vitamin B12 or folate metabolism
- Drugs
  - Folate antagonists – methotrexate, trimethoprim
  - Antimetabolite chemotherapy drugs causing defective/altered DNA synthesis

## Treatment

- **B12 (Cobalamin IM) / Folate Supplementation**

# MEGALOBLASTIC ANEMIA

## Vitamin B12 Deficiency Causes

### Nutritional

- Vegan diet

### Decreased Absorption

- Vitamin B12 is absorbed in the **terminal ileum and requires IF** which is released by parietal cells in the stomach
- **Gastric Causes:**
  - Pernicious anemia – antibody to intrinsic factor (needed for absorption)
  - Congenital lack or abnormal intrinsic factor
  - Total or partial gastrectomy
- **Intestinal Causes:**
  - Ileal resection
  - Crohn's Disease

# MEGALOBLASTIC ANEMIA

## Folate Deficiency Causes

### Nutritional

- **Old age**, poverty, goat's milk anemia

### Excess Utilization

- Pregnancy, lactation, prematurity
- Hemolytic anemia

### Decreased Absorption

- **Extensive jejunal resection**

### Others

- Liver Disease
- Alcoholism (folate is more affected by alcoholism than B12)
- Drugs

# MEGALOBLASTIC ANEMIA

## Comparing these deficiencies (distinctive features)

### Vitamin B12 Deficiency

- Can take years (but more common)
- Increased methylmalonate AND homocysteine
- **Think vegan diet** (no redmeat)
- **Ileum issues**
- **Peripheral neuropathy (B12 only)**



### Folate Deficiency

- Can take months
- Increased homocysteine ONLY
- **Think old age, inadequate diet**
- **Jejunum issues**
- More affected by alcohol

**Heme Corrects in 48h... but neuropathy takes a while

# MEGALOBLASTIC ANEMIA

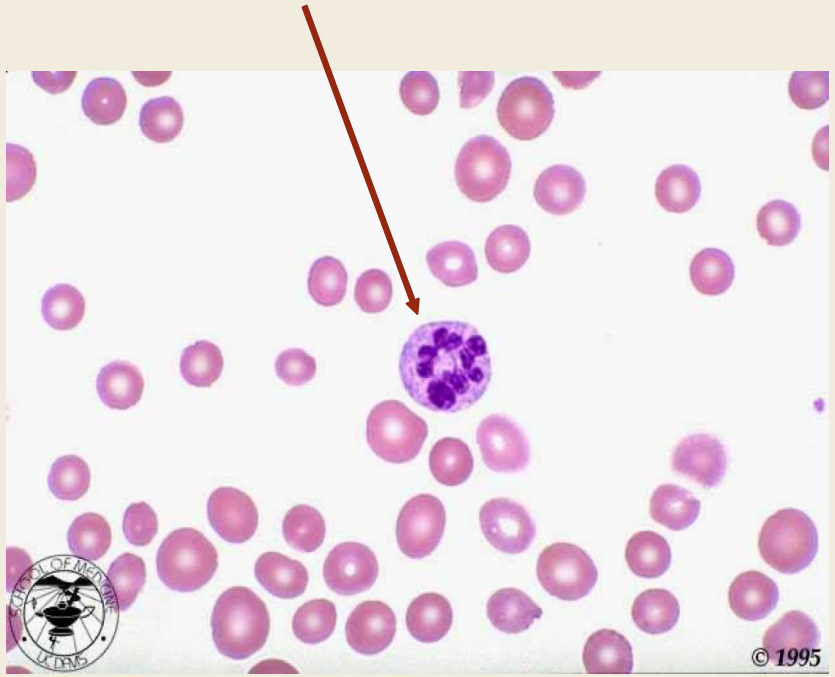
## CBC

- Pancytopenia

## Blood Film

- Oval macrocytes with less central pallor
- **Hypersegmented neutrophils**

- Recall Bonus: who had hyposegmented?

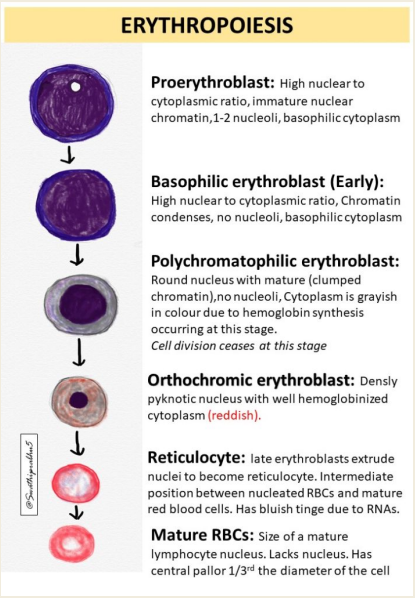


# NON-MEGALOBLASTIC ANEMIA

## Causes

- **Increased RBC membrane**
  - Liver Disease
  - Alcoholism
- **Increased RBC turnover**
  - Reticulocytosis

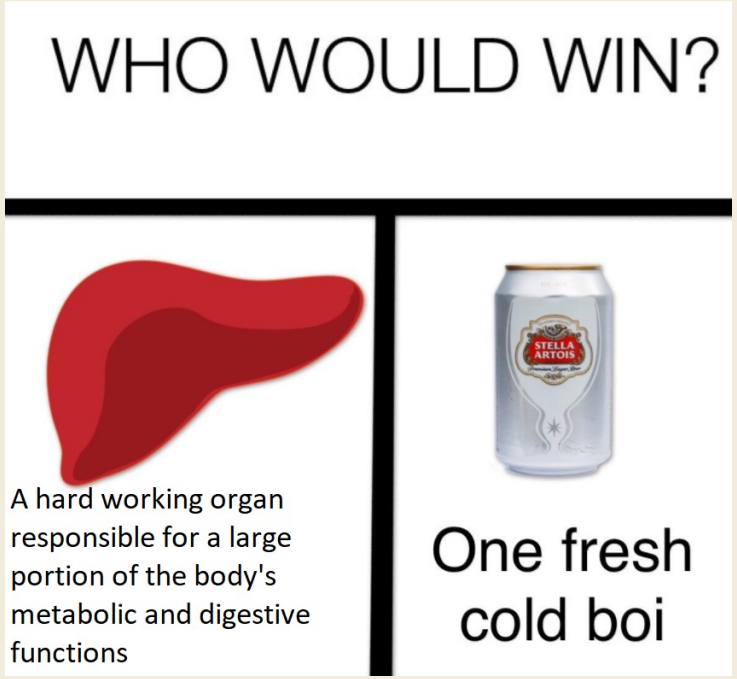
    Artifact high reticulocytes increasing MCV
- **Pseudomacrocytosis – RBC Clumping**
  - Multiple myeloma
  - Cold Agglutinin Disease
- **Myelodysplastic Syndrome (MDS)**
- **Hypothyrodism (just check TSH)**



# NON-MEGALOBLASTIC ANEMIA

## Increased RBC Membrane

- Occurs in **liver disease and alcoholism**
- Excess lipids = fatter RBCs
- Target cells are formed where the excess lipids are concentrated in the center



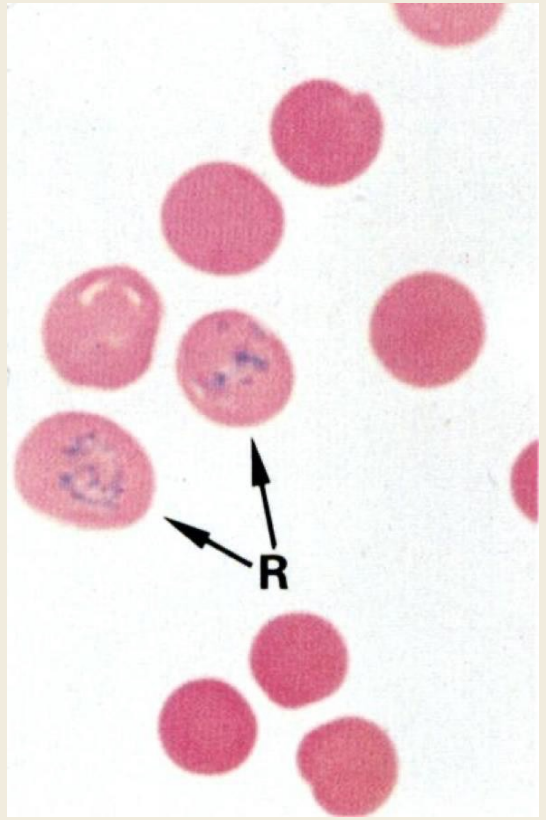

## Management

- Treat liver disease
- Alcohol cessation, replace associated deficiency (Thiamine aka B1)

# NON-MEGALOBLASTIC ANEMIA

## Increased RBC Turnover - Reticulocytosis

- Reticulocytes are bigger than normal RBCs –so if you have a lot of reticulocytes the MCV can look bigger
- Blood film will show reticulocytes – polychromasia

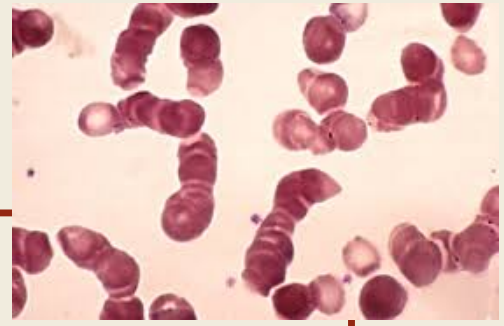



## Management

- Identify cause of **increased RBC turnover** – look for sources of bleeding, indicators of hemolysis

# NON-MEGALOBLASTIC ANEMIA

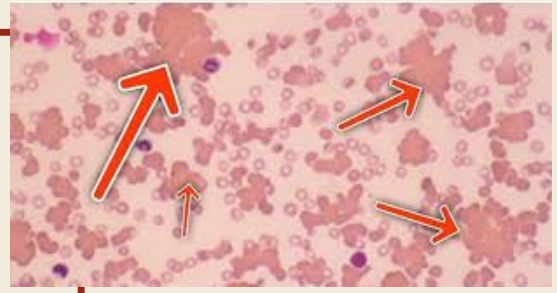
## Pseudomacrocytosis – RBC Clumping



### Multiple Myeloma

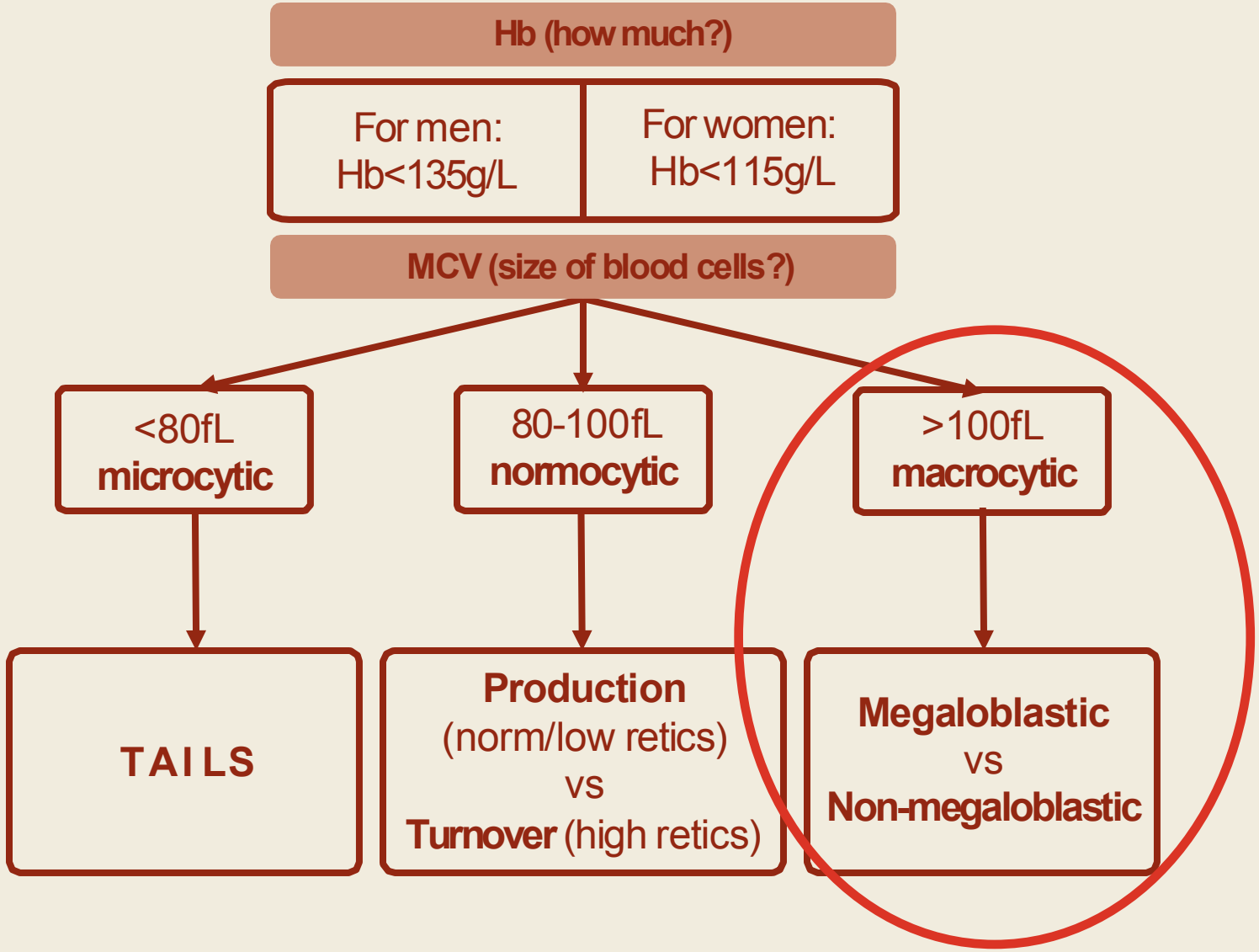
- Non-specific agglutination
- Increased plasma proteins non-specifically stick to the surface of the RBCs
- Causes cells to join together in **rows**
- Rows of RBCs are interpreted as single large RBCs on the CBC

### Cold Agglutinin Disease

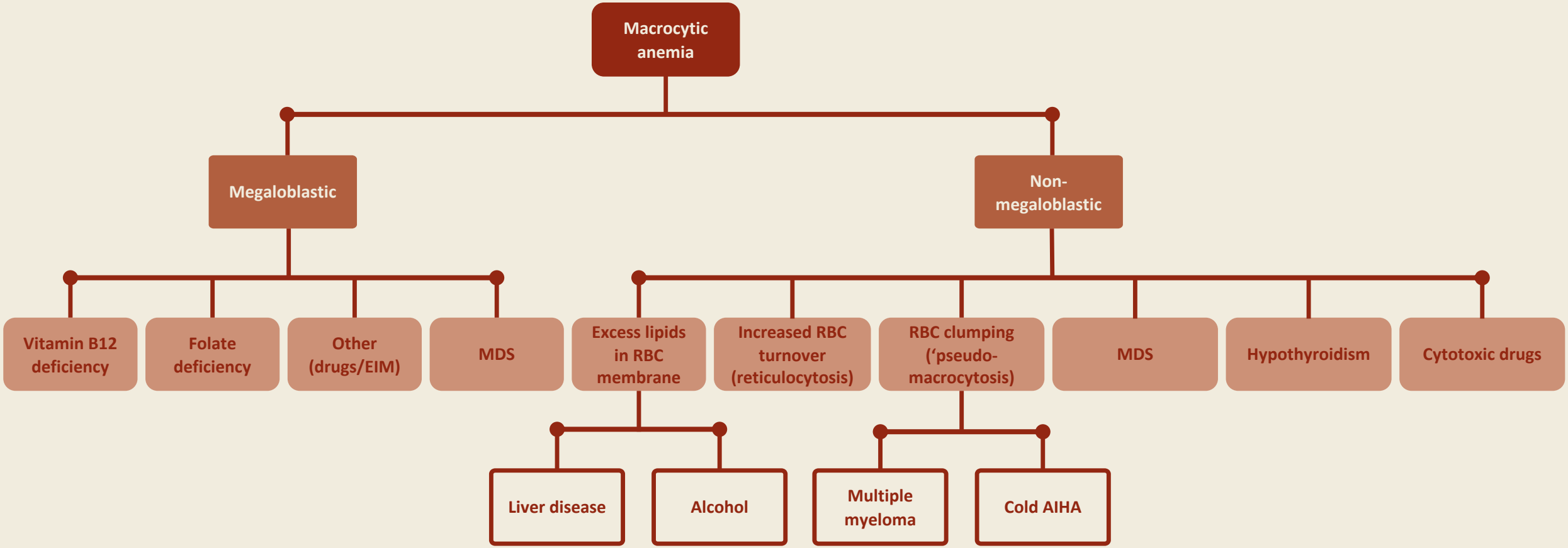


- Specific agglutination
- IgM antibodies (5 binding sites) targeted to RBCs bind to them
- Causes cells to join together in **clumps**
- Clumps are RBCs are interpreted as single large RBCs on the CBC

# OVERVIEW OF ANEMIA & CBC



# MACROCYTIC ANEMIA - REVIEW



# GENERAL ADVICE

- Read the question well (but don’t overthink it)
- ~~Keep track of your KFQs~~
- Hb → MCV → branch-specific paths
- Defining features – what sets the dx apart?
- Overlapping features – what can it be confused with?
- Options vs management
- Pick and choose your battles (repetition and big clinical picture)
- Maps

# Week 9: Anemia

**Hemoglobin:** Men <135g/L Women <115 g/L

## Anemia

### "TAILS" MCV<80fL Microcytic

**Decreased globin**

**T: thalessemia**

**alpha**
- 2 genes, 4 alleles total
- S/E Asian, African population at risk
- 1/4 silent carrier
- 2/4 alpha trait
- 3/4 HbH disease
- 4/4 lethal (hydrops fetalis)

**beta**
- 1 gene, 2 alleles total
- Mediterranean population at risk
- 1/2 minor/trait
- 1/2 intermediate
- 2/2 major (can't make HbA at all)

**Heme**

**A: anemia of chronic inflammation**
- Can occur with other inflammatory disorders
- High ferritin

**I: iron deficiency anemia**
- Underlying cause important
- Physical: hair, nails, tongue
- High RDW, plt
- Low RBC, ferritin

**L: lead poisoning**
**S: sideroblastic anemia**
- Look for the rings on film
- B6 deficiency, lead, history important

### MCV 80-100fL Normocytic

Norm/low reticulocytes

**Production**

**No BM pathology**
- Renal failure (no EPO)
- **Chronic inflammation issues**

**Yes BM pathology**

**Empty BM**

**Pure RBC aplasia**
- No RBC
- Polychromasia and erythroblasts on film

(polychromasia) (erythroblasts)

**Aplastic anemia**
- No RBC, WBC, plts

(fat cells on film)

**Abnormal BM**

**MDS**
- Poor hematopoiesis

**Replaced BM**
- Myelofibrosis (teardrops)
- Myelophthisis (teardrops)
- TB
- Blood cancers (leukoerythroblastics)

High reticulocytes

**Turnover**

**Loss**
- GI
- Non-GI

**Destruction (hemolysis)**

**HI:** LDH, indirect bili, reticulocytes
**LO:** haploglobin

**Hereditary**

**Membrane Defects**
- Hereditary Spherocytosis
- Hereditary Elliptocytosis

**Enzyme Defects**
- G6PD Deficiency

**Hemoglobin Defects**
- Thalassemia
- Sickle Cell Disease

**More on sickle cell**
Screening:
- Sickledex sticky cells
- HPLC (better)

Can do punnett square with gametes:
HbA=normal
HbS=sickle cell
Outcomes:
HbA+HbA=normal
HbA+HbS=not sick, trait/carrier
HbS+HbS=sick

**Acquired**

**Immune**
- Infections
- Alloantibodies
- Autoantibodies

**Non-Immune**
- Mechanical Damage
- Physiochemical Damage
- Membrane Abnormalities

### MCV>97fL Macrocytic

**Megaloblastic**

**Drugs**

**Deficiencies**

**B12**
- Methylmalonate
- homocysteine

**Folate**
- Homocysteine

**MDS**

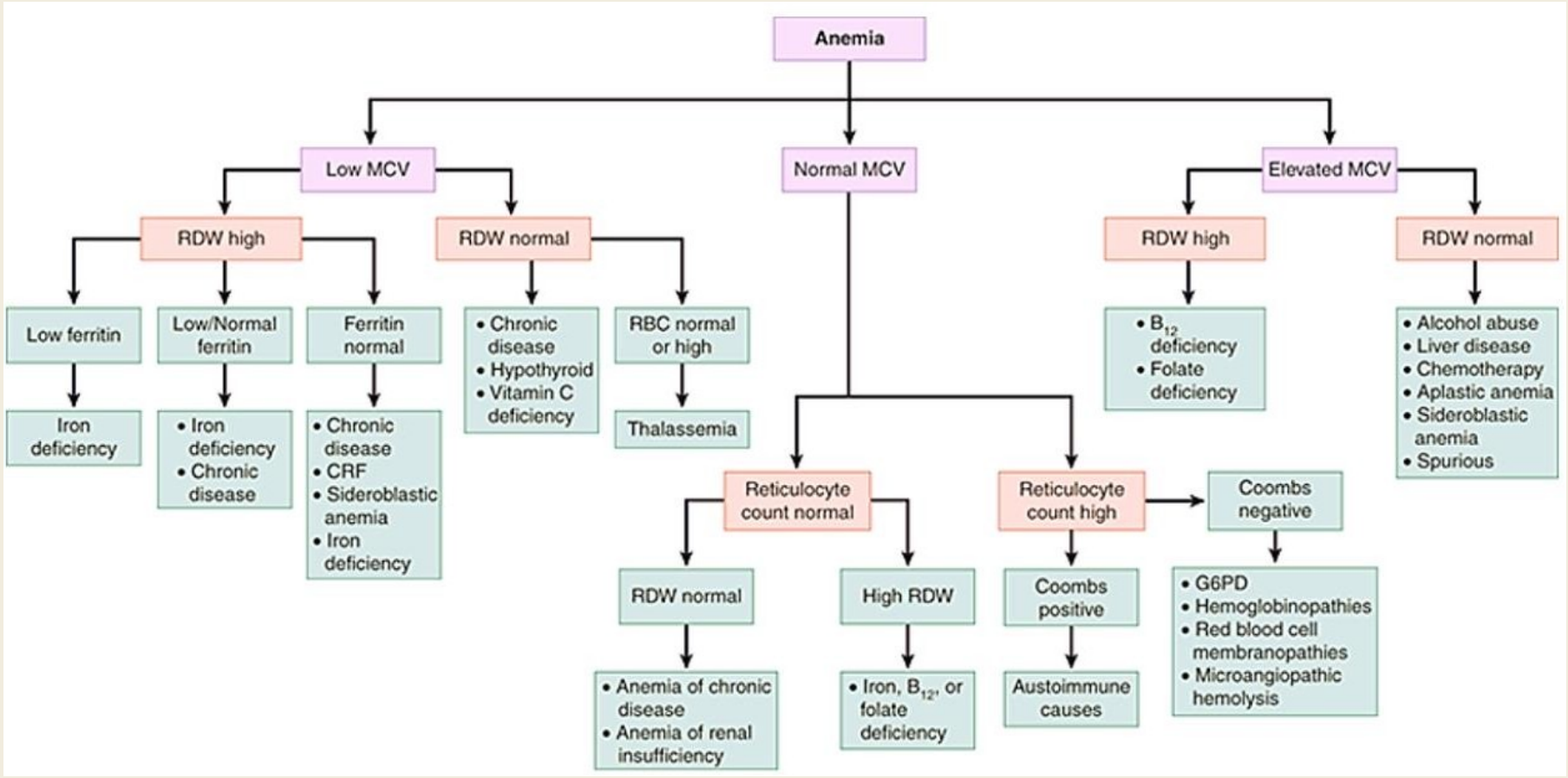
**Non-megaloblastic**

**Varies reasons**
- Drugs
- Alcohol/liver disease
- Hypothyroidism
- High reticulocytes
- Pseudomacrocytosis
  - Multiple myeloma
  - Cold agglutin

Blue – topic shows up in other branches
Red – hemolytic

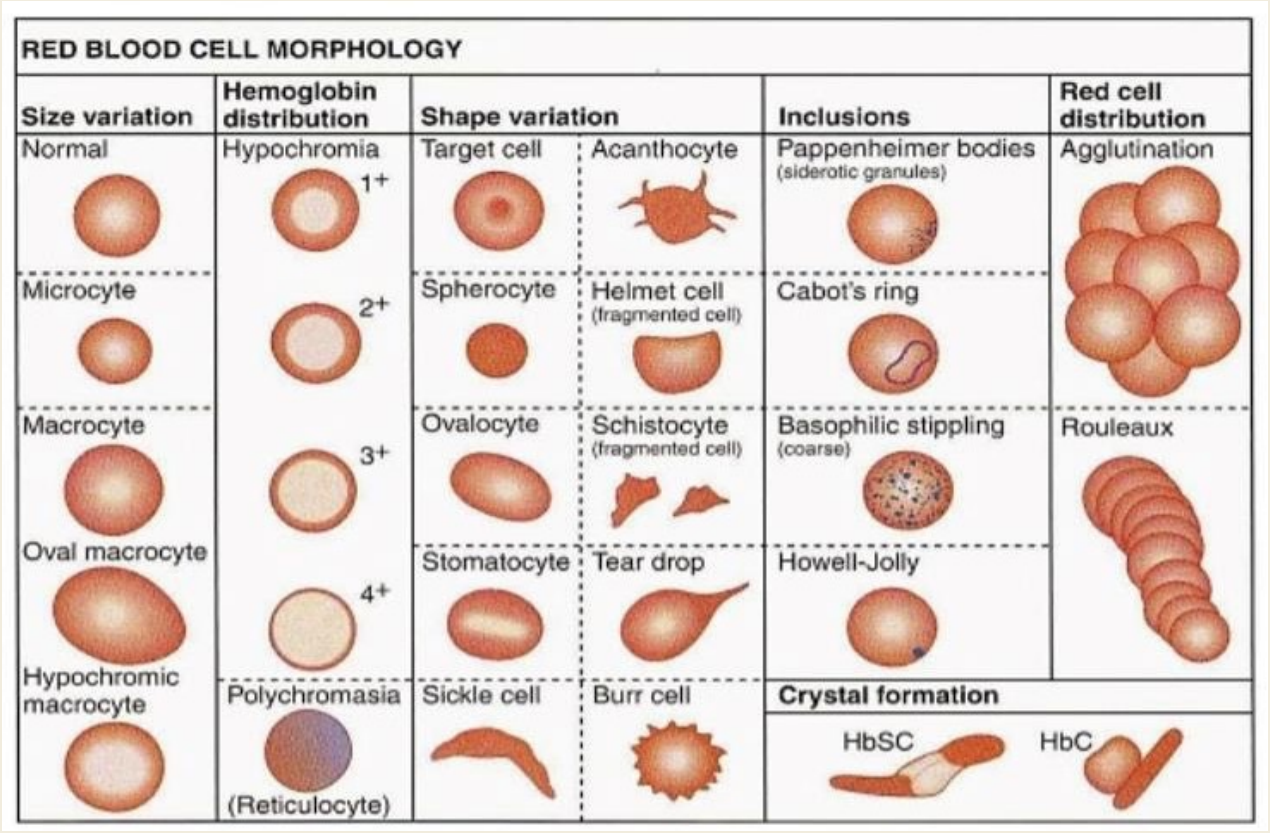
# OTHER RESOURCES

## Maps



# OTHER RESOURCES

## Cell Morphology



# HEMATOLOGY REVIEW WEEK 10: HEMOSTASIS

November 21, 2023

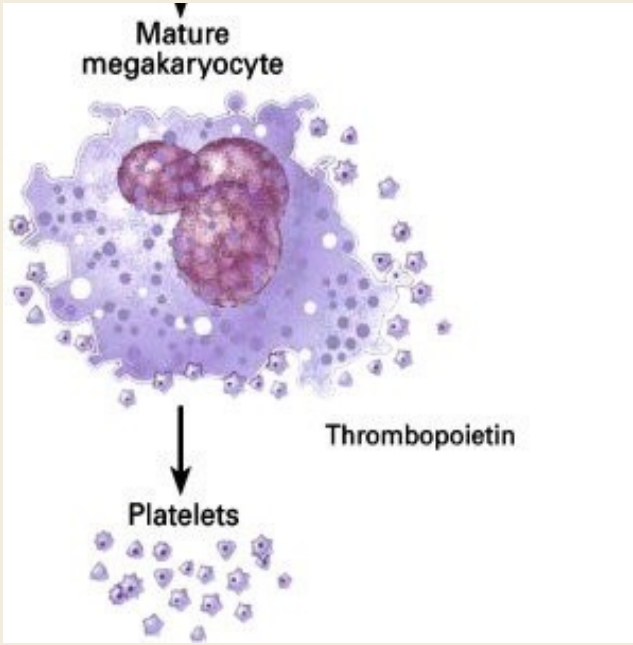
Schulich Reviews

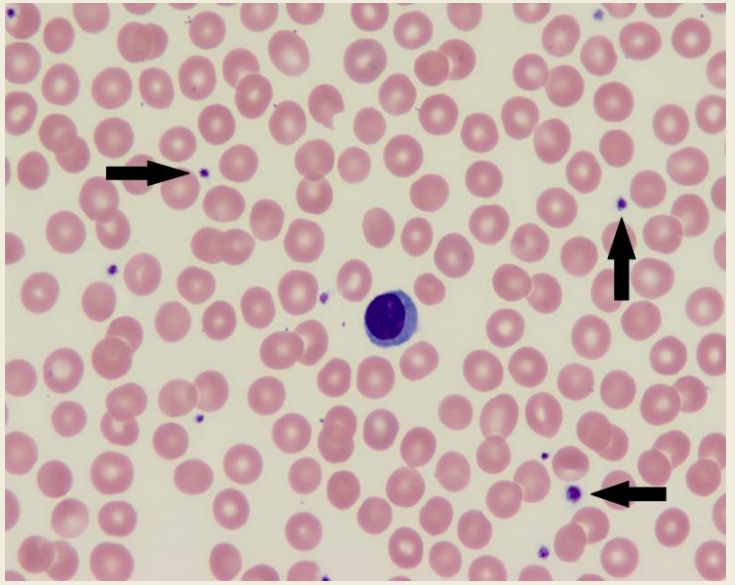
# PLATELETS

## Overview

# PLATELETS OVERVIEW

- Cute
  - 1/12 size of RBCs
- Short life span
  - ~10 days
- Normal count: 150-400 x 109/L
- No nucleus
  - Derived from megakaryocyte cytoplasm



# HEMOSTASIS

Primary and secondary hemostasis
Regulation

# HEMOSTASIS

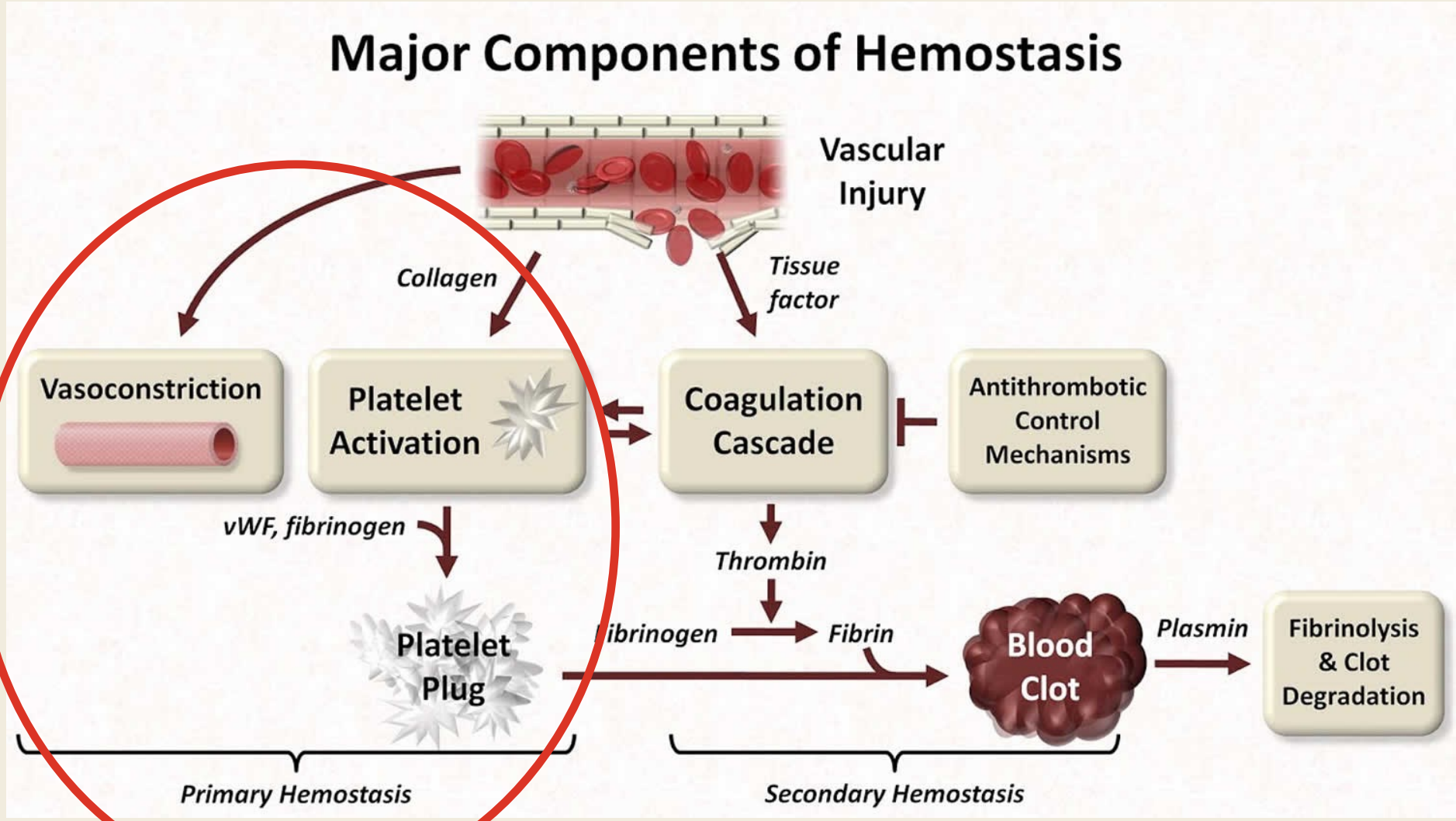
## Definition

- The stopping of a flow of blood; to keep blood within a damaged vessel
- The opposite of hemostasis is hemorrhage

## Two phases:

- **Primary hemostasis**: formation of platelet plug
- **Secondary hemostasis**: make the platelet plug stronger (clot formation)

# HEMOSTASIS


Major Components of Hemostasis
Vascular Injury
Collagen
Tissue factor
Vasoconstriction
Platelet Activation
Coagulation Cascade
Antithrombotic Control Mechanisms
vWF, fibrinogen
Thrombin
Platelet Plug
Fibrinogen
Fibrin
Blood Clot
Plasmin
Fibrinolysis & Clot Degradation
Primary Hemostasis
Secondary Hemostasis

# PRIMARY HEMOSTASIS



1. **Vasoconstriction**
   - Mediated by endothelium and Neurogenic reflex

2. **Platelet plug formation (Primary hemostasis)**
   - a) Adhesion
   - b) Activation
     - Contraction
     - Secretion
   - c) Aggregation

# PRIMARY HEMOSTASIS

## Adhesion

### a) adhesion

- "stick" to the site of injury
- **Von Willebrand factor (vWF)** adheres to:
  - Exposed **collagen** under damaged endothelium
  - vWF-collagen complex binds to **GpIb/IX** on platelets which activates them (next step)



# PRIMARY HEMOSTASIS

## Activation

### b) activation

- Activated platelets change **shape** (contraction)
  - Increase surface area for aggregation
  - **Discoid → spheroid**
- Granules release contents
  - ADP, TXA2, and more
  - **GpIIb/IIIa** receptors change conformation and become activated

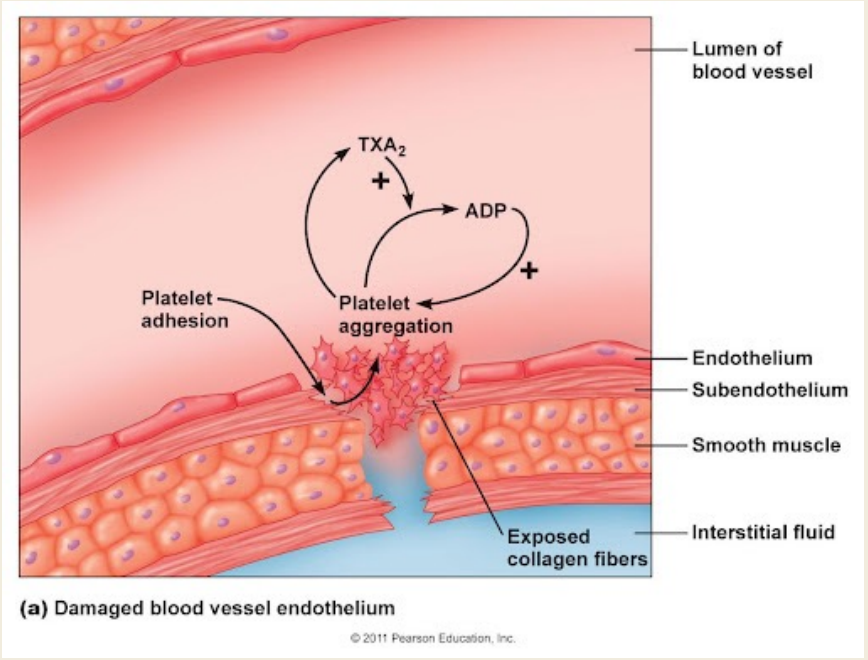


# PRIMARY HEMOSTASIS

## Aggregation

### c) aggregation

- GpIIb/IIIa bind to fibrinogen linking platelets together
- Provide **phospholipid membrane** for assembly of coagulation pathway
- Negatively charged - interacts with positively charged clotting factors



# PRIMARY HEMOSTASIS

## Anti-Platelet Drugs

- E.g. aspirin, clopidogrel
- **Mechanism of action:**
  - Platelet aggregation inhibitors
  - Platelet GpIIa/IIIa inhibitors
  - Therefore they **inhibit primary hemostasis** → bleeding
- *Important to ask about medications!*
  - Even aspirin for headaches, for example



# SECONDARY HEMOSTASIS

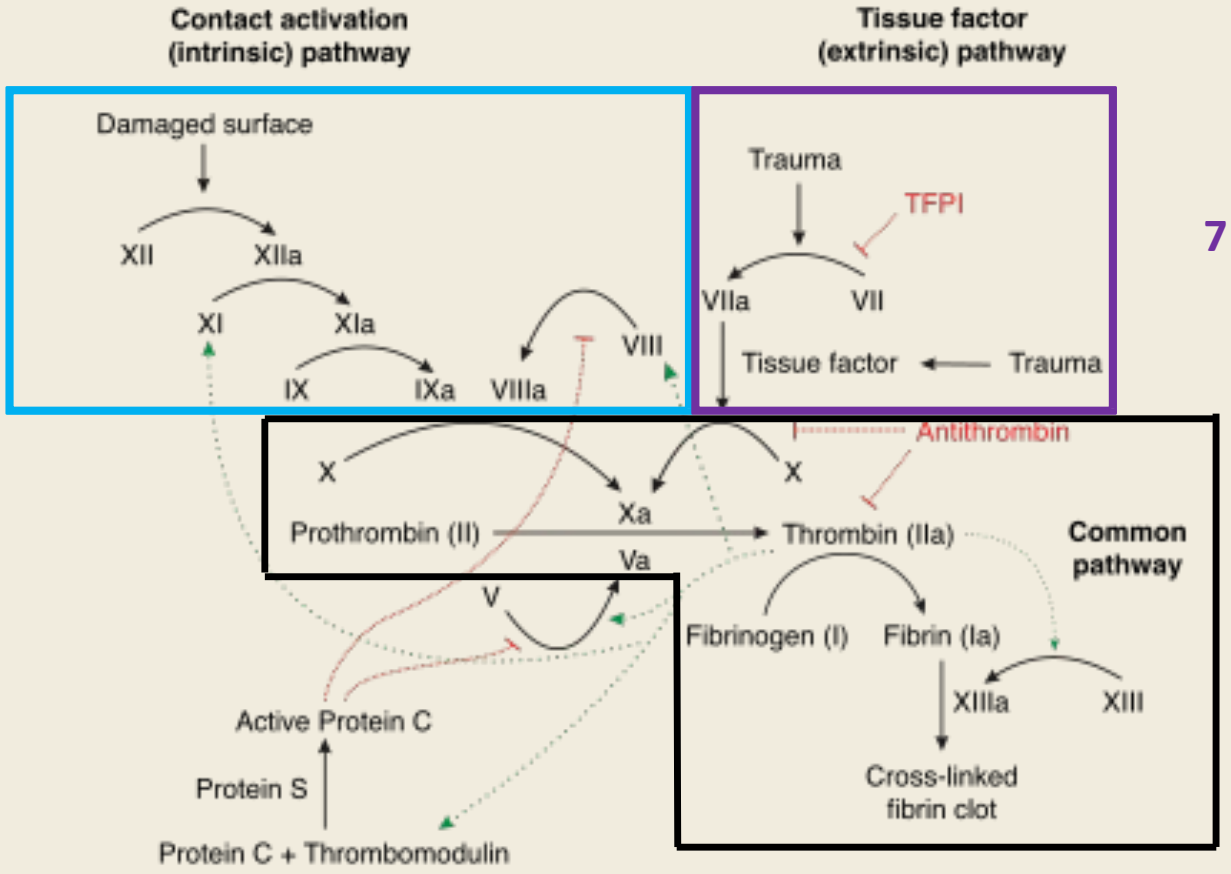
- Stabilize the plug through a fibrin mesh
- **Coagulation cascade**
  - Contact activation (Intrinsic) pathway
  - Tissue factor (extrinsic) pathway
  - Common pathway



# SECONDARY HEMOSTASIS

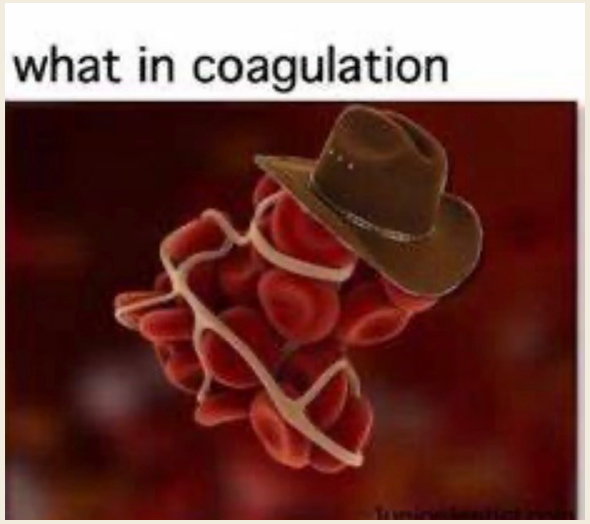
## Coagulation Cascade

12, 11, 9, 8

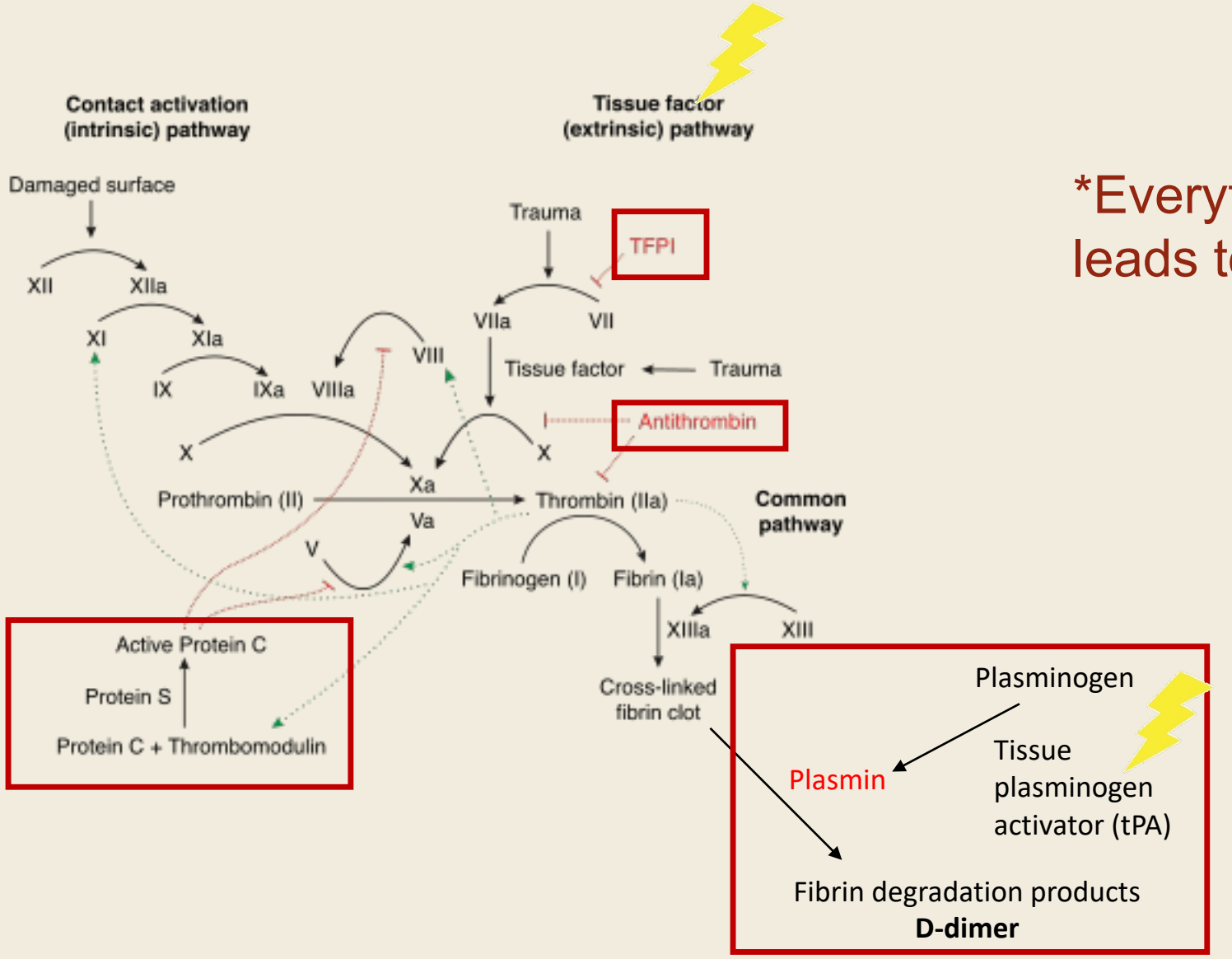



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10, 5, 2, 1



# REGULATION OF HEMOSTASIS



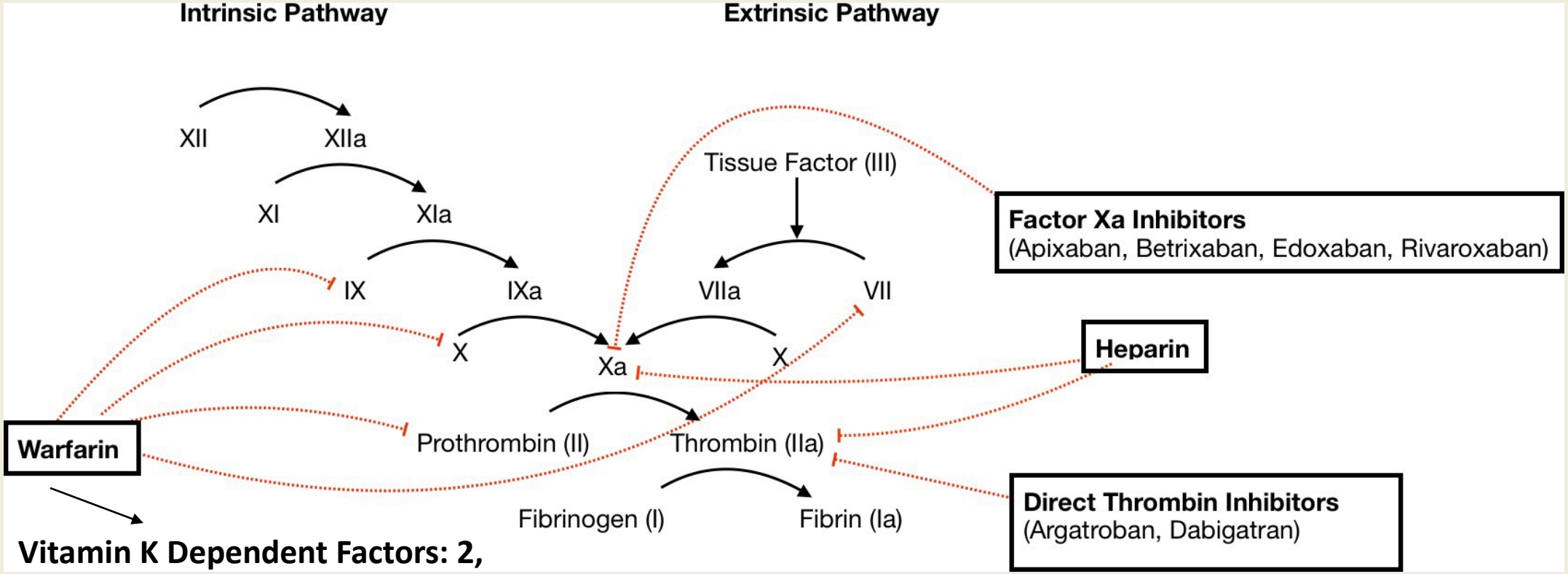

*Everything in a box leads to bleeding

**Fibrinolytic System**

# ANTICOAGULANTS → attacks 2* hemostasis

## Mechanism of Action

Recall: aspirin/clopidegrol attack 1*




**Vitamin K Dependent Factors: 2, 7, 9, 10, proteins C and S**

# COAGULOPATHY

Approach
Specific Coagulopathies

# APPROACH TO COAGULOPATHY

## Definition

- Impairment in coagulation resulting in **excessive bleeding**

## Signs & Symptoms

- Easy bleeding/bruising
- Excessive bleeding after injury/surgery/dental work
- Heavy periods
- Epistaxis
- Mouth/gum bleeding
- Joint bleeding
- Hematemesis, hematochezia, hematuria

# APPROACH TO COAGULOPATHY

## History

### ABCs

### History

- Bleeding Hx
  - Type of bleed
  - Provoked or spontaneous
  - Delayed or instant
  - Systemic or localized
- PMHx
  - Meds
  - Surgeries
  - Menorrhagia +/- obstetric
- Comorbidities
- FHx bleeding

# APPROACH TO COAGULOPATHY

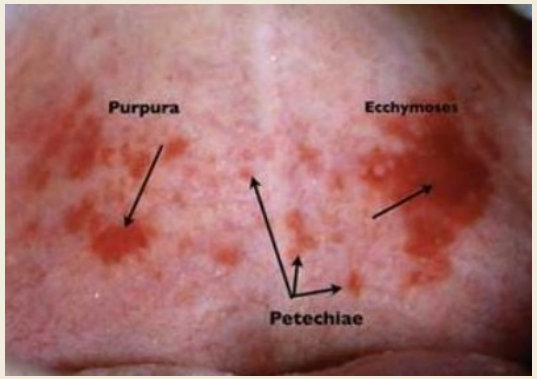
## Physical Exam

### Primary Hemostasis

- Immediate
- Mucocutaneous
- Surface bleeding
  - Petechiae
  - Purpura
  - Ecchymoses

### Secondary Hemostasis

- Less immediate
- Muscles, joints, soft tissues
- Deep bleeding
  - Hematoma
  - Hemarthroses






# APPROACH TO COAGULOPATHY

## DDx

anything that stops platelet plug

### Primary Hemostasis

- **Thrombocytopenia**
  - Decreased production
  - Increased destruction
  - Spleen sequestering
- **Dysfunctional platelet plug**
  - Hereditary/acquired i.e. vWD
  - Antiplatelet drugs
  - Kidney disease
- **Vascular disorders**
  - Connective tissue disease
  - Hereditary hemorrhagic telangiectasia
  - Trauma

anything impacting coagulation cascade

### Secondary Hemostasis

- **Hereditary**
  - Hemophilia
  - Factor deficiency
  - vWD
  - Fibrinogen problem
- **Acquired**
  - Clotting factor inhibitors
  - Anticoagulant drugs
  - DIC
  - Hypocalcemia

- **Hyperfibrinolysis**
- ***Child Abuse**

# APPROACH TO COAGULOPATHY

## Initial Investigations

- **CBC**
- **INR/PT, PTT**
- **Liver and renal function**
- Calcium
- Blood group
- pH
- Specialized testing as 1st or 2nd line
  - Specific factor levels
  - Tests for vWF disease
  - Fibrinolytic assays

# APPROACH TO COAGULOPATHY

## Initial Investigations

**Prothrombin time (PT)**

- **Extrinsic** + common pathway
  - Play Tennis outside
  - PT shorter abbrev. = only 1 factor (7)
- International Normalized Ratio (**INR**)
  - Calculated based on PT

INR/PT

**Partial thromboplastin time (PTT)**

- **Intrinsic** + common pathway
  - Play Table Tennis inside
  - + phospholipid source

**Time for clot formation**



Something wrong w/ coagulation cascade

# APPROACH TO COAGULOPATHY

## Initial Investigations

| | Normal INR | ↑ INR |
|---|---|---|
| **Normal PTT** | **Usually primary hemostasis problems**<br>- Thrombocytopenia<br>- Congenital platelet disorders<br>- Anti-platelet drugs (e.g., aspirin)<br>- Von Willebrand disease<br>- Kidney disease<br>- Blood vessel/connective tissue abnormalities | **Extrinsic Pathway** → mostly factor 7<br>- Liver disease<br>- Vitamin K deficiency → F 2, 7, 10, 9<br>- Deficiency/inhibitor of factor 7<br>- Warfarin<br>→ F7 runs out first, shortest ½ life (liver disease) |
| **↑ PTT** | **Intrinsic Pathway**<br>- Heparin<br>- Deficiency/inhibitor of factor 12, 11, 9, 8 (including hemophilia)<br>- Lupus anticoagulant<br>- Severe vWD | **Common Pathway or Intrinsic + Extrinsic**<br>- Multiple factor deficiencies<br>- DIC<br>- Severe liver disease<br>- Severe vitamin K deficiency<br>- Warfarin<br>- High dose heparin<br>- DOACs<br>- Inhibitor/deficiency of factor 10, 5, 2,1 |

7

*Know this table! Understand > memorize

# APPROACH TO COAGULOPATHY

## Initial Investigations

| | Normal INR | ↑ INR |
|---|---|---|
| **Normal PTT** | **Usually primary hemostasis problems**<br>- Thrombocytopenia<br>- Congenital platelet disorders<br>- Anti-platelet drugs (e.g., aspirin)<br>- Von Willebrand disease<br>- Kidney disease<br>- Blood vessel/connective tissue abnormalities | **Extrinsic Pathway**<br>- Liver disease<br>- Vitamin K deficiency<br>- Deficiency/inhibitor of factor 7<br>- Warfarin |
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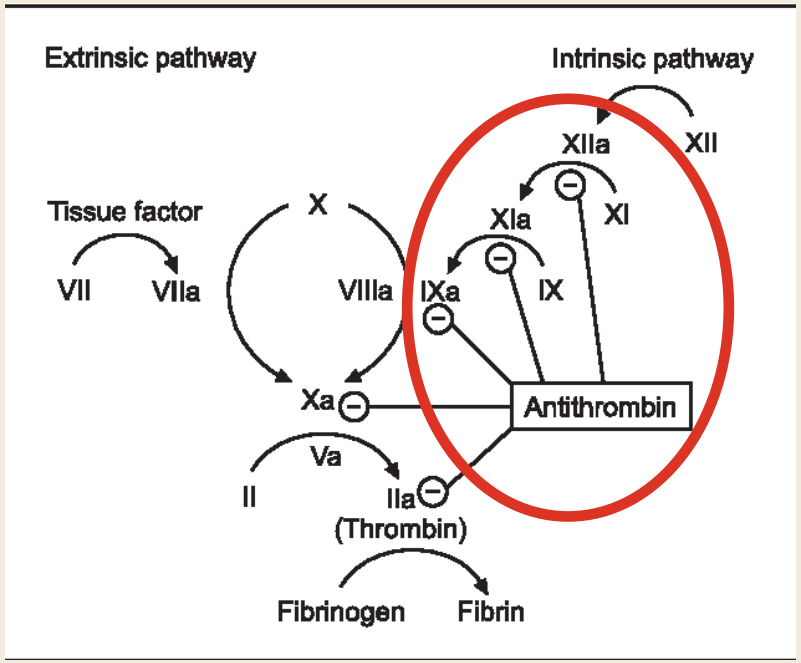
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*Know this table! Understand > memorize

# INTRINSIC PATHWAY

## Heparin

- Binds to **antithrombin**
- Heparin-antithrombin complex inhibits **thrombin** and Factor **X**
  - But isn't this the common pathway?
  - Antithrombin inhibits also inhibits IXa, XIa, XIIa






# INTRINSIC PATHWAY

## Hemophilia

### Types

- **Hemophilia A** = Factor VIII deficiency
- **Hemophilia B** = Factor IX deficiency

### Etiology

- Genetic
  - X-linked recessive
- Acquired
  - Anti-Factor VIII, IX antibodies

### Mixing Study

- Mix normal control plasma + patient plasma
- Perform PTT
  - If PTT corrects = **factor deficiency**
  - If PTT does not correct = **factor inhibitors** or **lupus anticoagulant**

# INTRINSIC PATHWAY

## Lupus Anticoagulant

- Autoantibodies that target **phospholipids**
- Increases PTT
  - PTT is a phospholipid-dependent test (in vitro)
  - Antiphospholipid antibodies can prolong clotting

# INTRINSIC PATHWAY

## Severe von Willebrand Disease

- We will talk more about this later!
- **Factor VIII** is bound to vWF to increase half-life
- **Decreased vWF = decreased Factor VIII**

# APPROACH TO COAGULOPATHY

## Initial Investigations

| | Normal INR | ↑ INR |
|---|---|---|
| **Normal PTT** | **Usually primary hemostasis problems**<br>- Thrombocytopenia<br>- Congenital platelet disorders<br>- Anti-platelet drugs (e.g., aspirin)<br>- Von Willebrand disease<br>- Kidney disease<br>- Blood vessel/connective tissue abnormalities | **Extrinsic Pathway**<br>- Liver disease<br>- Vitamin K deficiency<br>- Deficiency/inhibitor of factor 7<br>- Warfarin |
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7

*Know this table! Understand > memorize

# EXTRINSIC PATHWAY

## Liver Disease

Made by endothelial

- The liver synthesizes all coagulation factors (**except VIII**)
- **Factor VII has shortest half-life = first to depleted → EXTRINSIC PATH**

# EXTRINSIC PATHWAY

## Vitamin K Deficiency

- Vitamin K-dependent: **2, 7, 9, 10, Proteins C & S**
  - 2 + 7 = 9 NOT 10

### Causes

- Malabsorption
- Lack of consumption
- Antibiotics
- Sepsis, DIC, critical illness
- Newborns (need supplements)

- **Again… Factor 7-VII has shortest half-life = first to depleted → EXTRINSIC PATH**

# EXTRINSIC PATHWAY

## Warfarin

- Inhibits the enzyme that activates vitamin K (Vitamin K epoxide reductase)
- **Decreases vitamin K-dependent factors II, VII, IX, X, proteins C & S**
- Monitor: PT/INR
- **Reversal agent: Vitamin K, prothrombin complex concentrate**

- **Again... Factor 7-VII has shortest half-life = first to depleted → EXTRINSIC PATH**

# APPROACH TO COAGULOPATHY

## Initial Investigations

| | Normal INR | ↑ INR |
|---|---|---|
| **Normal PTT** | **Usually primary hemostasis problems**<br>- Thrombocytopenia<br>- Congenital platelet disorders<br>- Anti-platelet drugs (e.g., aspirin)<br>- Von Willebrand disease<br>- Kidney disease<br>- Blood vessel/connective tissue abnormalities | **Extrinsic Pathway**<br>- Liver disease<br>- Vitamin K deficiency<br>- Deficiency/inhibitor of factor 7<br>- Warfarin |
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# APPROACH TO COAGULOPATHY

## Initial Investigations

| | Normal INR | ↑ INR |
|---|---|---|
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7

*Know this table! Understand > memorize

# PRIMARY HEMOSTASIS

## von Willebrand Disease

### Definition

- Missing or defective vWF caused by a genetic mutation*
- **Most common hereditary coagulopathy**

*Can also be acquired

### Types

- **1: mild quantitative defect**
- **2: qualitative defect**
- **3: severe quantitative defect**

- May also be associated with low Factor VIII

# PRIMARY HEMOSTASIS

## von Willebrand Disease

### Investigations

- CBC, INR, PTT
- **vWF antigen, vWF activity assay**
  - **Proportional reduction in activity and antigen → quantitative (Type 1)**
  - **vWF activity not proportional to levels → qualitative (Type 2)**
- FVIII levels
- Blood group → Blood O group patients have lower levels naturally

### Treatment

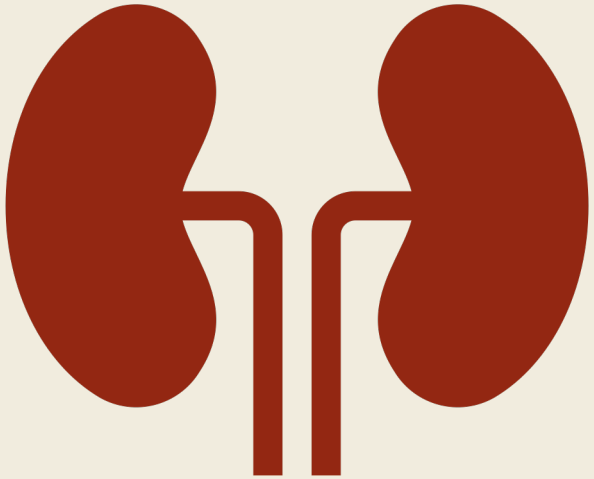
- **Desmopressin (DDAVP)**
- Anti-fibrinolysis (Tranexamic acid)
- Factor replacement
- OCP (heavy menstrual bleeding)

# PRIMARY HEMOSTASIS

## Kidney Disease

### Mechanism

- Platelet dysfunction caused by:
  - Granule contents
  - Impaired TXA2 synthesis
  - And more



- Important to test for renal function

# PRIMARY HEMOSTASIS

## Thrombocytopenia - DDx

- Low platelet count **≤ 150 x 10^9/L**

### Causes

- **Not enough production**
  - Liver disease (decreased thrombopoietin)
  - Hereditary, BM issue, Drugs, infection
- **Too much destruction (Thrombocytic microangiopathies)**
  - ITP
  - HUS
  - TTP
  - DIC
  - HIT



- **Sequestration**
  - Splenomegaly
- **False negative (pseudo)**
  - When blood is collected using EDTA

# PRIMARY HEMOSTASIS

## Thrombocytopenia - ITP

- Immune Thrombocytopenic Purpura
- **Diagnosis of exclusion (isolated platelet count <100)**
- Increased destruction + decreased production of plt

### Presentation

- **ANYTHING!**
- **Asymptomatic, mild bleeding or life-threaetening**

### Causes

- Primary → Idiopathic
- Secondary
  - Cancer
  - Viral infection
  - Autoimmune disease
  - Drug-induced

# PRIMARY HEMOSTASIS

## Thrombocytopenia - ITP

### Investigations

- CBC, INR, PTT
- Blood film
- Electrolytes, urea, creatinine, liver enzymes
- Others:
  - Pregnancy testing
  - Immunoglobulin levels

### Treatment

- **Immunosuppression**
  - Steroids – 1st line!
  - Intravenous immune globulin (IVIG)
  - Azathioprine
- **Rituximab****
- Splenectomy

# PRIMARY HEMOSTASIS

## Thrombocytopenia - HUS

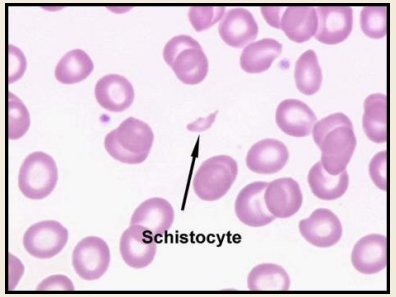
- Hemolytic Uremic Syndrome
- Bleeding and clotting

### Mechanism

- **Shiga toxin-producing bacteria** (i.e. E. coli)

### Diagnosis

- Symptom triad
  - **Acute thrombocytopenia**
  - **Hemolytic anemia**
  - **AKI** (decreased urine)
- **Schistocytes**








# PRIMARY HEMOSTASIS

## Thrombocytopenia - HUS

### Treatment

- Supportive – monitoring, IV fluids
- **AVOID antibiotics (HUS explodes and the toxin spills everywhere)**
- **AVOID platelet transfusion (this is HUS food)**
- Hemodialysis in some patients



# PRIMARY HEMOSTASIS

## Thrombocytopenia - TTP

- Thrombotic Thrombocytopenic Purpura

### What is it?

- Autoimmunity against ADAMTS-13

### Causes

- Primary (idiopathic)
- Secondary (Drugs, pregnancy complications, infection, stem cell transplantation

### Mechanism

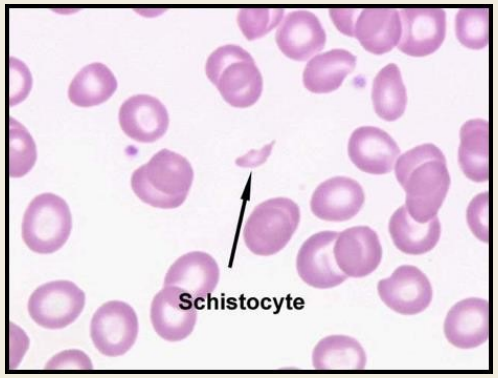
- **Reduced ADAMTS-13**
  - ADAMTS-13 normally regulates vWF size -> vWF multimers are prothrombogenic

# PRIMARY HEMOSTASIS

## Thrombocytopenia - TTP

### Diagnosis

- Symptoms (pentad)
  - thrombocytopenia, AKI, hemolysis, fever, neurologic
- Schistocytes
- ADAMTS-13 Assay




... hello again :)

### Treatment

- **Plasma exchange**
  - remove antibody and replace with normal ADAMTS-13 and vWF
- Corticosteroids and Rituximab** (immunosuppress the antibody)
- **Avoid platelet transfusion (antibody will just mess it up anyway)**

# PRIMARY HEMOSTASIS

## Thrombocytopenia - HIT

- Heparin-Induced Thrombocytopenia (and thrombosis)
- Low plt + Clotting

### Mechanism

- Platelets release **platelet factor 4 (PF4)**
- Heparin binds to PF4
- **Antibodies attach to Heparin-PF4 complex**
- **Platelets activate and clot**

### Causes

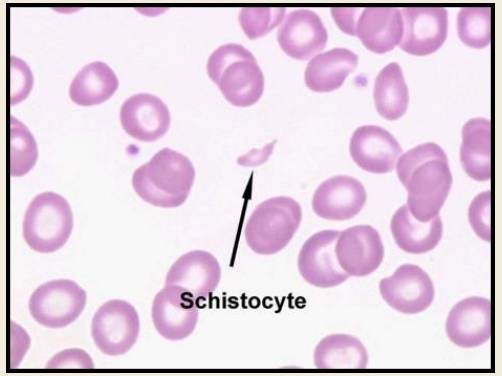
- Adverse drug reaction in 2% of patients
- **Exposure to heparin treatment > 4 days**
- More likely with unfractionated than LMWH

# PRIMARY HEMOSTASIS

## Thrombocytopenia - HIT

### Diagnosis

- **4 T's score probability**
  - Thrombocytopenia – how severe
  - **Timing of thrombocytopenia – (usually <1d or in 5-10d)**
  - Thrombosis
  - Other causes of Thrombocytopenia
- Investigations
  - **Anti-PF4 ELISA**
    - Confirms presence of anti-PF4 antibodies
  - **Serotonin release assay**
    - Gold standard but time consuming
- Schistocytes




hello again again again >:)

# PRIMARY HEMOSTASIS

## Thrombocytopenia - HIT

### Treatment

- **STOP HEPARIN** and start on alternate non-heparin anticoagulant
- Avoid platelet transfusions
- Start warfarin after platelets have normalized
- Continue anti-coagulation
- If confirmed thrombosis, treat for at least 3 months
- **Antidote: protamine sulfate**

# PRIMARY HEMOSTASIS

## Thrombocytopenia - DIC

- Disseminated Intravascular Coagulation
- Bleeding and clotting



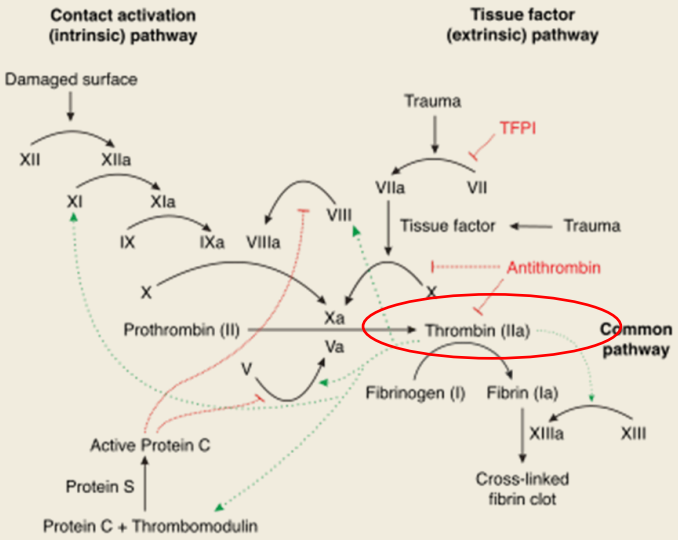
### Mechanism

- **Tissue factor** activation causes a hypercoagulablestate
  - **Small clots form in blood vessels**
  - **Clots can compromise blood flow to tissues and organs**
- Clotting factors consumed **resulting in excessive bleeding**

### Causes

- Infection
- Trauma
- Cancer
- Obstetric complications

**URGENT!** Can lead to **multi-organ failure and death**



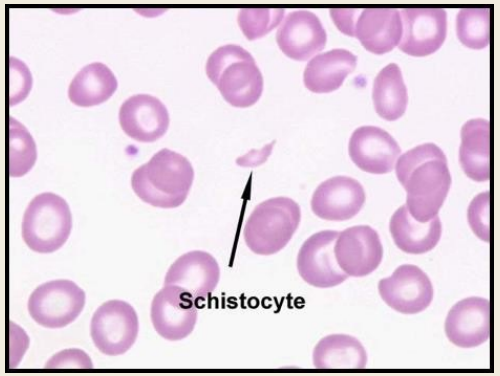
# PRIMARY HEMOSTASIS

## Thrombocytopenia - DIC

### Diagnosis

- Clinical features
  - Sick => Bleeding + clotting
- Everything is low!
  - Presence of underlying condition
  - **Fibrinogen <1 g/L**
  - **Elevated D-Dimer**
  - **Platelets <100**
  - **Elevated INR/PTT**
- Schistocytes on blood film




... hello again again :D

# PRIMARY HEMOSTASIS

## Thrombocytopenia - DIC

### Treatment

- **Supportive**
- If patient is bleeding, consider:
  - **Cryoprecipitate if fibrinogen < 1.0 g/L**
  - **Platelet transfusion if platelets <50**
  - **Fresh frozen plasma if INR > 1.5**
  - **Packed RBCs if Hg < 70-80 g/L**

# Transfusions

| Product | PRBC | Platelets | Plasma | Fibrinogen Concentrate | Cryoprecipitate |
|---|---|---|---|---|---|
| Contents | Blood (duh)<br>Plasma<br>Anticoagulants | Platelets from buffy coat<br><br>Male plasma (reduces adverse reactions) | All coagulation factors | fibrinogen | Also fibrinogen |
| Storage | 4 ℃ for 42 days | 24 ℃ for 7 days<br>(hard cuz they clot) | -18 ℃ for 1 year | 24 ℃ for 5 year<br>(best storage) | -18 ℃ for 1 year |
| Indication | Hb < 70 | Plt < 10<br><br>Plt < 50 in surgery or DIC | INR > 1.8-1.5<br><br>Massive bleeding, Surgery | fibrinogen <1.0 + bleeding | fibrinogen <1.0 + bleeding |

Don’t give platelets in TTP, HUS, HIT

# Transfusions Risks

## Testing

**ABO group, Cross match, infections**

## Universal Donors

**PRBC = O-  |  Plasma = AB+**

## Adverse Reactions

**Acute Hemolysis:** <24h, due to ABO incompatability, emergency

**Delayed Hemolysis:** up to 30 days later, non-ABO antibodies

**TRALI:** Transfusion Related Acute Lung Injury → Dyspnea, most common fatal

**TACO:** Transfusion Associated Cardiac Overload → Dyspnea, most common serious

**TA-GVHD:** Transfusion Graft Vs Host Disease → Cytopenia

**Anaphylaxis:** Allergic reaction

**Other benigns:** iron overload, febrile non-hemolytic

# Over-clotting problems

PE, DVT, thrombophillia and Anticoag Drugs

# Venous Thromboembolisms

## Virchow's Triad

- Stasis + Injury + Hypercoagulability

## Investigations

**DVT (swollen leg)**

- Gold = Ascending Venogram
- Alternative = Compression US

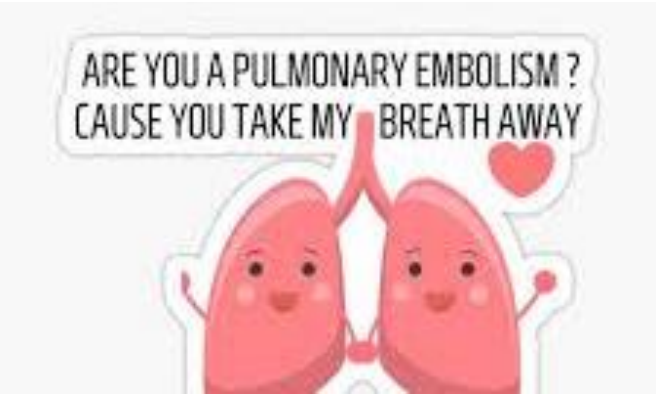
**PE (Tachy + pleuritic chest pain)**

- Gold = Pulmonary Angiogram
- Alternative = V/Q scan

**Unlikely VTE? = r/o with D-Dimer**

## Etiology → Treamtent

1. **Cancer → LMWH x 6 months or until cured**
2. **Injury/Joint Surgery → anticoagulate for 1 month**
3. **Idiopathic → Treat FOR LIFE**



# Hereditary Thrombophillias

## Deficiencies

1. Protein C or S Deficiency (these inhibit factor V and VIII)
2. Antithrombin Deficiency (inhibits… thrombin)

Deficiency = no inhibition = too much clotting!

## Strong Clotters

1. Prothrombin mutation (excess prothrombin)
2. Factor V Leiden (super resistant factor V)



# Anticoagulation Drugs

| Drug Name | Unfractionated Heparin (UFH) | LMWH (-parins) | Fonda-parinux | VKA (Warfarin) | DOAC Xa (-xabans) | DOAC IIa (dabigatran) | Other (-irudin, argatroban |
|---|---|---|---|---|---|---|---|
| Mechanis m | Pentasach (inhibits IIa) AND 18-chain (inhibits Xa) | Pentasach only (inhibits IIa only) | Pentasach only (inhibits IIa only) | Vit-K Antagonist (inhibits factors 2,7,9,10) | Inhibits Xa | Inhibits IIa | Inhibits thrombin |
| Antidote | Protamine Sulfate | Protamine Sulfate (Andexanet?) | Recomb VIIa (Andexanet?) | PCC + Vitamin K | Andexanet? | Idarucuzimab | ….. :/ |
| Pros/Cons | Good for kidney ☺<br><br>But more adverse reaction ☹ And needs IV, so only at hospital | More predictable, less reactions, and can take at home<br><br>But needs renal clearance | Stronger version of LMWH<br><br>…so also riskier | Best for inpatients (i.e. Heart Surgery)<br><br>But narrow window, drug interactions, patient variability | Convenient, rapid, predictable<br><br>But Expensive | convenient, rapid, predictable<br><br>But Expensive and bad on liver | Can inactivate fibrin -bound thrombin (unlike heparin)<br><br>But NO ANTIDOTE. Also, immunogenic |

# Rando Research Ones

## QI and Critical Appraisal

# Quality Improvement (QI)

## SMART Goals

- Specific
- Measurable
- Achievable
- Relevant
- Time-sensitive




## Steps

1. Identify the problem
2. Set a goal
3. **Root cause analysis (fishbone diagram) = Most important**
4. Generate & select solutions
5. Create a measurement plan
6. Try small tests of change
7. Analyze (Run charts, Process/ Outcome/Balance measures)
8. Sustain the gains or start again at step 3

# Critical Appraisal

## Equipose

Can only research if there is no way to know that there is something better

## Research

- **Superiority** (this is better) vs **non-inferiority** (this is not worse… but cheaper)
- **Per protocol** (assume perfect adherence) vs **Intent-To-Treat** (Includes non-adherence; More realistic… but harder to get good results)
- Confounding and Bias → address by randomization and blinding

## Errors

- **Type 1 = False Positive | Type 2 = False Negative | "Boy who cried wolf"**

Us before hematology:




Us after hematology:



# SCHULICH REVIEWS: HEMATOLOGY

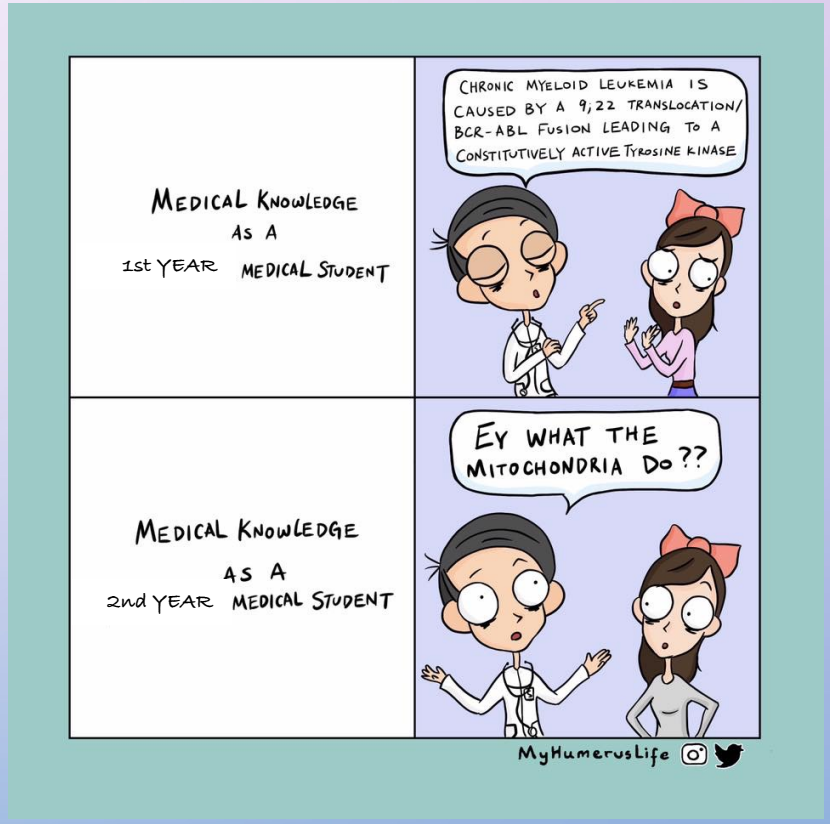
# WEEK 11-12

Hannah Skarnikat

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# DISCLAIMERS

- This is a non-exhaustive review meant to supplement, NOT REPLACE, your own notes
- Presentation will only focus on high yield topics and key points
- Opinions expressed are just my own
- My brain is empty



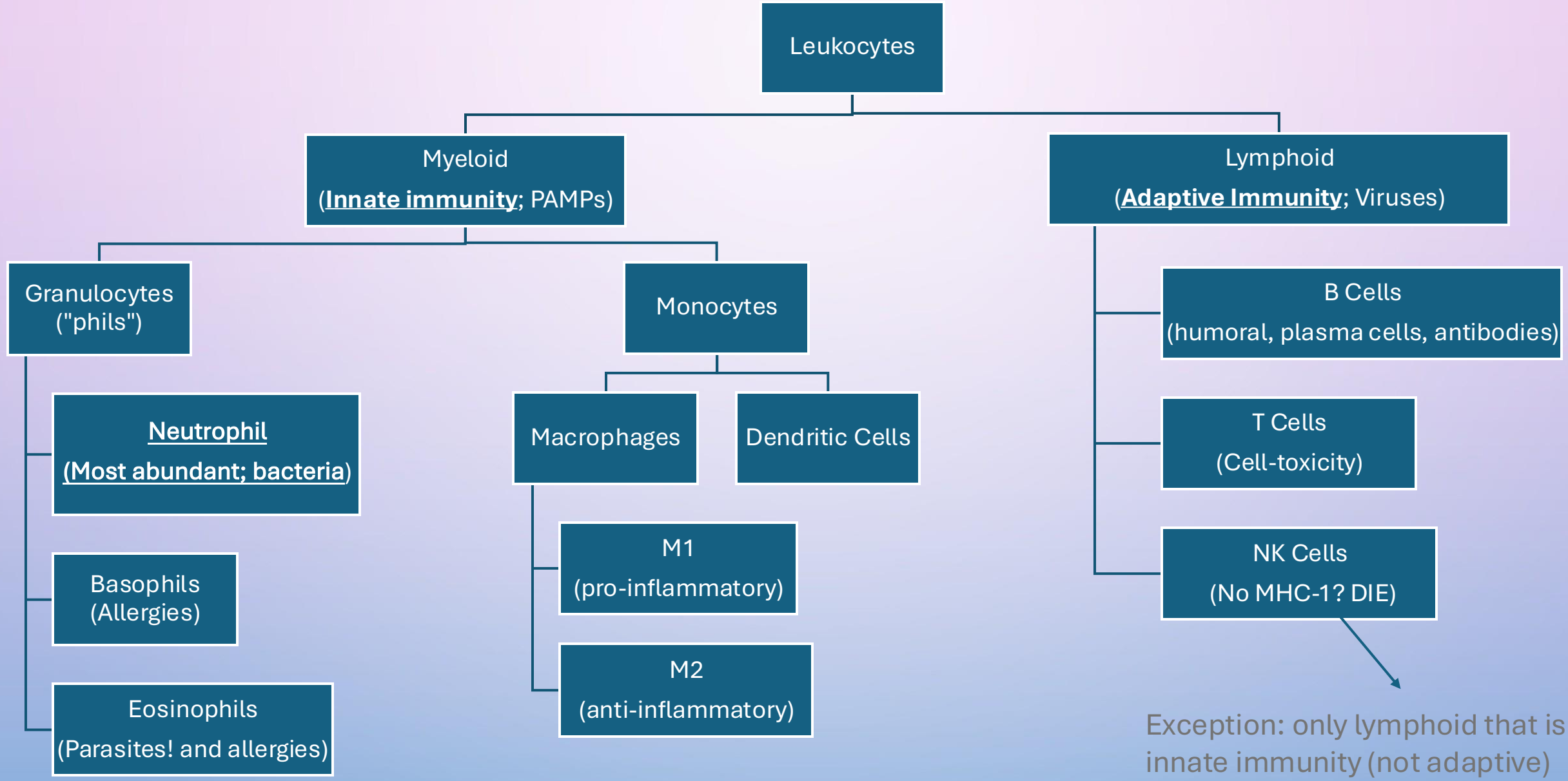
# LIST OF ALL DISORDERS COVERED IN WEEKS 11-12

- **Thrombocytosis:**
  - Primary
    - ET
    - MDS/MPN
  - Secondary causes
- **Benign Eosinophilia**
- **Benign Basophilia**
- **Benign Monocytosis**
- **Leukemias:**
  - AML
    - APL
  - ALL
  - CLL
  - CML
- **Myloproliferative Neoplasms**
  - CML
  - PV
  - ET
  - MF
- **Lymphomas:**
  - Non-Hodgkins:
    - Diffuse B cell
    - Follicular
  - Hodgkins:
    - Classical:
      - Nodular sclerosis
      - Mixed cellularity
      - Lymphocyte rich
      - Lymphocyte poor
    - Nodular lymphocyte predominant
- **Multiple Myelomas:**
  - MGUS
  - Smolder myeloma
  - Overt myeloma
  - Plasma cell leukemia
- **Mediastinal Masses:**
  - Anterior:
    - Thymus tumour
    - Thyroid tumour
    - Terrible lymphoma
    - Thoracic aorta tumour
    - Teratoma and germ cell cancer
  - Middle:
    - Lymphadenopathy
    - Benign cystic tumour
    - Esophageal tumor
    - Vascular masses and enlargement
  - Posterior:
    - Neurogenic tumour
    - Meningocele
    - Thoracic spine lesions

# Leukocytes!

When we have more, and when it’s too much (*cough * cough * leukemia)

# **Leukocytes**: Your Immune System




Exception: only lymphoid that is innate immunity (not adaptive)

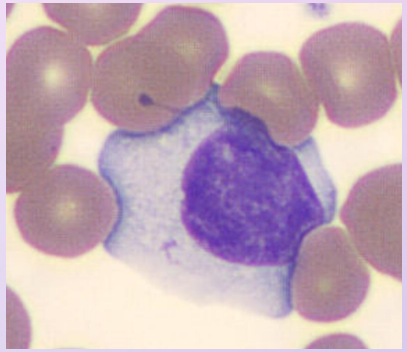
# NEOPLASM VS. REACTIVE LEUKOCYTOSIS

**Neoplasm:**

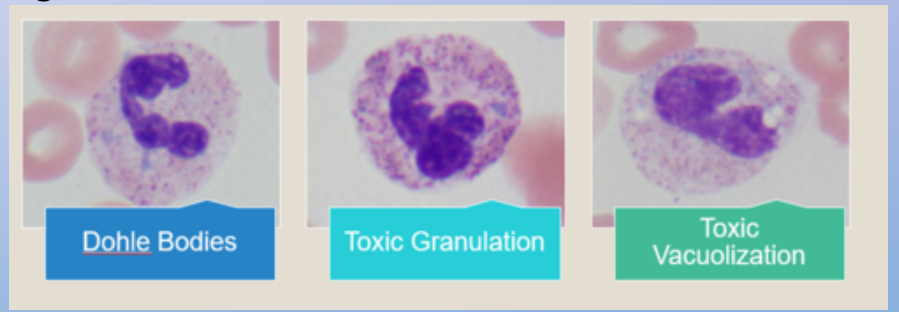
- Presence of **immature cells (including blasts) in PB**
- **WBC count > 30 x10⁹/L (over 100 is virtually always malignant)**
- Increased number of eosinophils and/or basophils
- Positive cytogenetics and/or molecular studies (eg. Philadelphia chromosome)

**Reactive:**

- **No blasts in PB*. Just reactive lymphocytes**



- **WBC count is 11-30 (lower than in neoplasm)**
- Presence of toxic granules, toxic vacuoles, and/or Döhle bodies
- Negative cytogenetics



# MOST COMMON - LEUKOCYTOSIS

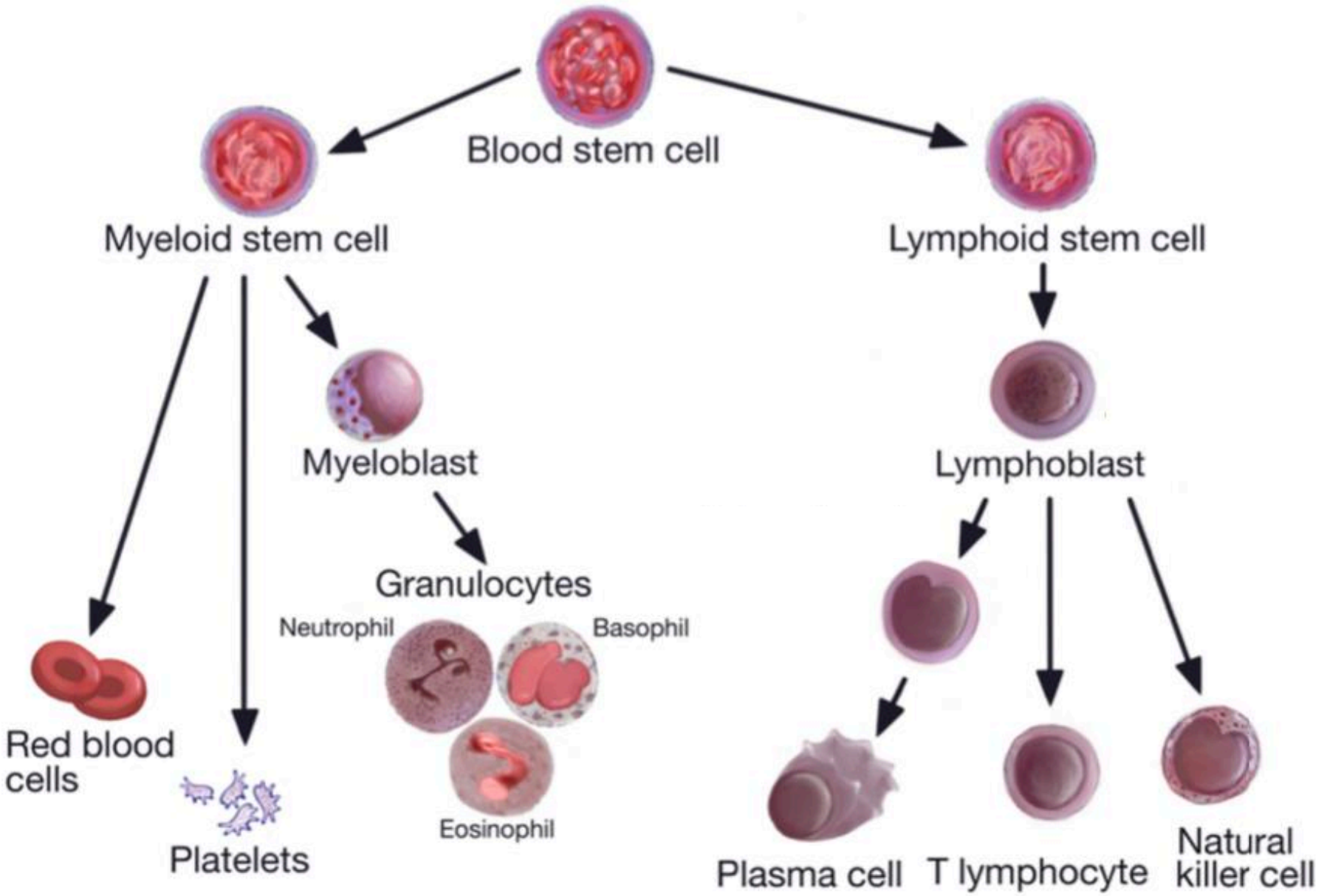
**CML** (most common malignant neutrophilia):

- Defining features:
  - Leukoerythroblastic picture ➔ disproportionate left shift with accompanying immature RBCs
  - Associated basophilia and eosinophilia
  - Philadelphia chromosome!

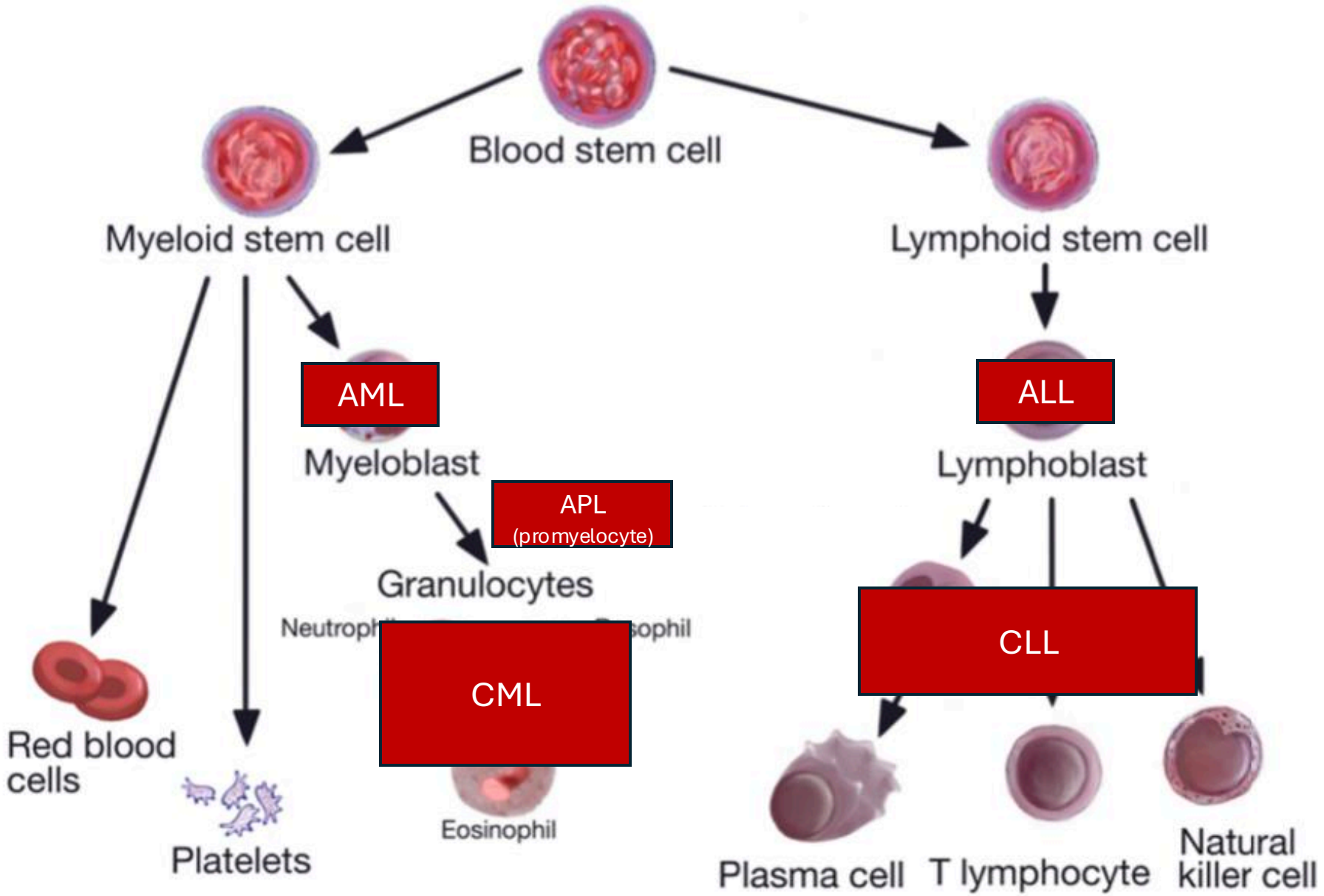
**EBV/Mono** (most common benign lymphocytosis):

- Defining features:
  - Monospot test ➔ reactive lymphocyte
  - Infectious symptoms (though often asymptomatic)

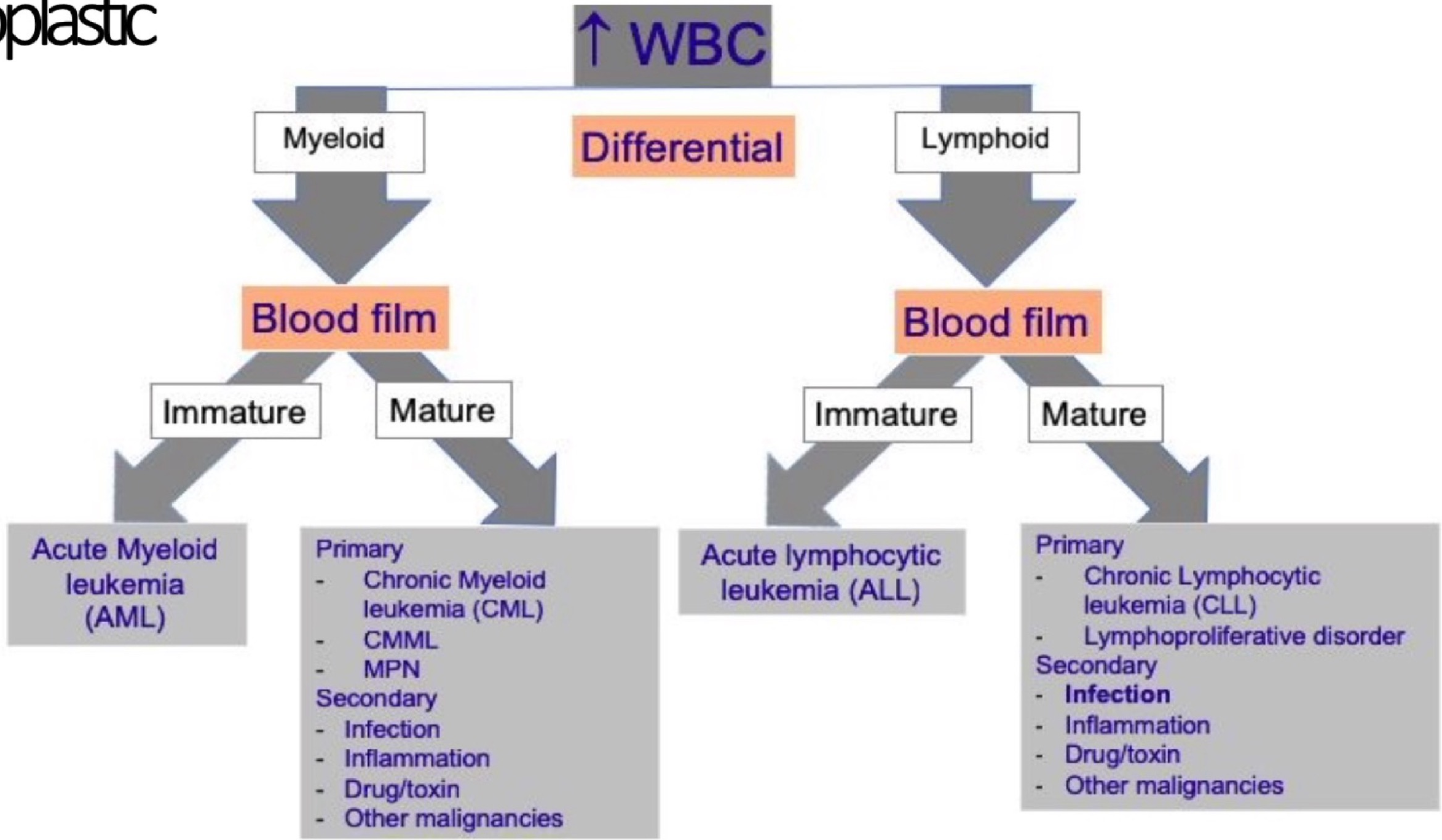
# Blood Cancer Family Tree



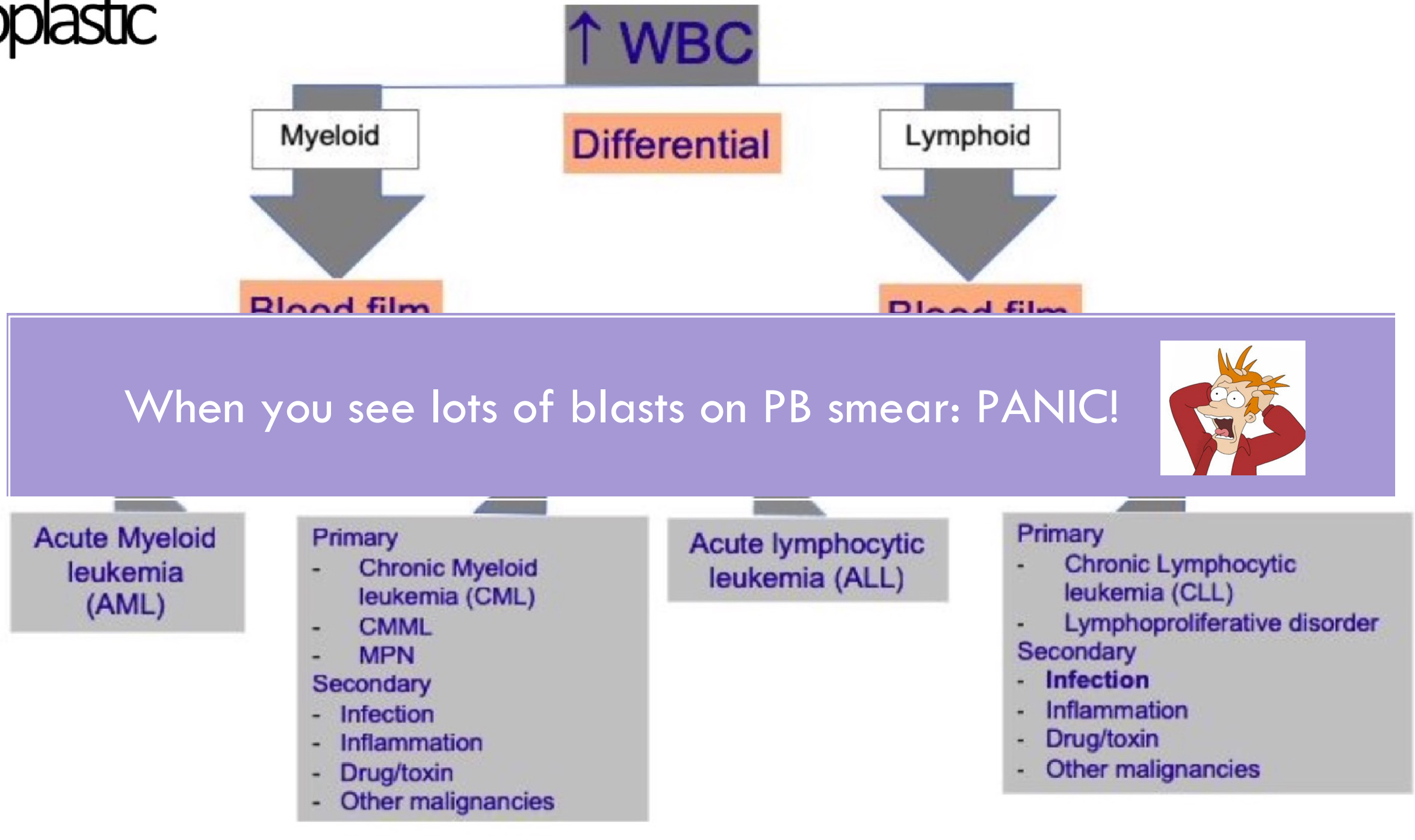
# Blood Cancer Family Tree



# Neoplastic

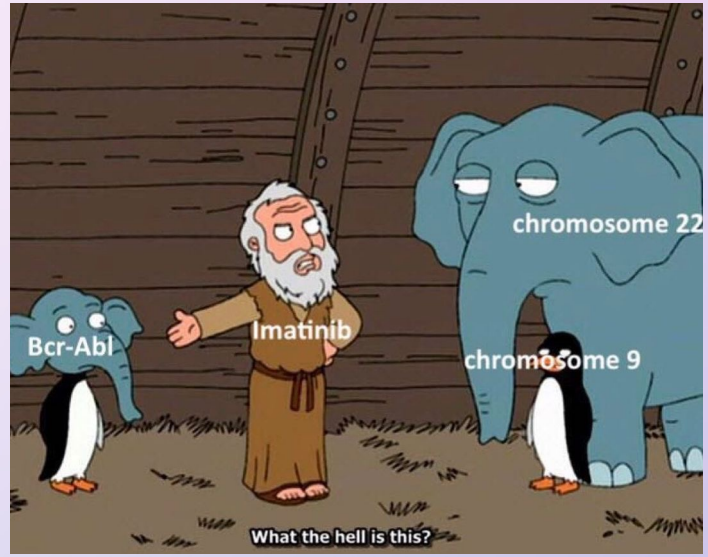

↑ WBC
Differential
Myeloid
Lymphoid
Blood film
Blood film
Immature
Mature
Immature
Mature
Acute Myeloid leukemia (AML)
Primary
- Chronic Myeloid leukemia (CML)
- CMML
- MPN
Secondary
- Infection
- Inflammation
- Drug/toxin
- Other malignancies
Acute lymphocytic leukemia (ALL)
Primary
- Chronic Lymphocytic leukemia (CLL)
- Lymphoproliferative disorder
Secondary
- Infection
- Inflammation
- Drug/toxin
- Other malignancies

# Neoplastic

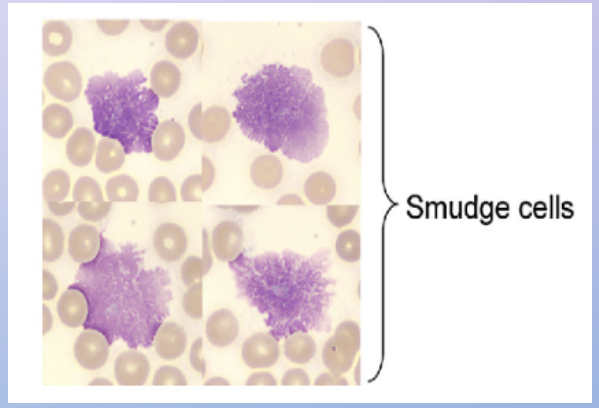

↑ WBC
Differential
Myeloid
Lymphoid
Blood film
Blood film
When you see lots of blasts on PB smear: PANIC!
Acute Myeloid leukemia (AML)
Primary
- Chronic Myeloid leukemia (CML)
- CMML
- MPN
Secondary
- Infection
- Inflammation
- Drug/toxin
- Other malignancies
Acute lymphocytic leukemia (ALL)
Primary
- Chronic Lymphocytic leukemia (CLL)
- Lymphoproliferative disorder
Secondary
- Infection
- Inflammation
- Drug/toxin
- Other malignancies

# LEUKEMIAS

| | AML | APL | CML |
|---|---|---|---|
| Defining Features | • An Auer rod<br>• Positive MPO<br>• >20% blasts (BM) | • Lots of Auer rods (2+)<br>• High risk of DIC!<br>• t(15,17)/PML-RARa | • Philadelphia chromosome (oncogene) ➔ t(9,22)/BCR-ABL |
| Management | • 3 + 7 regimen<br>• Shorter treatment than ALL (0.5y vs 3y) | • URGENT!<br>• ATRA + Arsenic | • Imatinib (TKI inhibitor) |



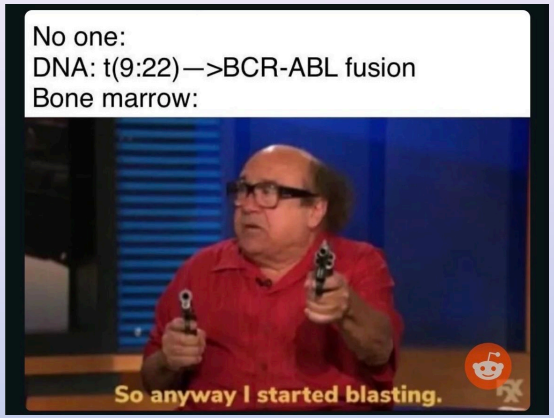

| | ALL | CLL |
|---|---|---|
| Defining Features | • Mostly in children<br>• B or T cell origin (80% B cell)<br>• >20% blasts (BM)<br>• Sanctuary in CNS / testes | • Generally B cell origin<br>• Smudge cells<br>• Late diagnosis since asymptomatic during earlier stages |
| Management | • induction → consolidation → intensification → maintenance<br>• Lumbar punctures with chemo for CNS protection | • NOT curable, only treat when symptomatic (Watch and Wait)<br>• Ibrutinib |

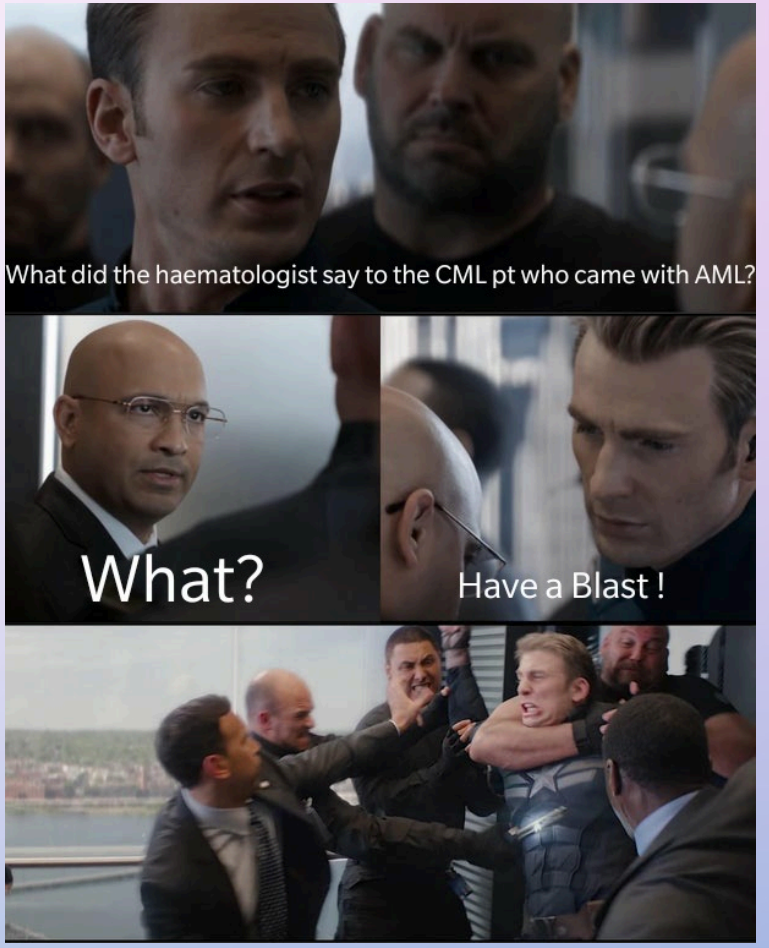


# BLAST CRISIS

**3 Phases of CML**

1. Chronic
    - <10% blasts
    - Mild symptoms, often when diagnosis occurs
2. Accelerated
    - Transitional phase
3. **Acute/Blast Crisis**
    - Essentially conversion to AML
    - >20% blasts in BM
    - More severe symptoms (fever, loss of appetite, weight loss)



# LEUKEMIA IN KIDS

- More aggressive treatment (kids are durable) with appropriate supportive care
- Better cure rates compared to adults (>90% in ALL)
- **ALL:**
  - Outpatient treatment
  - Need to target sanctuary sites with chemo or radiation: CNS, testes
- **AML:**
  - Inpatient treatment
  - Generally no sanctuary sites

# LEUKOCYTOSIS (LEUKEMIA) COMPLICATIONS

MEDICAL EMERGENCIES!!!

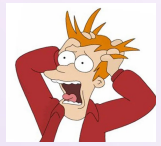


- **Leukostasis:** WBCs (large blasts) plug up microvasculature
  - Treatment: Cytoreduction via hydroxyurea or leukapheresis; supportive care
- **Tumor lysis syndrome:** tumour cells release internal contents into the bloodstream
  - Diagnosis: Hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, acidosis, acute renal failure
    - "Drinking from a KUP without the C makes the kidneys pHail"
  - Treatment: Dialysis, **allopurinol (prevents), rasburicase (treats)**
- **DIC:** clots in microcirculation leading to a bleeding disorder
  - Diagnosis: increased INR, PTT; decreased fibrinogen and platelets
  - Treatment: platelet transfusion, factor replacement
  - Highest risk in APL



# LEUKOPENIA (too little is equally bad)

- **Febrile neutropenia:**
  - MEDICAL EMERGENCY!!!

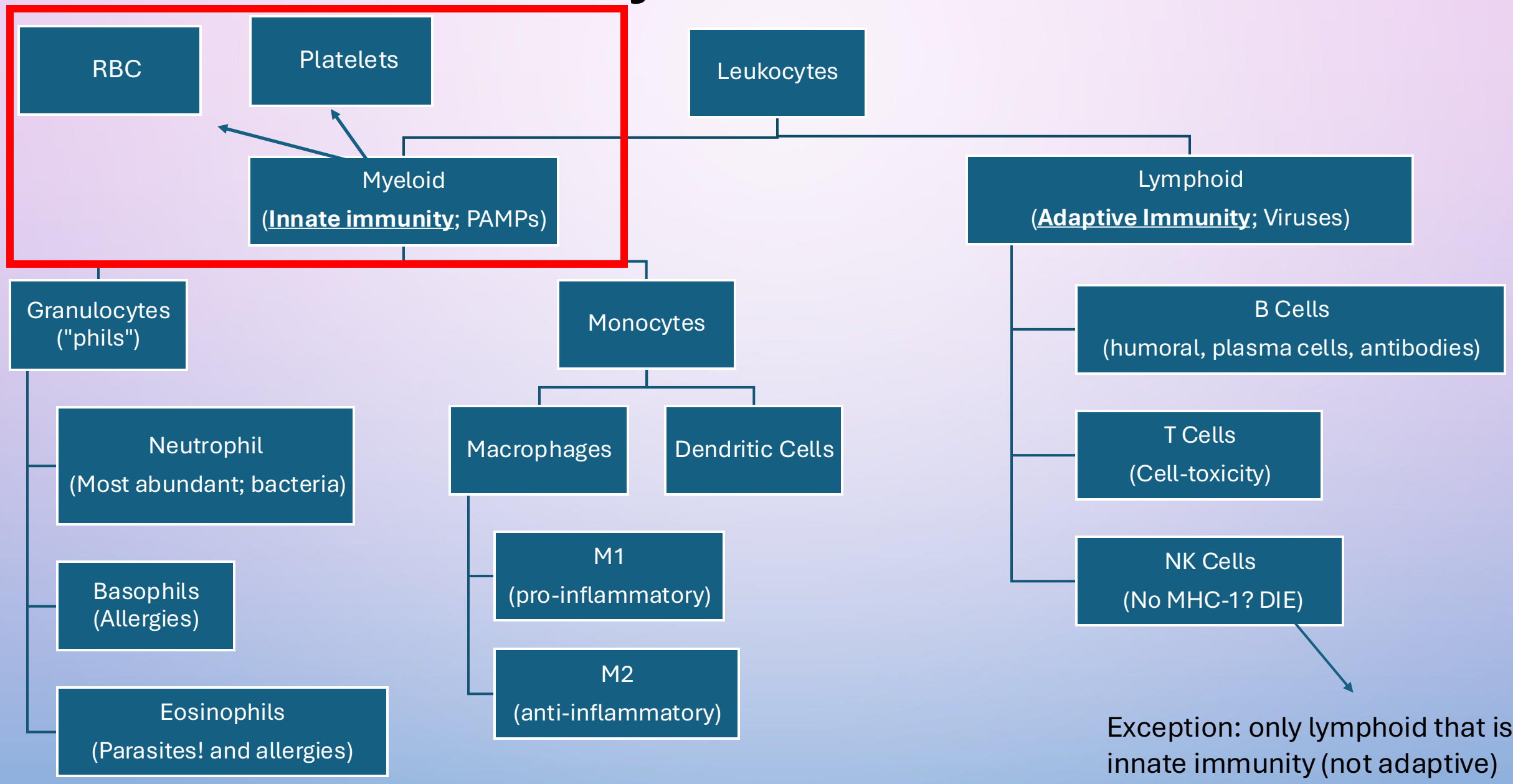


  - **Absolute Neutrophil Count <1.5x10$^3$,** severe= ANC<0.5x10$^3$
  - Single oral temp ≥38.3 or ≥38 for more than 1 hour
  - Common in those with chronic neutropenia or those undergoing chemotherapy
  - Urgent fluid resuscitation and empirical broad-spectrum antibiotics

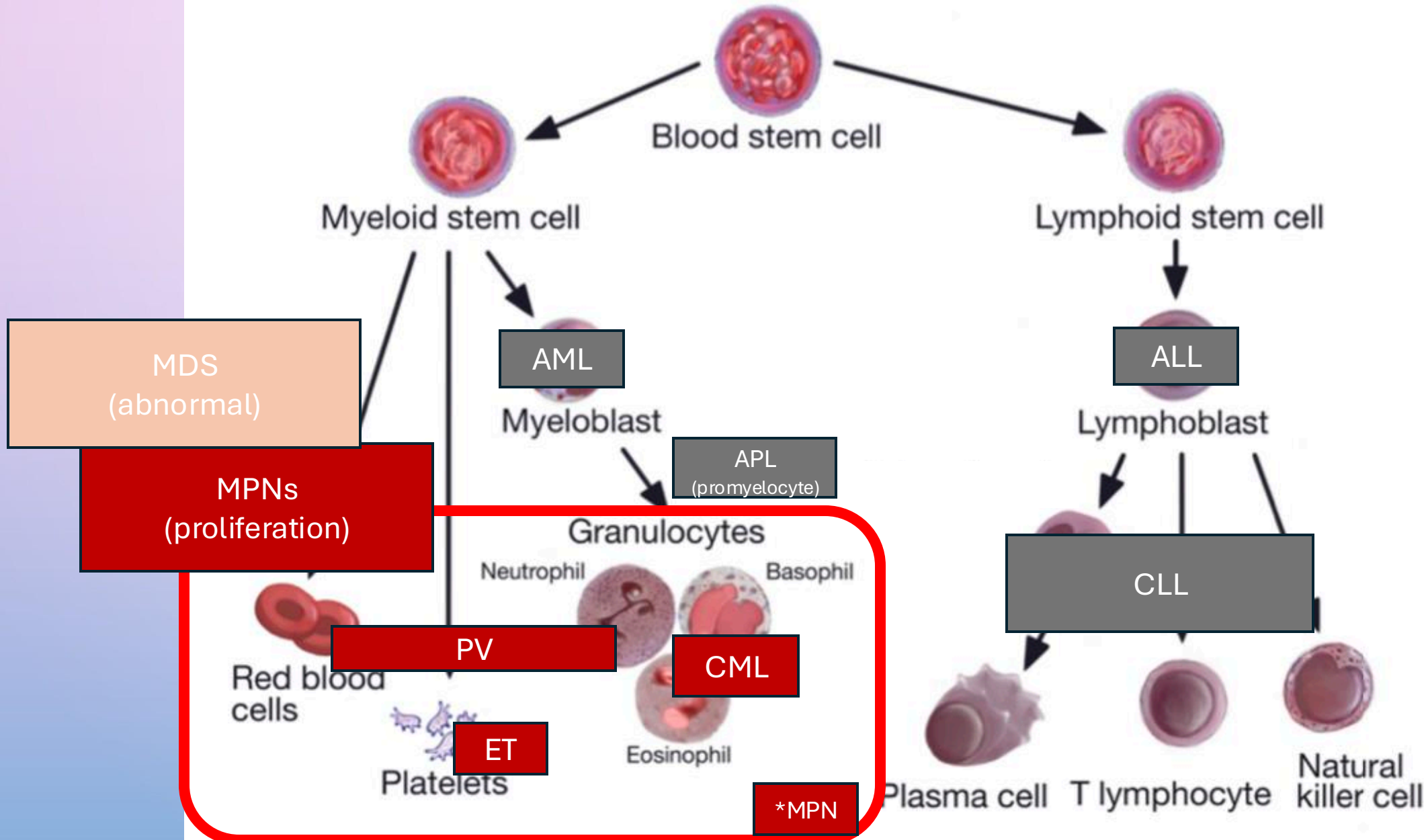
# MPNs (too much myeloid)

In contrast Leukemia = too much leukocytes

# Remember, **Myeloid** does RBCs + Plt too

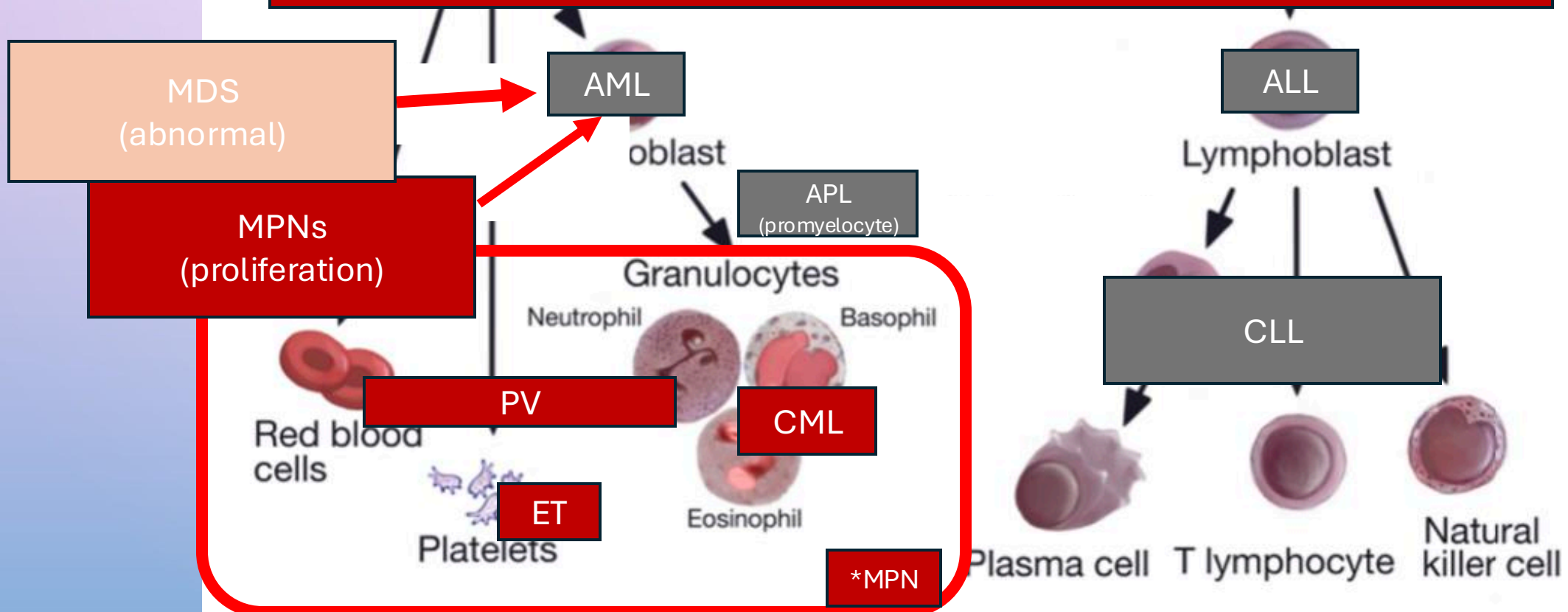


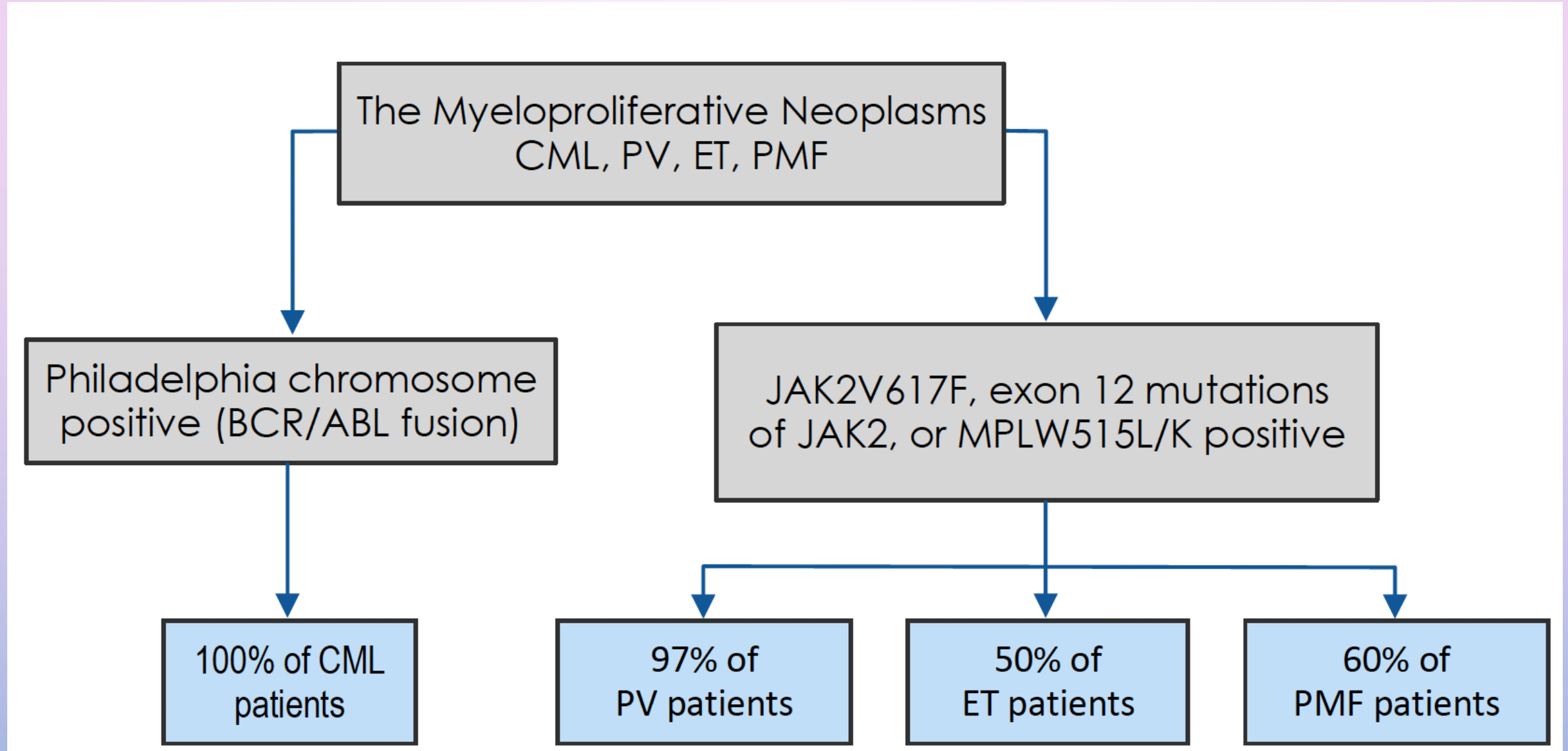
# Blood Cancer Family Tree



# Blood Cancer Family Tree

**CML + MPN + MDS**
**= Risk of converting to AML**



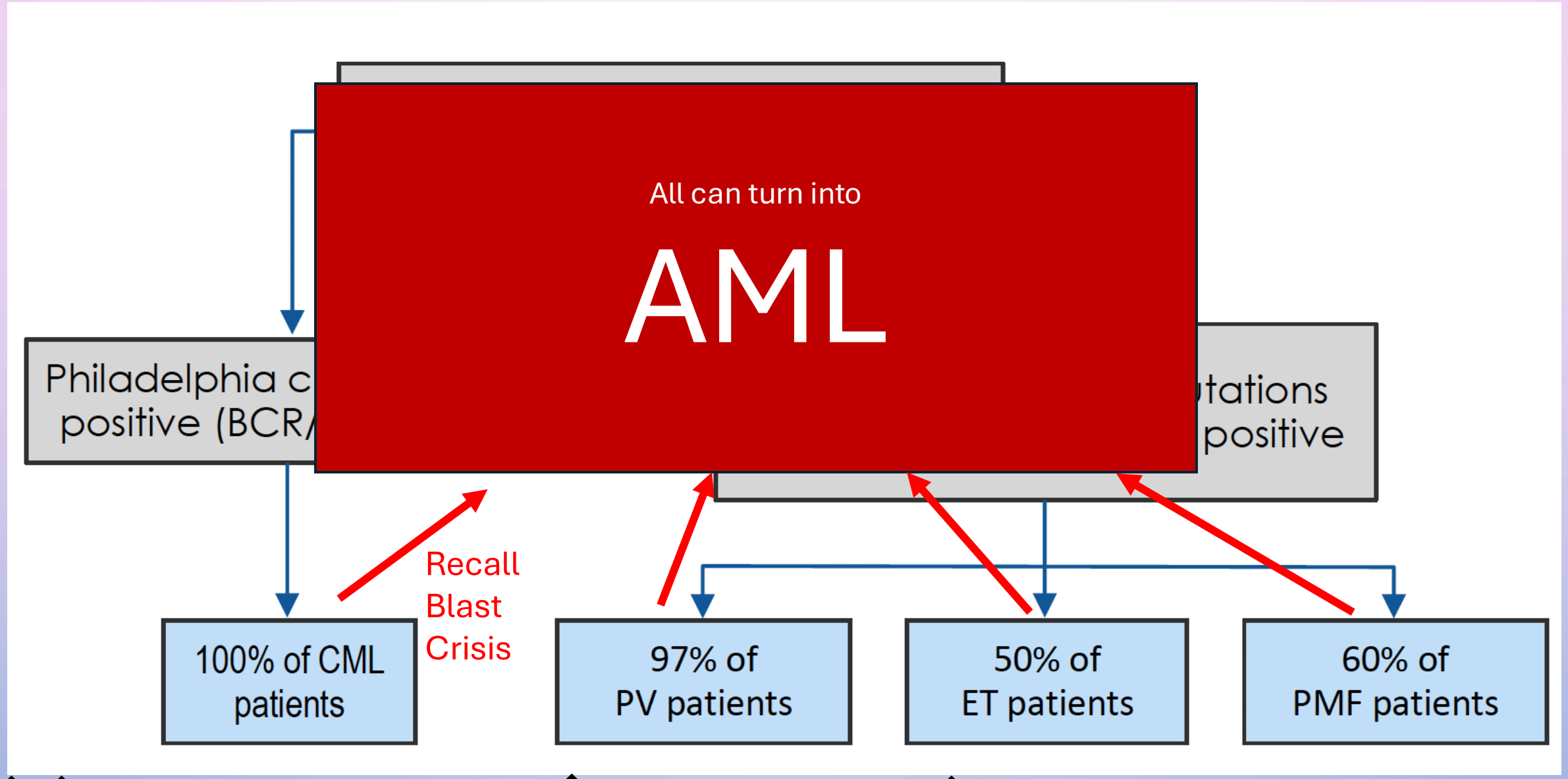



↑↑WBC (leukocytosis)

↑everything (RBC, plt, WBC)

↑Plt ONLY

↓RBC (recall anemia) + Tear Drops

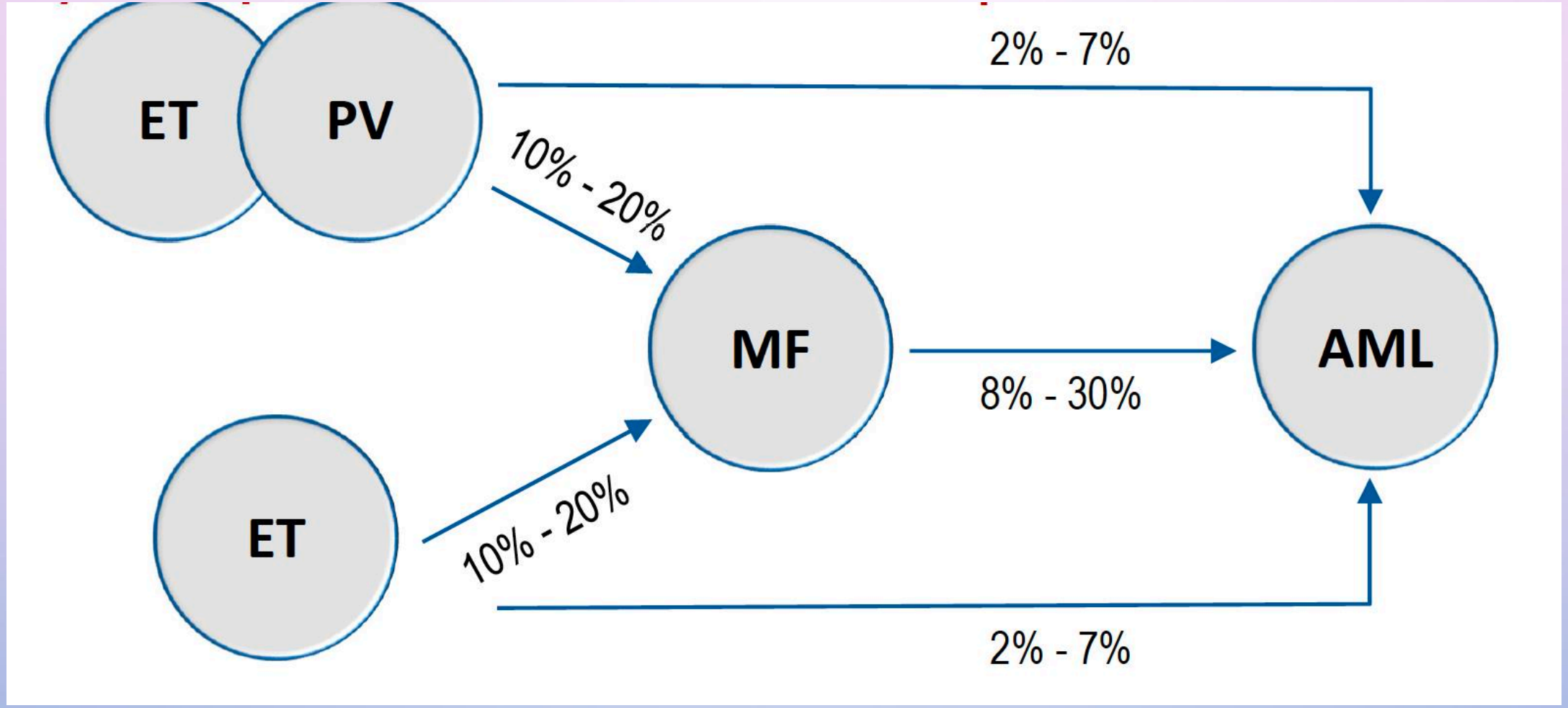



↑↑WBC (leukocytosis)

↑everything (RBC, plt, WBC)

↑Plt ONLY

↓RBC (recall anemia) + Tear Drops


ET
PV
2% - 7%
10% - 20%
MF
AML
8% - 30%
ET
10% - 20%
2% - 7%

# MYELOPROLIFERATIVE NEOPLASMS

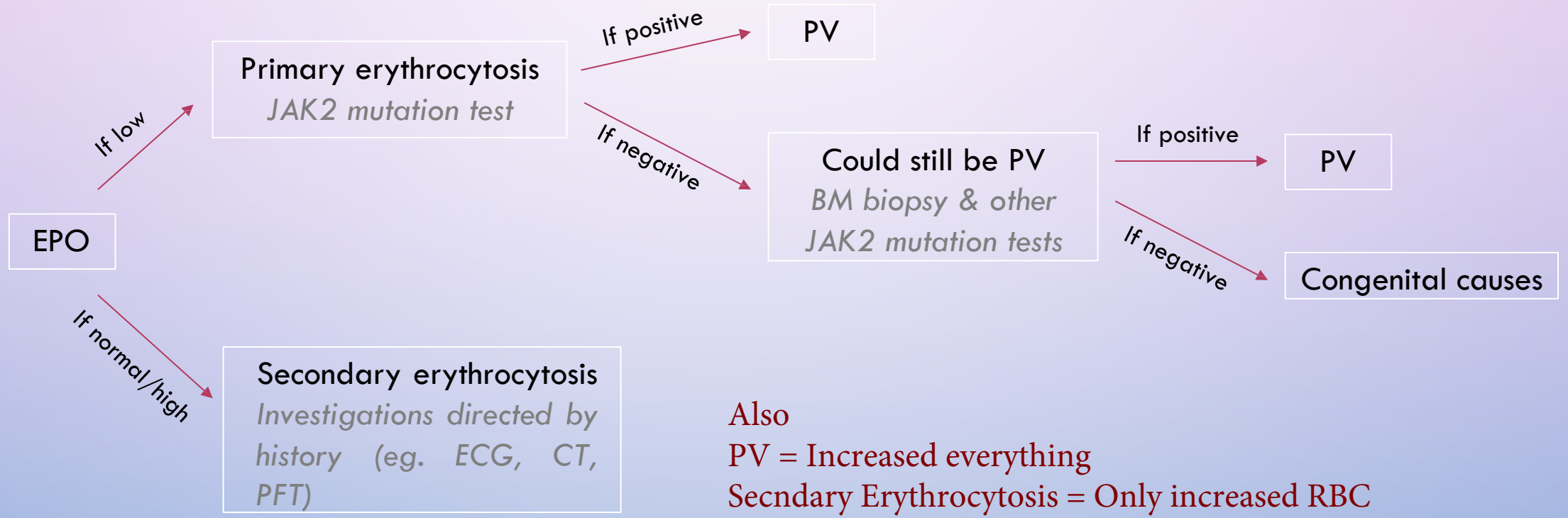
- MPN: proliferation of clonal stem cells that lead to cytosis within the myeloid lineage
  - **Common features:** splenomegaly, increased risk of AML

**Defining features**

| CML | Polycythemia Vera | Essential Thrombocytosis | Myelofibrosis |
|---|---|---|---|
| • Most common cause of malignant **Neutrophilia**<br>• Leukoerythroblastic picture (immature cells)<br>• Philadelphia chrom<br>• (No Jak here) | • Erythrocytosis (↑RBC) …. but also ↑EVERYTHING<br>• **Pruritis after bathing**<br>• JAK2 mutation<br>• Hematocrit >49% or Hb>165 | • Thrombocytosis<br>• JAK2 mutation | • Pancytopenia<br>• Bone marrow fibrosis<br>• Tear drop cells in PB<br>• Leukoerythroblastic picture<br>• JAK2 mutation |

# ERYTHROCYTOSIS ( ↑ RBC)

**Investigative pathway:**



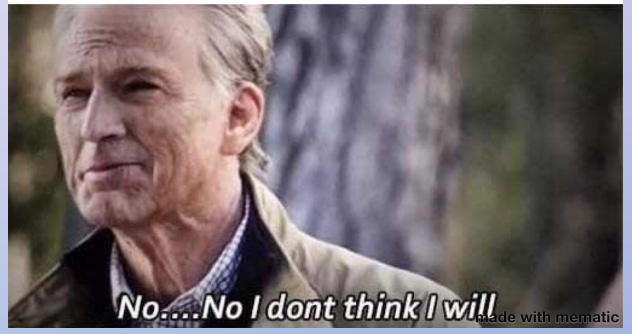

Also
PV = Increased everything
Secndary Erythrocytosis = Only increased RBC

# POLYCYTHEMIA VERA (PV… ↑ everything)

- Most common myeloproliferative neoplasm
- Often associated with elevated WBCs and platelets too
- Due to acquired **JAK2 mutation**
- **Diagnostic investigation:** BM biopsy showing hypercellularity for age and panmyelosis
- **Classic presentation:**
  - Thrombosis ( ↑ plt)
  - Hypertension ( ↑ RBC)
  - ***Pruritis after bathing (aquagenic pruritis)
- Management:
  - If low clotting risk (age < 60, no prior thrombosis): phlebotomy (reduces RBC)
  - If high clotting risk: hydroxyurea (reduces everything)
  - Clotting prevention: low dose aspirin (test for vWBD first), reduce cardiovascular risk factors

Normal erythropoiesis: EPO is gone, you can stop phosphorylating now

JAK2 V617F mutation:



WHAT IS THE BEST MARKER TO DISTINGUISH BETWEEN PRIMARY AND SECONDARY ERYTHROCYTOSIS?

A. Hemoglobin

B. Erythropoietin level

C. Mean corpuscular volume

D. Hematocrit

WHAT IS THE BEST MARKER TO DISTINGUISH BETWEEN PRIMARY AND SECONDARY ERYTHROCYTOSIS?

A. Hemoglobin

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D. Hematocrit

# HOW DO PHLEBOTOMY AND HYDROXYUREA HELP WITH POLYCYTHEMIA VERA?

A. Phlebotomy and hydroxyurea reduce all cell types

B. Phlebotomy reduces RBCs/Hb only and hydroxyurea reduces cell types

C. Phlebotomy reduces all cell types and hydroxyurea reduces only RBCs/Hb

D. Bone marrow transplant is the preferred treatment over phlebotomy or hydroxyurea

# HOW DO PHLEBOTOMY AND HYDROXYUREA HELP WITH POLYCYTHEMIA VERA?

A. Phlebotomy and hydroxyurea reduce all cell types

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D. Bone marrow transplant is the preferred treatment over phlebotomy or hydroxyurea

## WHAT IS THE MOST COMMON CAUSE OF MALIGNANT NEUTROPHILIA?

A. Chronic myelogenous leukemia (CML)
B. Acute myelogenous leukemia (AML)
C. Acute promyelocytic leukemia (APL)
D. Myelodysplastic syndromes (MDS)

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# WHAT IS THE MOST COMMON CAUSE OF BENIGN LYMPHOCYTOSIS?

A. Hypersensitivity reactions (allergies)

B. Acute lymphoblastic leukemia

C. Epstein-Barr Virus

D. Bacterial cellulitis

# WHAT IS THE MOST COMMON CAUSE OF BENIGN LYMPHOCYTOSIS?

A. Hypersensitivity reactions (allergies)

B. Acute lymphoblastic leukemia

C. Epstein-Barr Virus

D. Bacterial cellulitis

A 6-year-old child complains of fatigue, gingival bleeding, epistaxis, lymphadenopathy and bone pain. Which condition is most likely the cause of all these symptoms?

A. The flu
B. ALL
C. Epstein-Barr Virus
D. CML

A 6-year-old child complains of fatigue, gingival bleeding, epistaxis, lymphadenopathy and bone pain. Which condition is most likely the cause of all these symptoms?

↑ lots of blasts in bone marrow hurt

A. The flu

B. ALL → explains all

C. Epstein-Barr Virus

D. CML

A 40-year-old woman presents with sudden fatigue, epistaxis, recurrent infections and lymphadenopathy. The medical staff suspect an acute leukemia. Which of the following confirms the diagnosis of an acute leukemia?

A. >20% blasts in peripheral blood

B. Presence of CD19 marker on flow cytometry

C. Acute onset of symptoms

D. >20% blasts in bone marrow

A 40-year-old woman presents with sudden fatigue, epistaxis, recurrent infections and lymphadenopathy. The medical staff suspect an acute leukemia. Which of the following confirms the diagnosis of an acute leukemia?

A. >20% blasts in peripheral blood → suspicious

B. Presence of CD19 marker on flow cytometry

C. Acute onset of symptoms

D. >20% blasts in bone marrow → confirmed diagnosis

Why does APL have such a high risk of DIC?

A. Malignant promyelocytes consume coagulation factors and platelets
B. Malignant promyelocytes have an anticoagulant effect
C. All acute leukemias have equal risk of DIC
D. Malignant promyelocytes release procoagulants and fibrinolytics

Why does APL have such a high risk of DIC?

A. Malignant promyelocytes consume coagulation factors and platelets

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C. All acute leukemias have equal risk of DIC

D. Malignant promyelocytes release procoagulants and fibrinolytics

What is blinatumomab a treatment for?

A. AML
B. ALL
C. APL
D. CML

What is blinatumomab a treatment for?

A. AML
B. ALL
C. APL
D. CML

Which of the following has the lowest risk of transformation to acute leukemia?

A. CML
B. Myelodysplastic syndrome
C. Myelofibrosis
D. Diffuse large B cell lymphoma

Which of the following has the lowest risk of transformation to acute leukemia?

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C. Myelofibrosis
D. Diffuse large B cell lymphoma

A 42-year-old female with APL presents to the emergency department with new onset fever, SOB, chest pain, jaundice, and bilateral leg swelling. Her HR is 110, BP is 98/60, Temp 39, RR 22 and her Sp02 is 95%. When your nursing staff insert an IV for prompt fluid resuscitation, the site begins to ooze blood. Based on your most likely diagnosis, what would you expect to find in your investigations?

A. Schistocytes on peripheral blood smear
B. Hyperuricemia
C. Absolute Neutrophil Count <1500
D. High conjugated (direct) bilirubin

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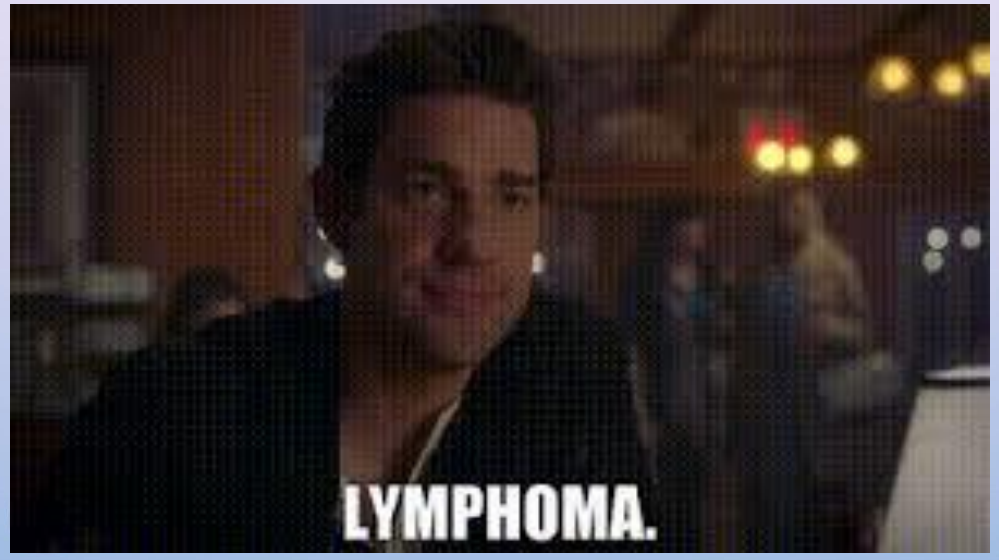
The following treatments are indicated *after* the diagnosis of tumor lysis syndrome has been made EXCEPT:

A. Correction of serum potassium and calcium levels
B. Hemodialysis for patients with signs of renal insufficiency
C. Allopurinol
D. Rasburicase
E. Fluid resuscitation with normal saline

The following treatments are indicated *after* the diagnosis of tumor lysis syndrome has been made EXCEPT:

A. Correction of serum potassium and calcium levels
B. Hemodialysis for patients with signs of renal insufficiency
C. Allopurinol → prophylaxis treatment
D. Rasburicase
E. Fluid resuscitation with normal saline

# Lymphoma



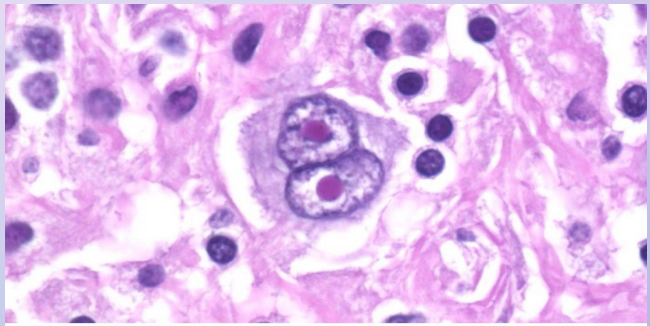
# CONCERNING FEATURES - LYMPHADENOPATHY

- Systemic symptoms (eg. fever, fatigue, night sweats, weight loss)
- Absence of ear, nose, and throat symptoms
- Supraclavicular nodes
- Generalized lymphadenopathy
- Fixed, non-tender, rapidly growing nodes that don't respond to antibiotics
- Abnormal CXR or CBC
- Persistently elevated or rising inflammatory markers

# LYMPHOMAS

| | Hodgkins | Non-Hodgkins |
|---|---|---|
| Defining features | • **R-S cells** reed sternberg cells<br>• Spreads contiguously<br>• young adults<br>• Almost cells all are nodal origin and mature<br>• Presents with pruritis and **nodal pain with alcohol*** | • Cytogenetics useful for classifying (monoclonal)<br>• older adults |
| Subtypes (of note) | • Classical HL:<br>  • **Nodular sclerosing** (most common)<br>  • B cell origin<br>  • **CD20/45 –ve, CD15/30 +ve**<br>• Nodular lymphocyte predominant (NLPHL)<br>  • 5% of HL<br>  • Popcorn cell<br>  • **CD20/45 +ve, CD15/30 -ve** | • **Diffuse large B cell lymphoma**<br>  • **Most common,** very aggressive<br>  • Highly sensitive to chemo - curative intent<br>• **Follicular**<br>  • **Indolent,** slow growing<br>  • Common in elderly, diagnosed late, not curable |
| Treatment | • **ABVD + radiation** (generally good prognosis) | • **CHOP-R** (variable prognosis) BR regimen |



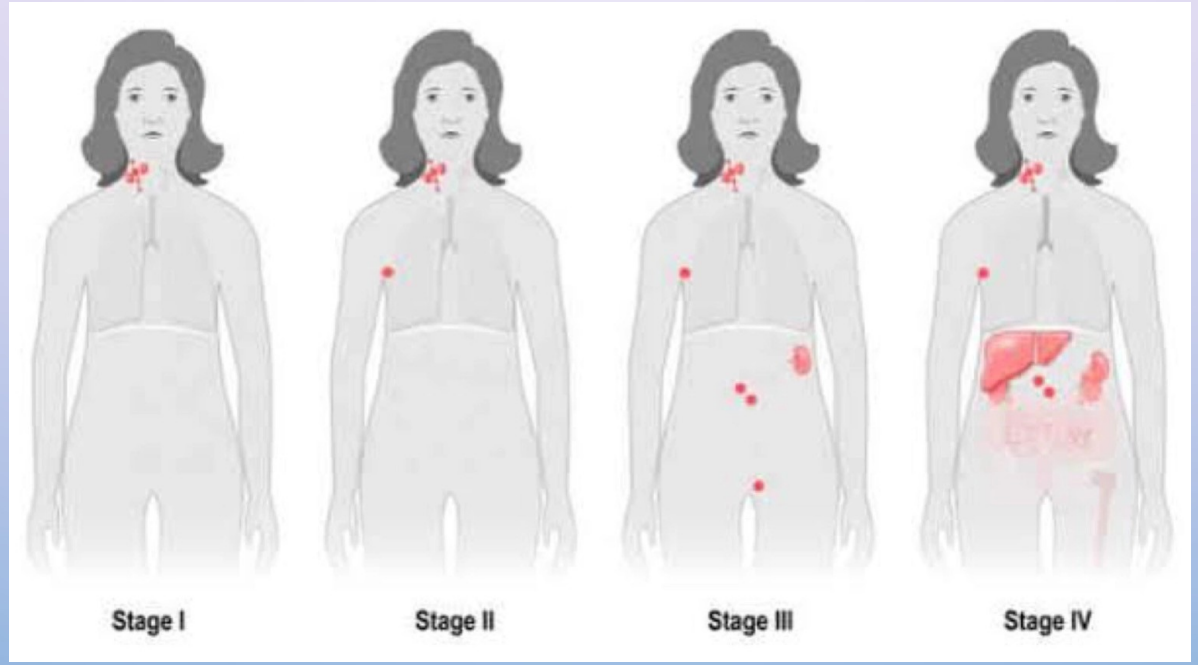





# LYMPHOMA DIAGNOSIS AND STAGING

- Diagnosis requires a biopsy – subtype important to guiding management (especially for NHL)
  - Biopsy only when lymph nodes are >1cm
- Staging requires imaging (CT, PET for functional scan)
  - **Ann Arbor Staging:**
    - 1 = 1 site | 2=2+ sites | 3 = across both sides of diaphragm | 4 = extranodal site
    - A = Absence of symptoms - B = B symptoms (fever, night sweats, 10% weight loss in 6 months)




Fever, night sweats, weight loss (10% body weight in 6 months)

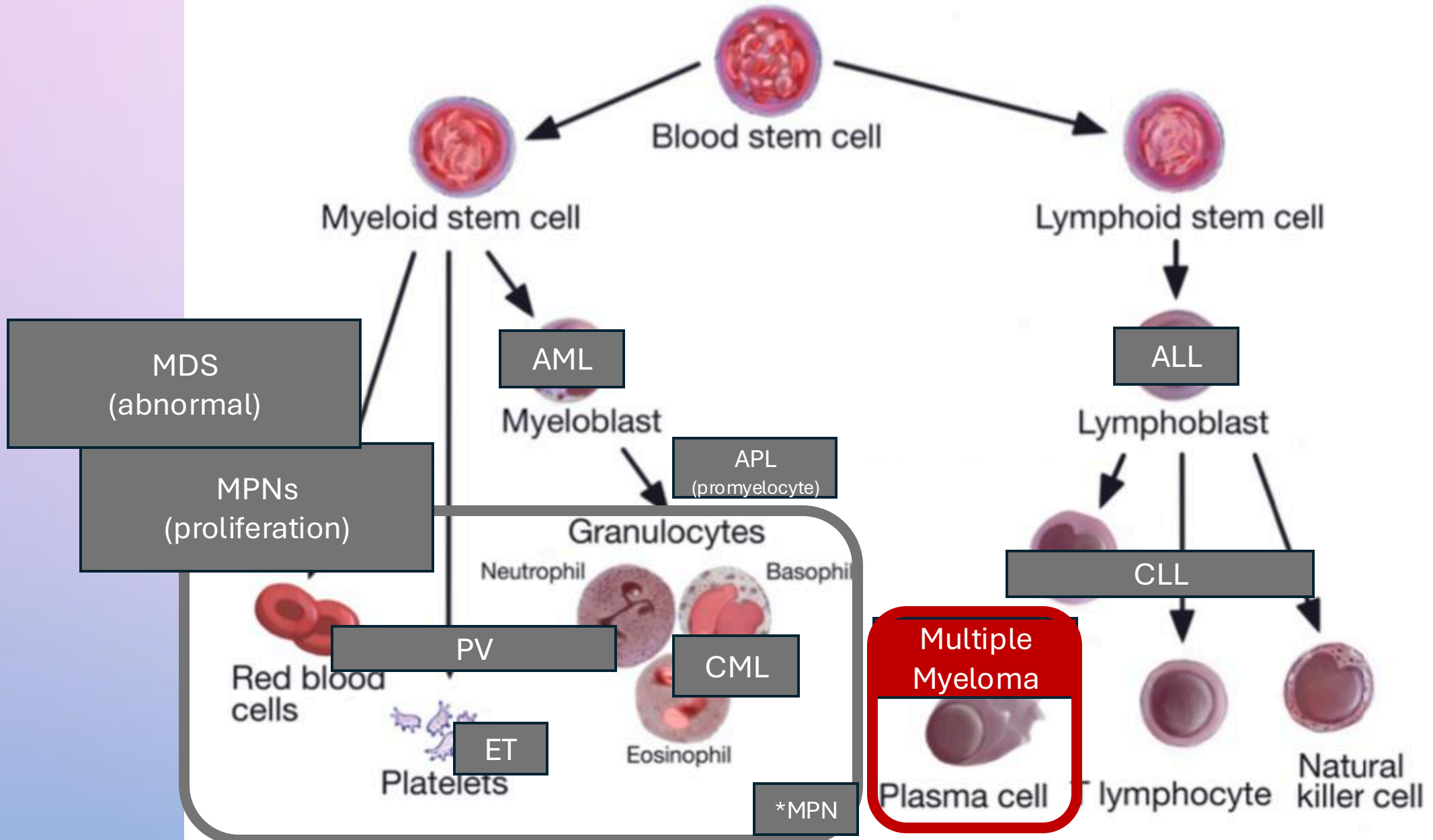
# Prognosis of Lymphomas

- Diffuse Large B-Cell (APLES):
  - Age > 60, Performance on ECOG, ↑ LDH, Extranodal sites > 1, Stage 3+
- Follicular (No LASH):
  - Nodal areas > 4, ↑ LDH, Age > 60, Stage 3+, Hemoglobin < 120
- Early Hodgkin, Stage I/II (No LEE)
  - Nodal area > 2, Large mediastinal mass, ↑ ESR, Extranodal site
- Late Hodgkin, Stage III/IV
  - So many… just if their labs are werid, male and old… it's bad

# Myeloma



# Blood Cancer Family Tree



# MULTIPLE MYELOMA

- Excess and uncontrolled monoclonal antibody production by plasma cells
- Diagnosed with **serum protein electrophoresis**

**Development:**

- Monoclonal gammopathy of undeterminate significance (MGUS) – pre-phase
  - Asymptomatic, **M protein abnormalities detectable**
  - BM < 10% plasma cells
- Smolder myeloma
  - Asymptomatic
  - **BM > 10% plasma cells**
- Overt multiple myeloma
  - **Symptomatic:**
- Plasma cell leukemia:
  - **Plasma cells in blood > 20%**





# Overt Multiple Myeloma (sorry it's so dense)

- **Diagnosis:**
  - ≥10% monoclonal plasma cells in bone marrow
  - M-protein (serum or urine electrophoresis or free light chains)
  - **CRAB (↑ Calcium, Renal damage, Anemia, Bone lesion)**

- **Prognosis (ISS)**
  - ISS 1 (60m prognosis): $\beta_2$M < 3.5 mg/L and albumin ≥ 35 g/L
  - ISS 2 (40m prognosis): in the middle
  - ISS 3 (20m prognosis): $\beta_2$M ≥ 5.5 mg/L OR HIGH LDH / high-risk FISH mutations
  - Plasmocytoma (solid tumor): Solitary = good prognosis ; Multiple = End-stage

- **Treatments**
  - Anti-myeloma therapy (not really taught)
  - Cord compression = Urgent surgery
  - Treat symptoms (Fractures = ortho, hypercalcemia = Hydration + Bisphosphonates, renal failure = dialysis)

- **Complications:**
  - Amyloidosis: If MM creates insoluble (amyloidotic) proteins, you get amyloidosis
  - Pancytopenia: either MM or the anti-myeloma treatment will wipe out your bone marrow

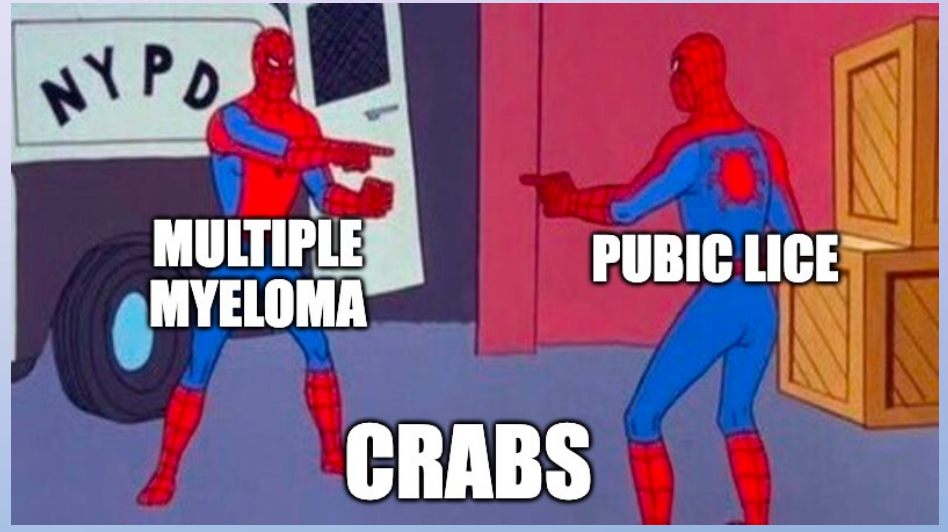
# WHAT DOES THE ACRONYM CRAB REPRESENT IN MM?

A. Hypocalcemia, renal insufficiency, anemia, breast tenderness
B. Hypercalcemia, renal insufficiency, anemia, bone pain/lesions
C. Hypocalcemia, renal insufficiency, anemia, bone pain/lesions
D. Increased risk of public lice



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A 60-year-old man presents for his annual visit with his physician. Upon physical examination, enlarged non-tender and fixed right cervical lymph nodes are found. The patient explains that for the last three years he has noticed his right cervical lymph nodes to be enlarged. He mentions that sometimes they are bigger and sometimes smaller in size. The rest of the physical examination show splenomegaly and no other noticeable findings. A CBC and excisional biopsy of an affected lymph node is performed. A diagnosis of Follicular lymphoma is made. What is the clinical severity of this type of lymphoma and its prognosis, assuming treatment is attempted?

A. Indolent lymphoma, no complete remission possible
B. Aggressive lymphoma, complete remission possible
C. Highly aggressive lymphoma, variable prognosis
D. Indolent lymphoma, complete remission possible
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A. Indolent lymphoma, no complete remission possible → slow growing, not able to fully get rid of
B. Aggressive lymphoma, complete remission possible
C. Highly aggressive lymphoma, variable prognosis
D. Indolent lymphoma, complete remission possible
E. None of the above

WHICH METHOD IS GOLD STANDARD FOR DIAGNOSIS OF LYMPHOMA?

A. Fine needle aspiration
B. Bone marrow biopsy
C. Excisional Biopsy
D. PET-CT

# WHICH METHOD IS GOLD STANDARD FOR DIAGNOSIS OF LYMPHOMA?

A. Fine needle aspiration
B. Bone marrow biopsy
C. Excisional Biopsy → gather lots of information
D. PET-CT

A 25-year-old male presents to his family physician because of painless lymphadenopathy. He explains that he has had a “firm bump on the left side of his neck for the past 12 weeks but thought nothing of it”. Last week, after an office party where he consumed 10 beers, he felt pain at the site previously mentioned. He explains having lost a lot of weight in the last three months (he used to weigh 250lb and now weighs 190lb) without any changes in his active lifestyle and nutrition. He sometimes wakes up in the middle of the night drenched in sweat and has to change the bedding. An excisional biopsy of the single enlarged cervical lymph node is performed and demonstrates cells that are CD15 and CD30+ positive. A chest XR and abdominal CT demonstrate no other affected sites. Using the Ann Arbor Stage, what stage is the patient?

A. Stage 1B

B. Stage 1A

C. Stage 2B

D. Stage 2A

E. Ann Arbor Staging is only for Non-Hodgkin Lymphoma and this patient has Hodgkin

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use for both

# Other Cancer Stuff



# MEDIASTINAL MASSES

5Ts
Most Important

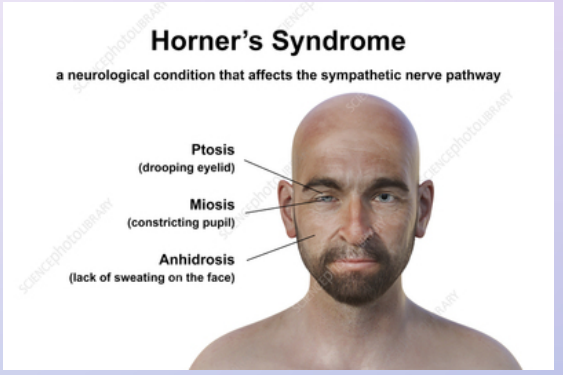
| Anterior compartment<br>5Ts | Middle compartment | Posterior compartment |
|---|---|---|
| ➢Thymus<br>➢Terrible Lymphoma<br>➢Teratoma and Germ cell tumor<br>➢Thyroid<br>➢Thoracic aorta<br>➢Uncommon<br>• Parathyroid adenoma<br>• Hemangioma<br>• Lipoma<br>• Liposarcoma<br>• Fibroma<br>• Fibrosarcoma | ➢Lymphadenopathy (lymphoma, sarcoid, metastatic lung cancer)<br>➢Benign cystic tumor (20%)<br>• Bronchogenic<br>• Pericardial<br>• Enteric<br>➢Esophageal tumors<br>➢Vascular masses and enlargement<br>**Everything Else - Soft tissues** | ➢Neurogenic tumors<br>➢Meningoceles<br>➢Thoracic spine lesions<br>**Neural Stuff** |

★ 5 Ts for DDx of Anterior Mediastinal Mass- Thymoma, Teratoma, Terrible Lymphadenopathy, Thoracic Aortic Aneurysm, Thyroid Mass

# MEDIASTINAL MASSES

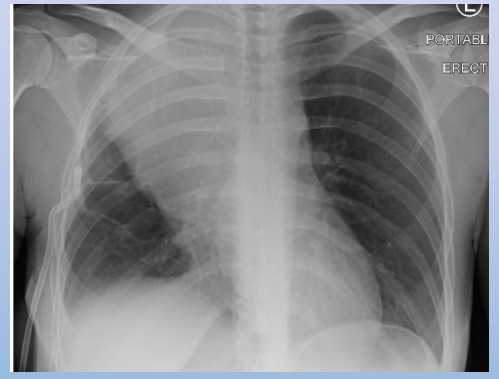


- **Superior vena cava sign:** from obstruction of the SVC
  - Edema of face, neck, upper chest
  - Difficulty breathing, swallowing
  - Pemberton's sign




- **Horner's syndrome:** disruption of sympathetic nerve supply to the face causes unilateral Miosis (constricted pupil) + ptosis (drooping eye lid) + Anhidrosis (lack of sweating)

- **X Ray:** Widened Mediastinum



# Quick Tumor Markers

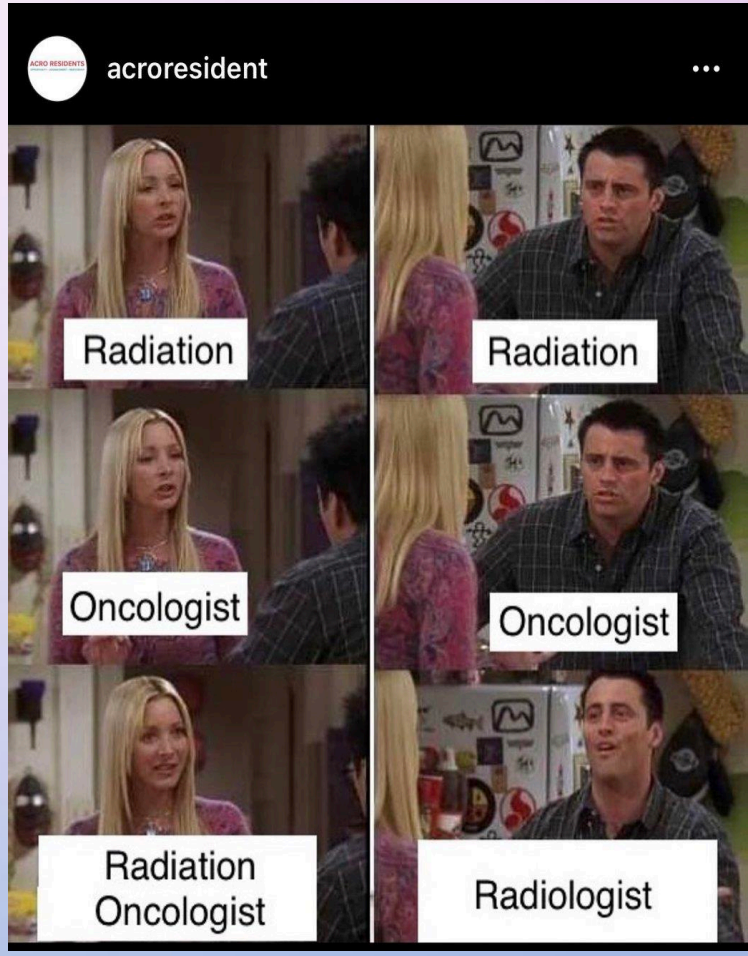
| Tumor marker | DDx |
| --- | --- |
| Anti-AchR (acetylcholine receptor) | Thymic tumor (esp in myasthenia gravis) |
| AFP (alpha-fetoprotein) | Germ cell tumors |
| Beta-HCG (human choriogonadotropin) | Germ cell tumors |
| LDH (lactate dehydrogenase) | Lymphoma |

# Rad Onc (all you need to know)

- **Most Common Form:** External Beam Radiation Therapy (EBRT)

- **4 R's**
  - Repair (normal cells can repair)
  - Repopulation (normal cells can regrow)
  - Redistribution (tumors cells shift to sensitive phases)
  - Reoxygenation (tumors cells oxygenate = easier to kill)

- **Fractionation**
  - Divide total dose into small daily fractions
  - Exploits better repair in normal cells vs. tumor cells
  - Standard: 1.8–2 Gy/fx  Hypo: >2 Gy/fx  Hyper: <1.8 Gy/fx



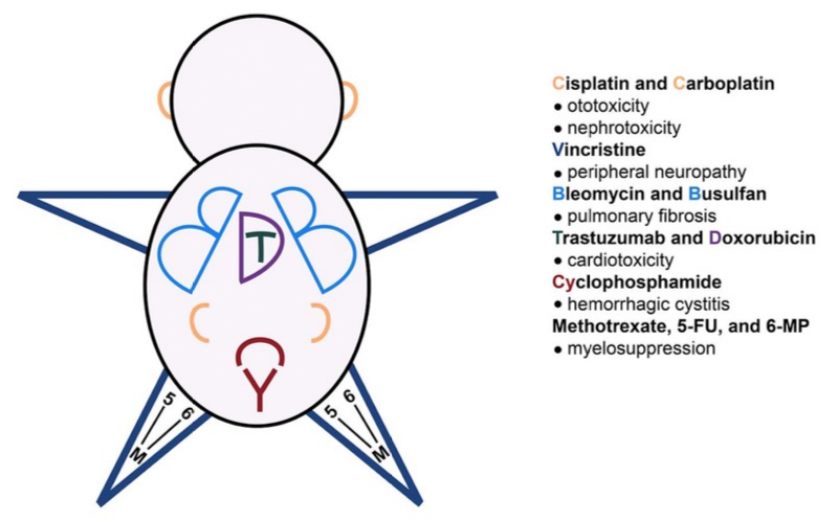
# RADIATION TOXICITY

- **Subacute:**
  - Myelosuppression
  - Radiation pneumonitis
  - Radiation pericarditis
  - L'Hermitte's sign (parasthesia into arms or legs with neck flexion)
  - Dry mouth
  - Fatigue
- **Late:**
  - Hypothyroidism
  - Infertility
  - Activation of latent viruses (eg. herpes zoster)
  - Secondary malignancy



# DRUGS

**Side effects lower yield imo*







| Class | Indications | Examples |
|---|---|---|
| Glucocorticoids | DLBCL (prednisone in CHOP-R) | prednisone, dexamethasone |
| Alkylating agents | General chemo (for many cancers), CHOP-R (cyclo) | cisplastin, cyclophosphamide |
| Anti-metabolites | General chemo | methotrexate, 5-FU, 6-MP |
| Anti-tumour antibiotics | CHOP-R (doxorubicin), ABVD for HL (bleomycin + doxo) | bleomycin, daunorubicin, doxorubicin (Adriamycin) |
| Topoisomerase inhibitors | General chemo | Etoposide, anthracyclines |
| Anti-microtubule agents | CHOP-R (oncovin), ABVD (vinblastine) | Vincristine (oncovin), vinblastine |
| Monoclonal antibodies | CHOP-R, MM (daratumumab) | rituximab, daratumumab |
| Tyrosine kinase inhibitor | CML (imatinib), CLL (ibrutinib) | Imatinib, ibrutinib |
| Differentiating molecules | APL | ATRA |

C- cyclophosphamide
H- hydroxyldaunorubicin (doxorubicin)
O- oncovin
P- prednisone
R- rituximab

For diffuse large B-cell lymphoma*

A- adriamycin (doxorubicin)
B- bleomycin
V- vinblastine
D- dacarbazine

For Hodgkin's lymphoma*

# Rituximab

- Monoclonal anitbody
- Targets CD20 on surface of B-cell lymphoma cells
- The “R” in “CHOP-R”
- Treats
  - Lymphomas
  - CLL
  - ITP and TTP **

# GENERAL TIPS

- Review weekly quizzes and readiness assessments
- Review Dr. Lam's jeopardy questions
- Don't need to know everything to ask on history or every single symptom – just the distinguishing features of each (eg. aquagentic pruritis for PV)
- Understand the labs/investigations and what each result indicates




- Be familiar with each of the blood cell types (including full WBC differential), what it's called when they're elevated and lowered, and the primary and secondary causes of each abnormality