c) Anemias resulting from bone marrow failure:

1. Aplastic anemia (AA): Normochromic, macrocytic

- Multipotent myeloid stem cells are damaged → ↓hematopoietic cells, peripheral blood pancytopenia (all blood cells are decreased except lymphocytes) → leukopenia → severe infections → thrombocytopenia → bleeding ⇒ So AA is considered an emergency that needs immediate intervention.

a. Acquired AA: extrinsic factors → ↑antibodies → react with stem cells → antigen cross-reactivity → activates T-lymphocytes to destroy stem cells.

* immunosuppressive drugs restore bone marrow.

b. Inherited AA: defects in telomerase enzymes → stem cells die early
↳ ↑ abnormal antigen attracting T-cells

* Fanconi anemia: special form of AA, defect in DNA repair proteins.

2. Pure red cell aplasia: affects only erythroid cells.

a. congenital: diamond-blackfan anemia

b. acquired: parvovirus B19 infection, autoimmune diseases

3. Myelophthisic anemia: infiltration (due to cancer, granulomatous disease "tuberculosis", storage disease "gaucher disease") → physical damage to hematopoietic cells, immature granulocytic & erythroid precursors in peripheral blood → leucoerythroblastic anemia (↑nucleated RBCs), hypercellular bone marrow, thrombocytopenia → skin bleeding neutropenia → infections & death, pancytopenia.

4. Anemia of renal disease: ↓erythropoietin, ↓reticulocytes

- Patients with uremia develop abnormal platelets function (bleeding) despite normal count. And echinocytes "burr cells" appear (RBCs appear with many projection).

- There is no correlation between kidney function & severity of anemia → So if we measured serum creatinine (high creatinines mean low kidney functions) it does <u>not</u> give an indication about the degree of anemia.

5. Anemia of liver disease: we need a multifactorial process to cause the anemia: decreased liver synthesis of clotting factors / bleeding from varices / decreased synthesis of transferrin.
- Acanthocytes (spur cells) can be seen "longer larger than burr cells".

6. Anemia of hypothyroidism: normocytic or macrocytic.
- ↓ thyroid hormones → ↓ erythropoiesis

7. Myelodysplastic syndrome: macrocytic
- neoplastic disease; stem cells have prolonged survival but defective maturation.
- refractory to treatment (doesn't respond to treatment).

Hemolytic anemia

- Life span of RBCs < 120 days
- Erythroid hyperplasia, reticulocytosis, extramedullary hematopoiesis.
- Destructed RBCs → ↑ free hemoglobin (toxic) → haptoglobin binds to it → ↓ serum haptoglobin.
- Jaundice.

* According to main site of hemolysis:
- Extravascular: primarily in spleen, patients have jaundice, pigmented gall bladder stones & splenomegaly.
- Intravascular: → hemoglobinemia, hemoglobinurea, hemosiderinuria & iron deficiency.

* According to cause of hemolysis:
- Extracorpuscular: antibodies, microorganisms.
- Intracorpuscular: enzymatic deficiencies, thalassemia.

Thalassemia (autosomal recessive)

- Deficiency in one of the globin chains → relative increase in other one → instability & hemolysis.
- Patients are resistant to infection by malaria falciparum.
- ↓hemoglobin → target cell appearance.
- Hypochromic, microcytic, reticulocytosis, basophilic stippling (small blue dots - remnants of ribosomes).

Alpha Thal.

- Deletion of α-chain (encoded by 2 genes on chromosome 16).
  - in 1, 2 gene(s) → silent carrier "asymptomatic".
  - if 3 genes → Hemoglobin H disease (extra β-chains bind each other → HgH "tetramer". Extra γ-chains → Hg-Barts "tetramer").
  - if 4 genes → hydrops fetalis (No HbA, HbA2, or HbF).

Beta Thal.

- Point mutations in β-chain (encoded by 1 gene on chromosome 11).
- Extra α-chain remain uncoupled → solid particle in the cytoplasm → hemolysis of RBCs

β = normal production of β-chain
β0 = no production β+ = decreased production

β/β+ : silent carrier or mild anemia (Thal-minor/trait) : normal lifespan RBCs are hypochromic & microcytic
β+/β+ : Thalassemia intermedia : moderate lifelong anemia (like HbH disease)
β0/β0 or β0/β+ : Thal-major (Cooley anemia) : don't require regular blood transfusion.

↑poikilocytosis & nucleated RBCs, ↑normoblast (nRBC) filling bone marrow spaces & expanding into the bone → abnormal bone growth (bones appear enlarged, thick & full of blood), hemosiderosis (high erythropoietin inhibits hepcidin synthesis)

- Can be ameliorated by regular blood transfusion.

* Diagnosis: hemoglobin electrophoresis.
- HbA2 is used for the diagnoses (normal range: 3.5%)
  ↳ in all types of β-thal.: ↑
- In β-thal major: HbA is absent or markedly decreased.
- In HbH disease: HbH & Hb Barts bands appear.
- In α-thal carrier & minor: no abnormality is found (↓ α-chains equal ↓ in HbA, HbA2 & HbF).

Sickle cell anemia (autosomal recessive)

- Substitution in β chain of hemoglobin at codon 6 (hydrophilic glutamic acid → hydrophobic valine amino acid)
- Patients are resistant to infection by malaria falciparum.
  ↳ homozygous (both genes are mutant): sickle cell disease → have HgS band but HgA is absent.
  ↳ heterozygous (one gene is mutant): sickle cell carrier → both HgA & HgS are present
- In deoxygenated state: HgS tends to polymerize → RBCs become sickle in shape (this change is reversible by re-oxygenation).
- In carrier patients: HgA interacts with HgS → inhibit polymerization
- We can treat patients with sickle cell anemia by ↑ HbF (high in newborns, decreases after the age of 6 months).
- ↑ HgS promotes sickling (dehydration & acidosis).
- Patients with additional α-thalassemia have lesser amount of HgS → sickling ↓

*Symptomes:
1. Chronic moderate severe hemolytic anemia: manifests after the age of 6 months, dependant on the fraction of sickled cells.
2. Vaso-occlusive crisis: sickled cells can form thrombus without the need of platelets & coagulation system, independant on fraction of sickled cells.
3. Hand foot syndrome: pain in digits
4. Acute chest syndrome 5. Stroke 6. Myocardial infraction.
7. Retinopathy: the blood vessels of the retina can directly cause thrombosis & ischemia. 8. Autosplenectomy
9. Aplastic crisis: infection by parvovirus B19, self-limited.
10. Susceptibility for encapsulated bacteria (pneumococcus & salmonella).

*Diagnosis:
- Routine blood smear: presence of sickle cells & target cells.
- Sickling test: we add hypoxic-agent "promote sickling".
- Hemoglobin electrapheresis. - DNA testing

Glucose 6-phosphate dehydrogenase deficiency (recessive)

- X-linked, this enzyme reduces $NADP^+$ to NADPH (important for the production of reduced glutathione → protects the cell from free radicals).
- G6PD → intravascular hemolysis

*Triggers of hemolysis:
- Infection (↑ ROS) - Antibiotic (sulfonamides, nitrofurantion)
- Large dose of aspirin, Vitamin K, antimalaria drugs (primaquine)
- Fava beans
- ↑oxidants → hemoglobin denaturation → solid particles (Heinz bodies) "are stained by supravital stain → dark dots"
- Other cells lose deformability & partially phagocytosed inside spleen → Bite cells

- G6PD-A type: ↓ G6PD, bonemarrow compensate by producing new RBCs.
- G6PD-Mediterranian: qualitative defect of enzyme (low function), severe symptomes.

Immune hemolytic anemia (IHA)

- Auto-antibodies against RBC, detected by Coombs test:
- Direct test: we add synthetic antibodies that targets the normal human ones which are attached to RBC → agglutination → disease.
- Indirect test: Patient's serum is added to "test RBCs" → have certain surface proteins (antigens) targeted by auto-antibodies in IHA.

Warm type IHA

- IgG, high affinity
- Binding occurs inside the body core (37°C)
- When RBCs reach the spleen, the macrophages remove the IgG.
- RBCs is biconcave but by removing multiple areas → ↓ surface area, appears like a ball
- Causes: associated with SLE, penicillin (coats the RBCs), α-methyl dopa
- mild chronic anemia, reticulocytosis & splenomegaly
  ↳ due to extravascular hemolysis
- Spherocyte
- Polychromasia.

Cold type IHA

- IgM, low affinity
- Binding occurs in peripheral area (<30°C)
- C3b follow IgM & bind RBCs. When RBCs return to core circulation, IgM dissociates & when it reaches to the spleen, C3b are removed by macrophages.
- IgM binds 5 RBCs → block small capillaries → Raynaud phenomenon
- Transient form (acute): after infection by mycoplasma pneumonia, infectious mononucleosis, - mild & self limited.
- Chronic persistant form: in B-cell lymphoma
- large clumps of RBCs
- Spherocyte

Hereditary spherocytosis

- Mutation is RBC cell membrane skeleton (ankyrin, band3 or spectrin), little cytoplasm is lost & the cell's surface area is decreased.
- Are nondeformable, entrapped in small vessels in spleen → extravascular hemolysis.
- Can function normally → So if we remove the spleen, spherocytes will persist in peripheral blood → anemia is corrected.
- Are small in size (↓MCV), normal MCH "hemoglobin content didn't change", ↑MCHC, don't have central pallor
- ↑fragility in hypotonic solution.

Paroxysmal nocturnal hemoglobinuria (PNH)

- Mutation in PIGA gene → deficiency in phosphatidylinositol glycan (PIG). Mutation occurs in BM stem cell (leukocytes, RBCs & platelets are all affected).
- C5b-C9 → create pores in the cell membrane
- In normal situations: blood cells protect themselves by CD55 & CD59 (normally attached to PIG)
- In PNH: RBCs, WBCs & platelets are lysed.
- Can cause thrombosis.
- During sleep: ↑CO_2, ↓blood PH, ↑complement system, ↑hemolysis

Traumatic hemolysis

- Direct physical force or turbulence → lysis of RBCs.
- Prosthetic heart valves, repetitive physical pounding (marathon, boxing, marching), disseminated thrombi (microangiopathic hemolytic anemia).
- Schistocytoss "the hallmark": torn & distorted RBCs.

Polycythemia

- ↑ total RBC mass
- Erythrocytosis : ↑ RBCs number.
- Relative polycythemia : secondary to ↓ plasma volume (water dehydration, severe diarrhea, diuretics).
- * Absolute polycythemia : true increase in RBC mass, secondary ("or primary") to ↑ BM production

1- Primary : polycythemia vera (→ neoplasm) : low erythropoietin, splenomegaly (negative feedback)

2- Secondary : adaptive (high altitude, cyanotic heart disease), paraneoplastic (renal cancer), surreptitious (endurance athletes).
↑ erythropoietin, no splenomegaly