

Hematology and Oncology

“You’re always somebody’s type! (blood type, that is)”

—BloodLink

“The best blood will at some time get into a fool or a mosquito.”

—Austin O’Malley

“A life touched by cancer is not a life destroyed by cancer.”

—Drew Boswell, *Climbing the Cancer Mountain*

“Without hair, a queen is still a queen.”

—Prajakta Mhadnak

“Blood can circulate forever if you keep donating it.”

—Anonymous

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.

Please note that solid tumors are covered in their respective organ system chapters.

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► HEMATOLOGY AND ONCOLOGY—EMBRYOLOGY

Fetal erythropoiesis

Fetal erythropoiesis occurs in:

- Yolk sac (3–8 weeks)
- Liver (6 weeks–birth)
- Spleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

Young liver synthesizes blood.

Hemoglobin development

Embryonic globins: ζ and ϵ .

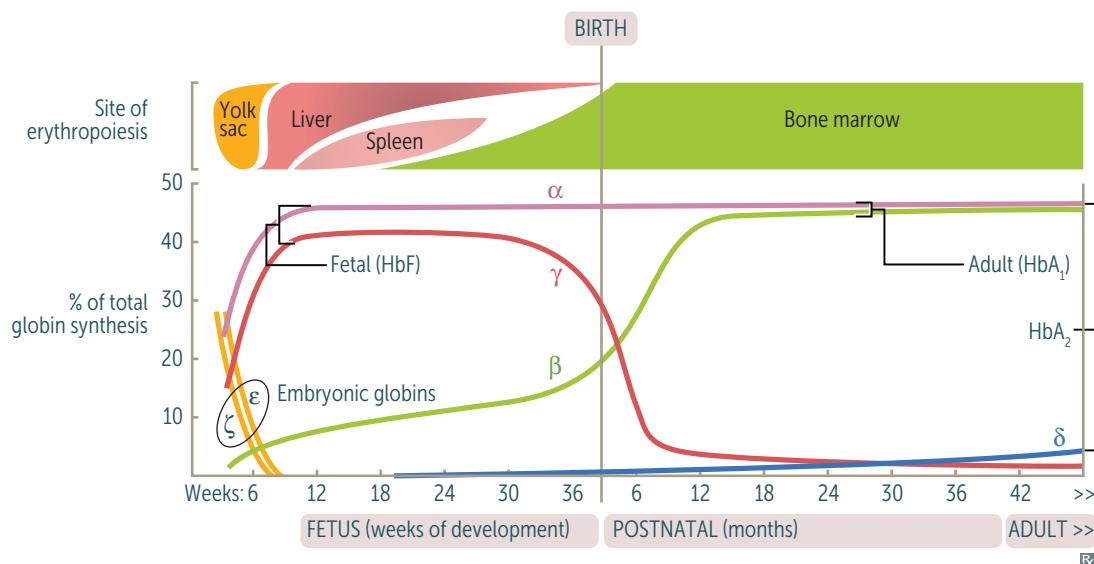
Fetal hemoglobin (HbF) = $\alpha_2\gamma_2$.

Adult hemoglobin (HbA_1) = $\alpha_2\beta_2$.

HbF has higher affinity for O_2 due to less avid binding of 2,3-BPG, allowing HbF to extract O_2 from maternal hemoglobin (HbA_1 and HbA_2) across the placenta. HbA_2 ($\alpha_2\delta_2$) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:

Alpha always; gamma goes, beta becomes.



Blood groups

	ABO classification				Rh classification	
	A	B	AB	O	Rh+	Rh-
RBC type						
Group antigens on RBC surface	A 	B 	A & B 	NONE	Rh (D) 	NONE
Antibodies in plasma	Anti-B 	Anti-A 	NONE	Anti-A Anti-B IgG (predominantly), IgM	NONE	Anti-D
Clinical relevance						
Compatible RBC types to receive	A, O	B, O	AB, A, B, O	O	Rh+, Rh-	Rh-
Compatible RBC types to donate	A, AB	B, AB	AB	A, B, AB, O	Rh+	Rh+, Rh-

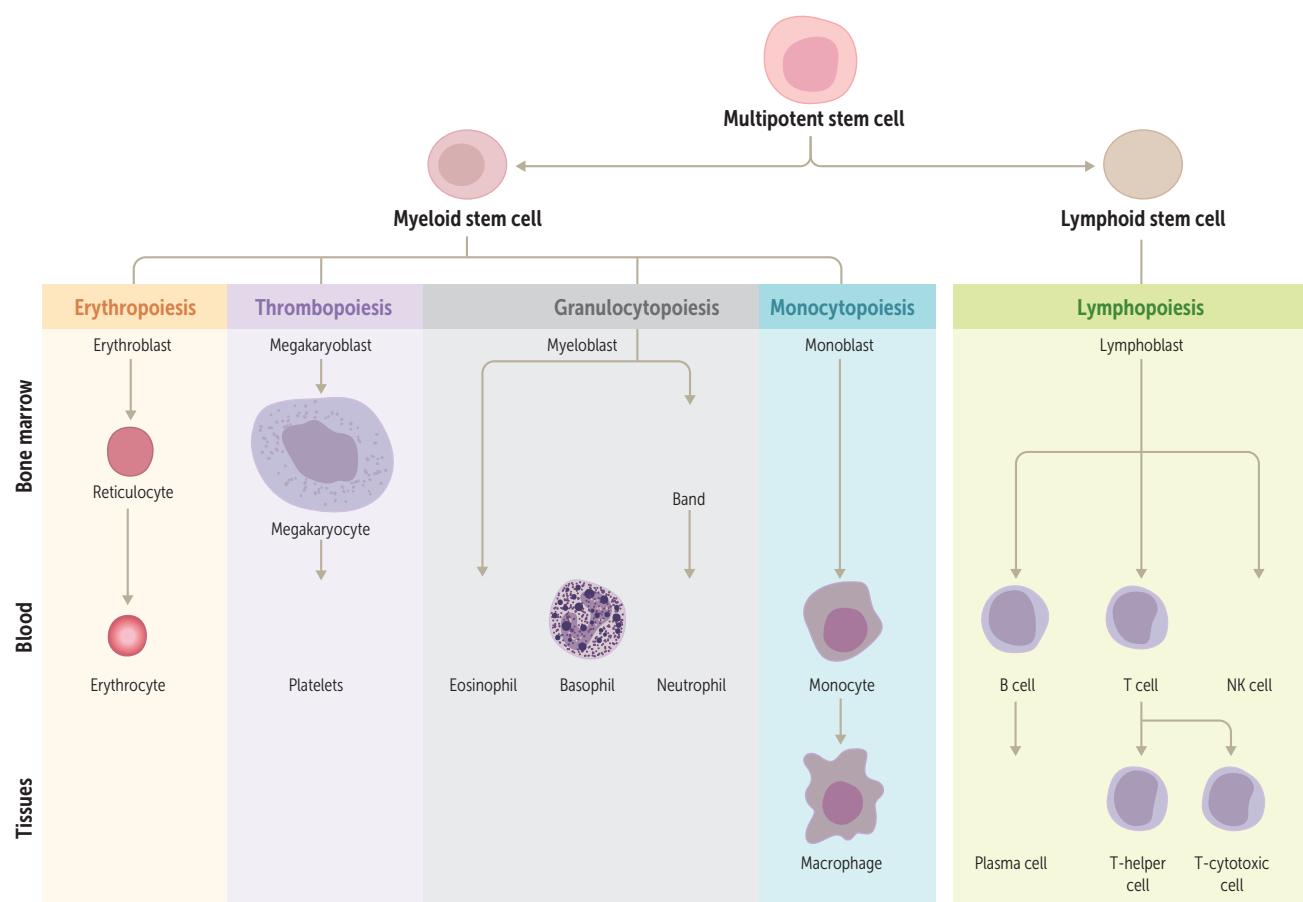
Rx

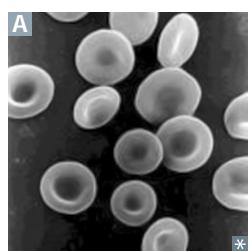
Hemolytic disease of the fetus and newborn

Also called erythroblastosis fetalis.

	Rh hemolytic disease	ABO hemolytic disease
INTERACTION	Rh- pregnant patient; Rh+ fetus.	Type O pregnant patient; type A or B fetus.
MECHANISM	First pregnancy: patient exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG. Subsequent pregnancies: anti-D IgG crosses placenta → attacks fetal and newborn RBCs → hemolysis.	Preexisting pregnant patient anti-A and/or anti-B IgG antibodies cross the placenta → attack fetal and newborn RBCs → hemolysis.
PRESENTATION	Hydrops fetalis, jaundice shortly after birth, kernicterus.	Mild jaundice in the neonate within 24 hours of birth. Unlike Rh hemolytic disease, can occur in firstborn babies and is usually less severe.
TREATMENT/PREVENTION	Prevent by administration of anti-D IgG to Rh- pregnant patients during third trimester and early postpartum period (if fetus Rh+). Prevents maternal anti-D IgG production.	Treatment: phototherapy or exchange transfusion.

► HEMATOLOGY AND ONCOLOGY—ANATOMY

Hematopoiesis

Erythrocytes

Carry O₂ to tissues and CO₂ to lungs. Anucleate and lack organelles; biconcave **A**, with large surface area-to-volume ratio for rapid gas exchange. Life span of ~120 days in healthy adults; 60–90 days in neonates. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain Cl⁻/HCO₃⁻ antiporter, which allow RBCs to export HCO₃⁻ and transport CO₂ from the periphery to the lungs for elimination.

Erythro = red; *cyte* = cell.

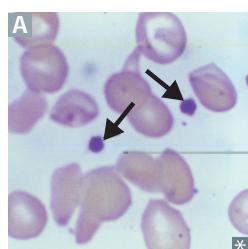
Erythrocytosis = polycythemia = ↑ Hct.

Anisocytosis = varying sizes.

Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Thrombocytes (platelets)

Involved in 1° hemostasis. Anucleate, small cytoplasmic fragments **A** derived from megakaryocytes. Life span of 8–10 days (pl8lets). When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (Ca²⁺, ADP, Serotonin, Histamine; CASH) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately 1/3 of platelet pool is stored in the spleen.

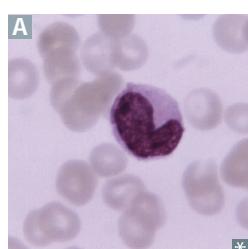
Thrombocytopenia or ↓ platelet function results in petechiae.

vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

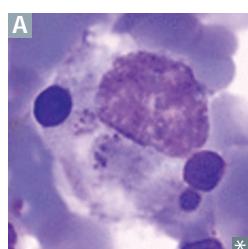
Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor four.

Monocytes

Found in blood, differentiate into macrophages in tissues.

Large, kidney-shaped nucleus **A**. Extensive “frosted glass” cytoplasm.

Mono = one (nucleus); *cyte* = cell.

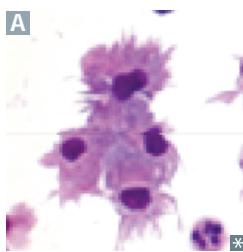
Macrophages

A type of antigen-presenting cell. Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues. Differentiate from circulating blood monocytes **A**. Activated by IFN-γ. Can function as antigen-presenting cell via MHC II. Also engage in antibody-dependent cellular cytotoxicity. Important cellular component of granulomas (eg, TB, sarcoidosis), where they may fuse to form giant cells.

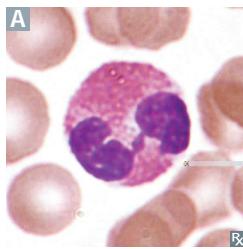
Macro = large; *phage* = eater.

Macrophage naming varies by specific tissue type (eg, Kupffer cells in liver, histiocytes in connective tissue, osteoclasts in bone, microglial cells in brain).

Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.

Dendritic cells

Highly phagocytic antigen-presenting cells (APCs) **A**. Function as link between innate and adaptive immune systems (eg, via T-cell stimulation). Express MHC class II and Fc receptors on surface. Can present exogenous antigens on MHC class I (cross-presentation).

Eosinophils

Defend against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size **A**. Highly phagocytic for antigen-antibody complexes. Produce histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin.

Eosin = pink dye; *philic* = loving.

Causes of eosinophilia (**PACMAN Eats**):

Parasites

Asthma

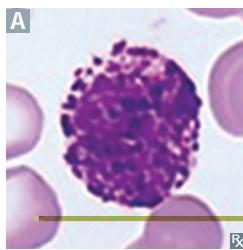
Chronic adrenal insufficiency

Myeloproliferative disorders

Allergic processes

Neoplasia (eg, Hodgkin lymphoma)

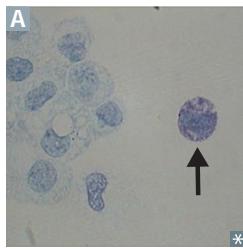
Eosinophilic granulomatosis with polyangiitis

Basophils

Mediate allergic reaction. Densely basophilic granules **A** contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.

Basophilic—stains readily with **basic** stains.

Basophilia is uncommon, but can be a sign of myeloproliferative disorders, particularly CML.

Mast cells

Mediate local tissue allergic reactions. Contain basophilic granules **A**. Originate from same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. Activated by tissue trauma, C3a and C5a, surface IgE cross-linking by antigen (IgE receptor aggregation) → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors.

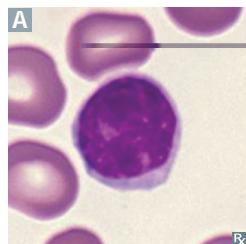
Involved in type I hypersensitivity reactions.

Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).

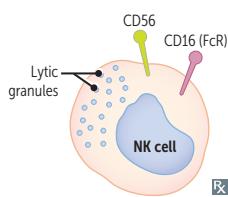
Vancomycin, opioids, and radiocontrast dye can elicit IgE-independent mast cell degranulation.

Mastocytosis—rare; proliferation of mast cells in skin and/or extracutaneous organs. Associated with c-KIT mutations and ↑ serum tryptase.

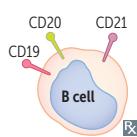
↑ histamine → flushing, pruritus, hypotension, abdominal pain, diarrhea, peptic ulcer disease.

Lymphocytes

Refer to B cells, T cells, and natural killer (NK) cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm **A**.

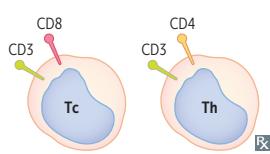
Natural killer cells

Important in innate immunity, especially against intracellular pathogens. NK cells are larger than B and T cells, with distinctive cytoplasmic lytic granules (containing perforin and granzymes) that, when released, act on target cells to induce apoptosis. Distinguish between healthy and infected cells by identifying cell surface proteins (induced by stress, malignant transformation, or microbial infections). Induce **apoptosis** (natural killer) in cells that do not express class I MHC cell surface molecules, eg, virally infected cells in which these molecules are downregulated.

B cells

Mediate humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC.

B = bone marrow.

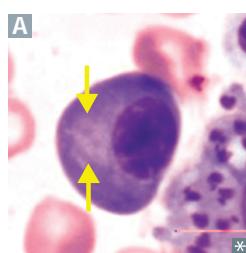
T cells

Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%).

T = thymus.

CD4+ helper T cells are the primary target of HIV.

Rule of 8: $MHC\ II \times CD4 = 8$;
 $MHC\ I \times CD8 = 8$.

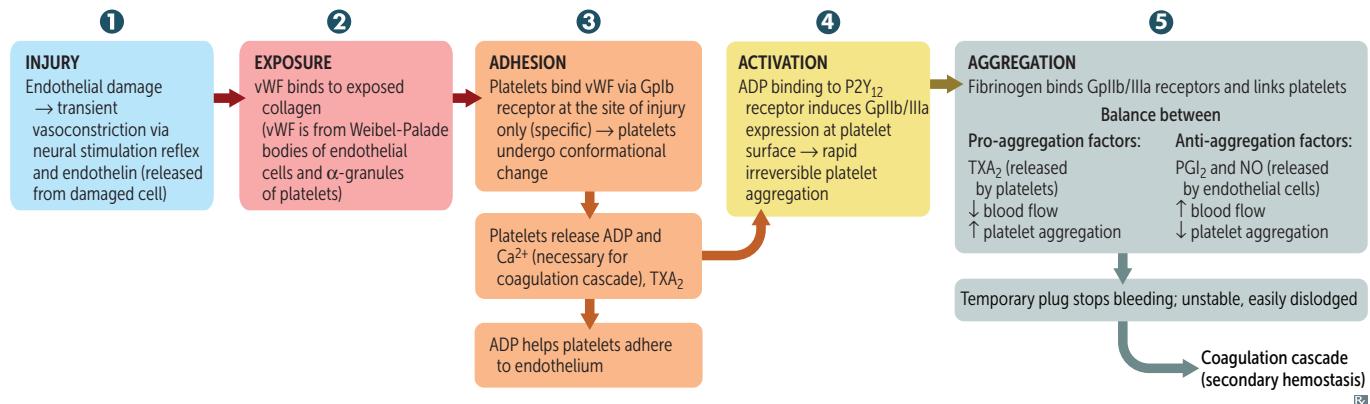
Plasma cells

Produce large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in **A**). Found in bone marrow and normally do not circulate in peripheral blood.

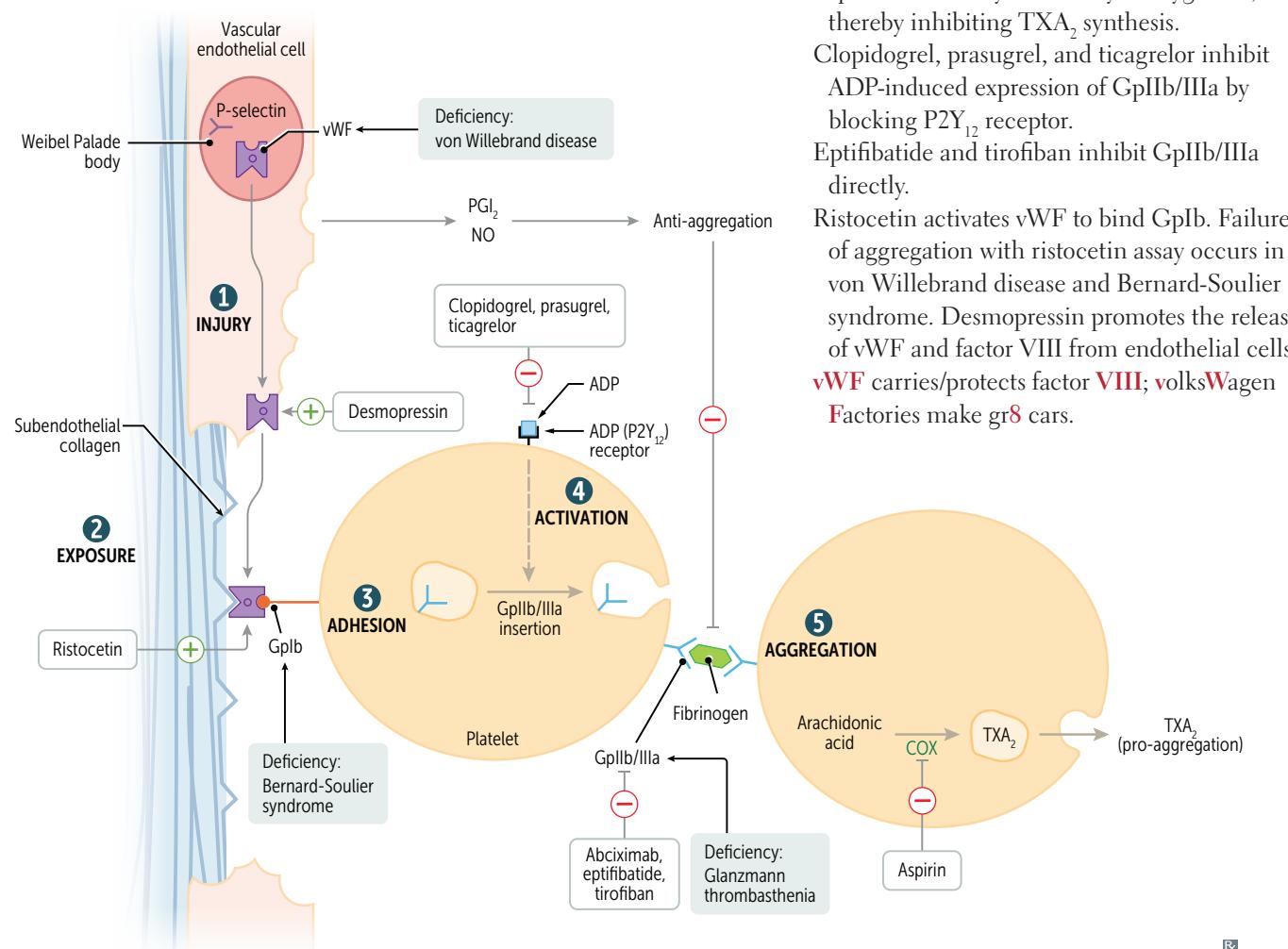
Multiple myeloma is a plasma cell dyscrasia.



Platelet plug formation (primary hemostasis)

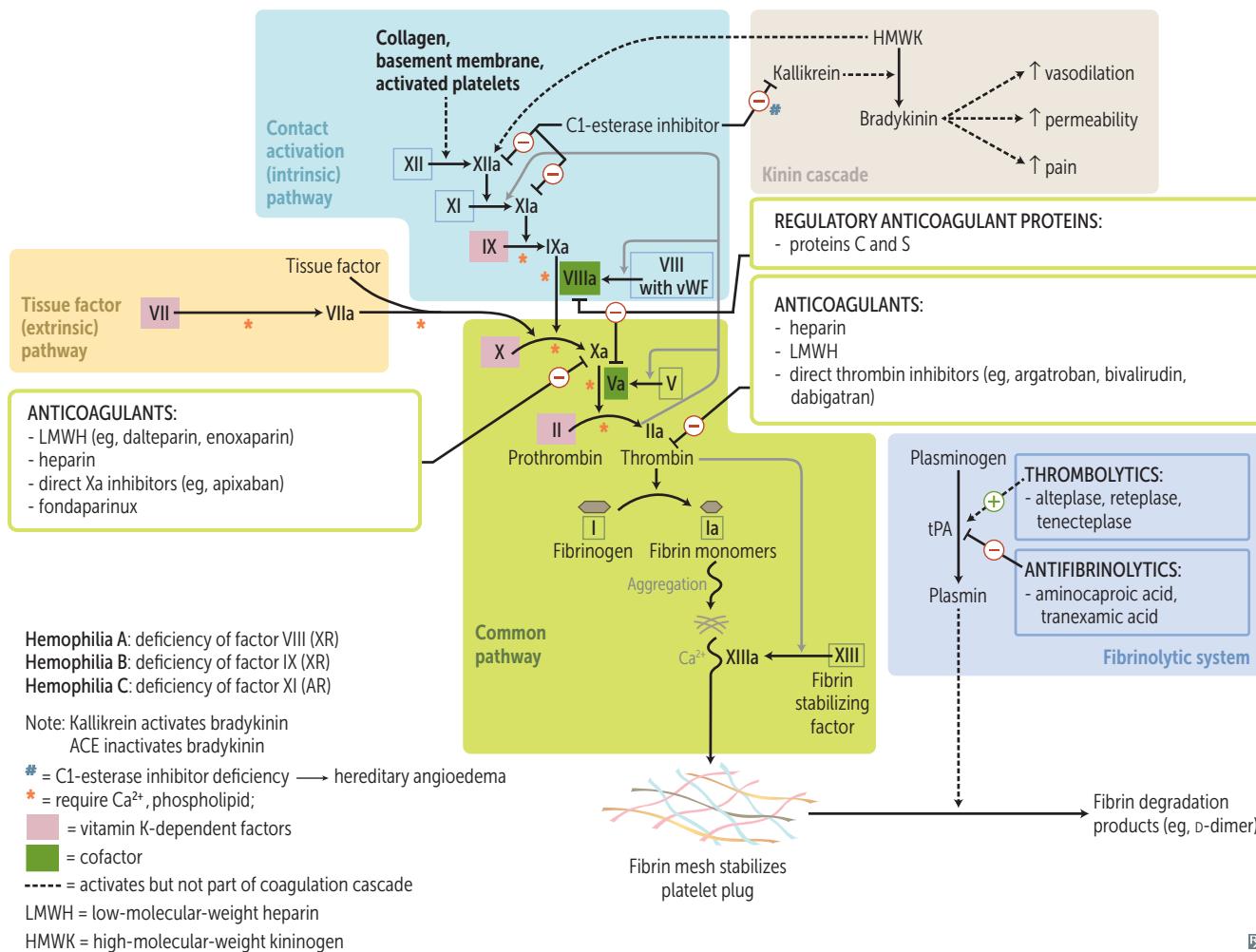


Thrombogenesis



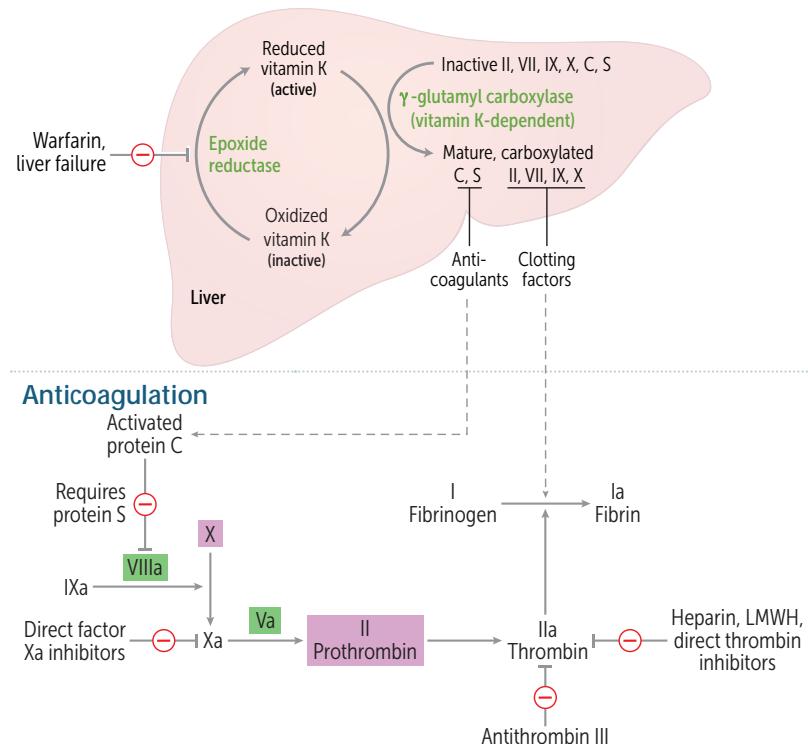
Coagulation and kinin pathways

PT monitors extrinsic and common pathway, reflecting activity of factors I, II, V, VII, and X.
 PTT monitors intrinsic and common pathway, reflecting activity of all factors except VII and XIII.



Vitamin K-dependent coagulation

Procoagulation



■ = vitamin K-dependent factors
■ = cofactor

— — = activates but not part of coagulation cascade
LMWH = low-molecular-weight heparin

Vitamin K deficiency → ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

Warfarin inhibits vitamin K epoxide reductase.

Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy. Suppression of gut flora by broad spectrum antibiotics can also contribute to deficiency.

Factor VII (seven)—shortest half-life.

Factor II (two)—longest (too long) half-life.

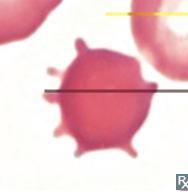
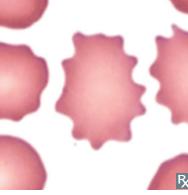
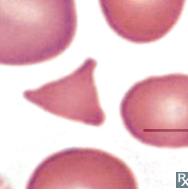
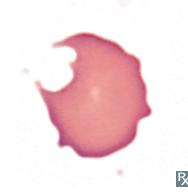
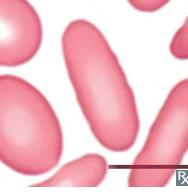
Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

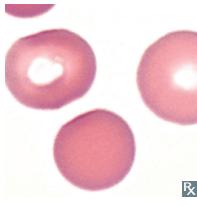
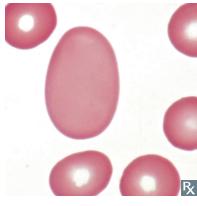
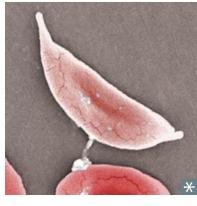
Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C. tPA is used clinically as a thrombolytic.

► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

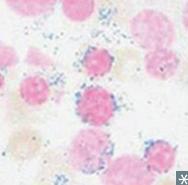
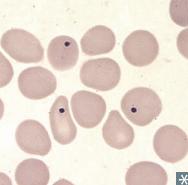
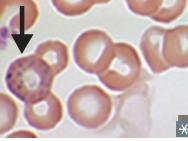
RBC morphology

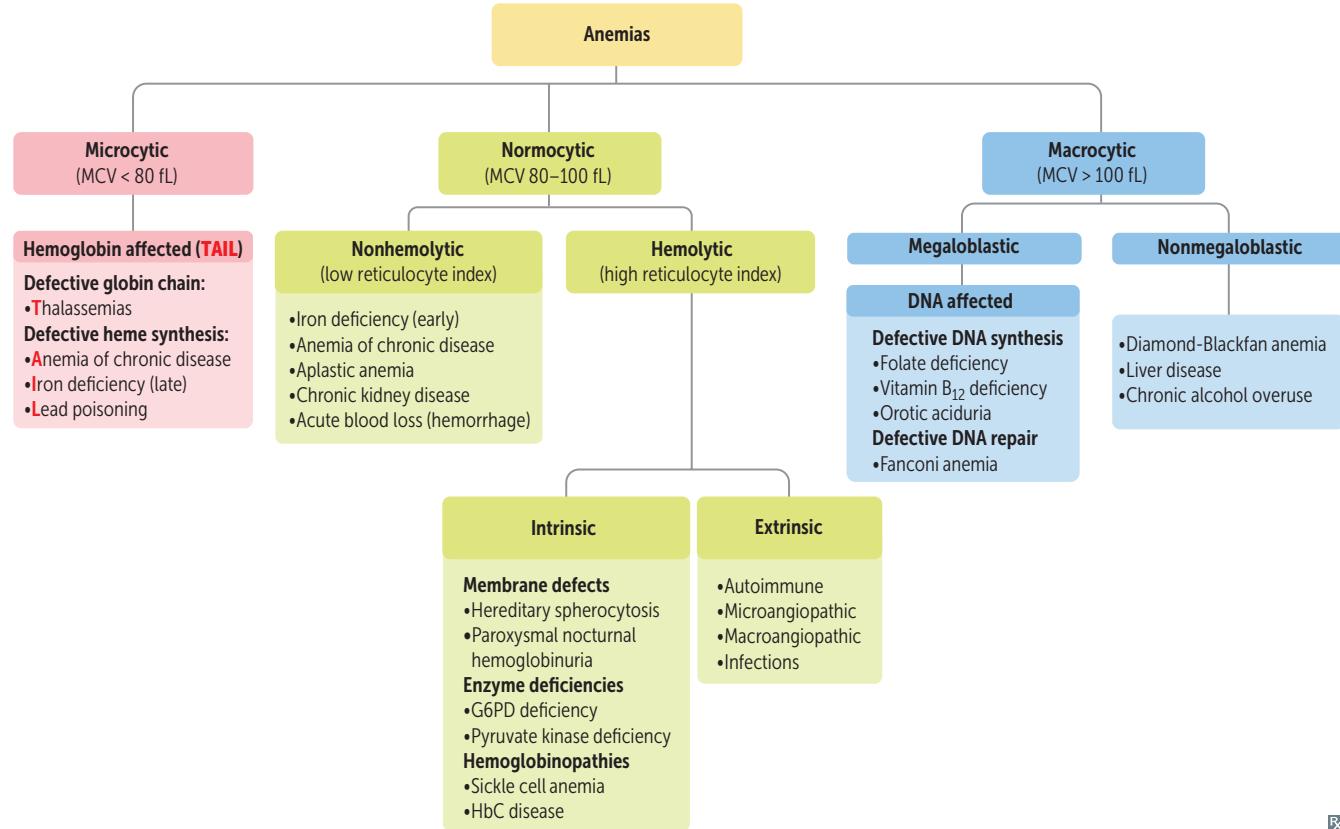
TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Acanthocytes (“spur cells”)	 Rx	Liver disease, abetalipoproteinemia, vitamin E deficiency	Projections of varying size at irregular intervals (acanthocytes are asymmetric).
Echinocytes (“burr cells”)	 Rx	Liver disease, ESRD, pyruvate kinase deficiency	Smaller and more uniform projections than acanthocytes (echinocytes are even).
Dacrocytes (“teardrop cells”)	 Rx	Bone marrow infiltration (eg, myelofibrosis)	RBC “sheds a tear” because it’s mechanically squeezed out of its home in the bone marrow
Schistocytes (“helmet” cells)	 Rx	MAHAs (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis)	Fragmented RBCs
Degmacytes (“bite cells”)	 Rx	G6PD deficiency	Due to removal of Heinz bodies by splenic macrophages (they “deg” them out of/bite them off of RBCs)
Elliptocytes	 Rx	Hereditary elliptocytosis	Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin)

RBC morphology (*continued*)

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Spherocytes		Hereditary spherocytosis, autoimmune hemolytic anemia	Small, spherical cells without central pallor ↓ surface area-to-volume ratio
Macro-ovalocytes		Megaloblastic anemia (also hypersegmented PMNs)	
Target cells		HbC disease, Asplenia, Liver disease, Thalassemia	“HALT,” said the hunter to his target ↑ surface area-to-volume ratio
Sickle cells		Sickle cell anemia	Sickling occurs with low O ₂ conditions (eg, high altitude, acidosis), high HbS concentration (ie, dehydration)

RBC inclusions

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Bone marrow			
Iron granules		Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes, chronic alcohol overuse)	Perinuclear mitochondria with excess iron (forming ring in ringed sideroblasts) Require Prussian blue stain to be visualized
Peripheral smear			
Howell-Jolly bodies		Functional hyposplenia (eg, sickle cell disease), asplenia	Basophilic nuclear remnants (do not contain iron) Usually removed by splenic macrophages
Basophilic stippling		Sideroblastic anemia, thalassemias	Basophilic ribosomal precipitates (do not contain iron)
Pappenheimer bodies		Sideroblastic anemia	Basophilic granules (contain iron) “Pappen-hammer” bodies
Heinz bodies		G6PD deficiency	Denatured and precipitated hemoglobin (contain iron) Phagocytic removal of Heinz bodies → bite cells Requires supravital stain (eg, crystal violet) to be visualized

Anemias

Rx

Reticulocyte production index

Also called corrected reticulocyte count. Used to correct falsely elevated reticulocyte count in anemia. Measures appropriate bone marrow response to anemic conditions (effective erythropoiesis). High RPI (> 3) indicates compensatory RBC production; low RPI (< 2) indicates inadequate response to correct anemia. Calculated as:

$$\text{RPI} = \% \text{ reticulocytes} \times \left(\frac{\text{actual Hct}}{\text{normal Hct}} \right) / \text{maturation time}$$

Interpretation of iron studies

	Iron deficiency	Chronic disease	Hemochromatosis	Pregnancy/OCP use
Serum iron	↓	↓	↑	—
Transferrin or TIBC	↑	↓ ^a	↓	↑
Ferritin	↓	↑	↑	—
% transferrin saturation (serum iron/TIBC)	↓↓	—/↓	↑↑	↓

↑↓ = 1° disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

^aEvolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

Microcytic,**hypochromic anemias**

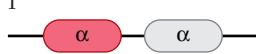
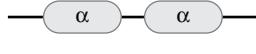
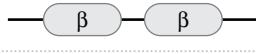
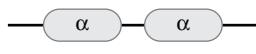
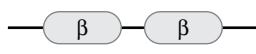
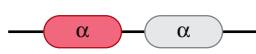
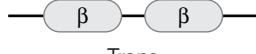
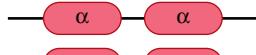
MCV < 80 fL.

Iron deficiency

↓ iron due to chronic bleeding (eg, GI loss, heavy menstrual bleeding), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.
 Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and hypochromasia (↑ central pallor) **A**.
 Symptoms: fatigue, conjunctival pallor **B**, restless leg syndrome, pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia).
 May manifest as glossitis, cheilosis, **Plummer-Vinson syndrome** (triad of iron deficiency anemia, esophageal webs, and dysphagia).

 α -thalassemia

α -globin gene deletions on chromosome 16 → ↓ α -globin synthesis. May have *cis* deletion (deletions occur on same chromosome) or *trans* deletion (deletions occur on separate chromosomes). Normal is $\alpha\alpha/\alpha\alpha$. Often ↑ RBC count, in contrast to iron deficiency anemia. ↑ prevalence in people of Asian and African descent. Target cells **C** on peripheral smear.

# OF α -GLOBIN GENES DELETED ^a	DISEASE	CLINICAL OUTCOME
1	α -thalassemia minima	No anemia (silent carrier)
		
		
		
2	α -thalassemia minor	Mild microcytic, hypochromic anemia
		
		
		
	Cis	
		
		
		
	Trans	
3	Hemoglobin H disease (HbH); excess β -globin forms β_4	Moderate to severe microcytic hypochromic anemia
		
		
		
4	Hemoglobin Barts disease; no α -globin, excess γ -globin forms γ_4	Hydrops fetalis; incompatible with life
		
		
		

β-thalassemia

Point mutation in splice sites or Kozak consensus sequence (promoter) on chromosome 11 → ↓ β-globin synthesis (β^+) or absent β-globin synthesis (β^0). ↑ prevalence in people of Mediterranean descent.

# OF β-GLOBIN GENES MUTATED ⁺	DISEASE	CLINICAL OUTCOME
1	β-thalassemia minor	Mild microcytic anemia. ↑ HbA ₂ .
2 (β^+/β^+ or β^+/β^0)	β-thalassemia intermedia	Variable anemia, ranging from mild/asymptomatic to severe/transfusion-dependent.
2	β-thalassema major (Cooley anemia)	Severe anemia (Hb 8-10 g/dL), splenomegaly, hepatosplenomegaly, gallstones, growth retardation, delayed puberty, and skeletal abnormalities (lumbar scoliosis, carpal tunnel syndrome). ↑ HbA ₂ and HbF.
1 (β^+/HS or β^0/HS)	Sickle cell disease	Anemia, pain crises, stroke, chronic lung disease, and increased risk of infection.

Lad poison

Leads to ferrochlatase deficiency → TIBC ↑, bilirubin ↑, ALA ↑, and ALA dehydrogenase ↑.

→ RBC aggregates of rRNA (asplenic spleen).

↓ poikilothermia (Buonadonna's ad on metapneumonia -9.6 (s o)3.7 (f l)12.6 (o)9.821nos).

- Encephopathy → ↓ ESR, ↓ serum ferritin, ↓ ferritin in bone marrow.
- Abnormal bone marrow findings.
- Demyelination.

Teaten: cholestasis with serum ALA, d-malonic acid.

Exposure to lead → ↑ serum lead levels -9.6 (s o)8.5 (f l)13.3 (m)0.5 (i)5.7 (l)16 (t b)4.821ef81hl07 (adults).

Sebastopol

Cause -9.6 (s o)14.3 (f l)6.821etc (e, X-linked defect).

Adolescent reversible (alcoholism, smoking, lead paint, lead dust, lead in water, lead in food).

Lab findings: ↑ lead in blood, ↑ lead in urine, ↓ hemoglobin, ↓ hematocrit, ↓ red blood cell count.

Blood lead levels -4.3 (d m)35821to chondroitinase -0.9 (epoxy resin, lead paint, lead in food, lead in water, lead in soil).

RBC: Sickle cell variants may be normal or slightly elevated.

Treatment: pyridoxine (B6).

↑ on x-ray.

↑ because

symptoms after having HF

dele -9.5 (s o)9.5 (f l)10.421bF iotve 69.3 (m)36.6 (i)C15.7

holysis → pig -9.8210ed gallstones.

+/HS)

or absence of fibroblast HS4210TSY Hb -24.6 Tf -8.2210 Tw 4.169 0

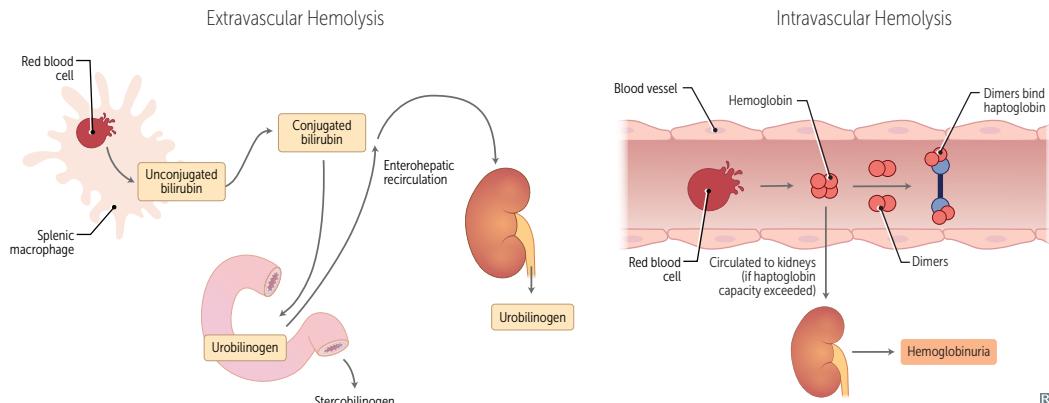
Macrocytic anemias

MCV > 100 fL.

	DESCRIPTION	FINDINGS
Megaloblastic anemia	<p>Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.</p> <p>Causes: vitamin B₁₂ deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs).</p>	RBC macrocytosis, hypersegmented neutrophils (arrow in A), glossitis.
Folate deficiency	<p>Causes: malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy).</p>	↑ homocysteine, normal methylmalonic acid. No neurologic symptoms (vs B ₁₂ deficiency).
Vitamin B₁₂ (cobalamin) deficiency	<p>Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), <i>Diphyllobothrium latum</i> (fish tapeworm).</p>	↑ homocysteine, ↑ methylmalonic acid. Neurologic symptoms: reversible dementia, subacute combined degeneration (due to involvement of B ₁₂ in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin B ₁₂ deficiency can correct the anemia, but worsens neurologic symptoms. Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption. Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B ₁₂ (vs folate deficiency, which takes weeks to months).
Orotic aciduria	<p>Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase.</p> <p>Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B₁₂. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).</p>	Orotic acid in urine. Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme.
Nonmegaloblastic anemia	Macrocytic anemia in which DNA synthesis is normal. Causes: chronic alcohol overuse, liver disease.	RBC macrocytosis without hypersegmented neutrophils.
Diamond-Blackfan anemia	A congenital form of pure red cell aplasia (vs Fanconi anemia, which causes pancytopenia). Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells.	↑ % HbF (but ↓ total Hb). Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases.

Normocytic, normochromic anemias

Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of hemolysis (intravascular vs extravascular). Hemolysis can lead to ↑ in LDH, reticulocytes, unconjugated bilirubin, pigmented gallstones, and urobilinogen in urine.



Intravascular hemolysis

Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

Extravascular hemolysis

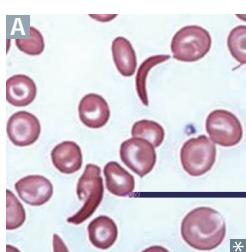
Mechanism: macrophages in spleen clear RBCs. **Findings:** splenomegaly, spherocytes in peripheral smear (most commonly due to hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine.

Nonhemolytic, normocytic anemias

	DESCRIPTION	FINDINGS
Anemia of chronic disease	Inflammation (eg, ↑ IL-6) → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis).	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease).
Aplastic anemia	Failure or destruction of hematopoietic stem cells. Causes (reducing volume from inside diaphysis): <ul style="list-style-type: none"> ▪ Radiation ▪ Viral agents (eg, EBV, HIV, hepatitis viruses) ▪ Fanconi anemia (autosomal recessive DNA repair defect → bone marrow failure); normocytosis or macrocytosis on CBC. Common associated findings include short stature, café-au-lait spots, thumb/radial defects, predisposition to malignancy. ▪ Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis ▪ Drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites) 	↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia (vs aplastic crisis, which causes anemia only). Normal cell morphology, but hypocellular bone marrow with fatty infiltration A . Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF).

Intrinsic hemolytic anemias

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	<p>Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin).</p> <p>Small, round RBCs with no central pallor. ↓ surface area/dehydration → ↑ MCHC → premature removal by spleen (extravascular hemolysis).</p>	<p>Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection). Labs: ↓ mean fluorescence of RBCs in eosin 5-maleimide (EMA) binding test, ↑ fragility in osmotic fragility test (RBC hemolysis with exposure to hypotonic solution). Normal to ↓ MCV with abundance of RBCs. Treatment: splenectomy.</p>
Paroxysmal nocturnal hemoglobinuria	<p>Hematopoietic stem cell mutation → ↑ complement-mediated intravascular hemolysis, especially at night. Acquired PIGA mutation → impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59), which protect RBC membrane from complement.</p>	<p>Triad: Coombs ⊖ hemolytic anemia (mainly intravascular), pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome). Pink/red urine in morning. Associated with aplastic anemia, acute leukemias. Labs: CD55/59 ⊖ RBCs on flow cytometry. Treatment: eculizumab (targets terminal complement protein C5).</p>
G6PD deficiency	<p>X-linked recessive. G6PD defect → ↓ NADPH → ↓ reduced glutathione → ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, fava beans) → hemolysis.</p> <p>Causes extravascular and intravascular hemolysis.</p>	<p>Back pain, hemoglobinuria a few days after oxidant stress. Labs: ↓ G6PD activity (may be falsely normal during acute hemolysis), blood smear shows RBCs with Heinz bodies and bite cells. "Stress makes me eat bites of fava beans with Heinz ketchup."</p>
Pyruvate kinase deficiency	<p>Autosomal recessive. Pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for O₂.</p>	<p>Hemolytic anemia in a newborn. Labs: blood smear shows burr cells.</p>
Sickle cell anemia	<p>Point mutation in β-globin gene → single amino acid substitution (glutamic acid → valine) alters hydrophobic region on β-globin chain → aggregation of hemoglobin. Causes extravascular and intravascular hemolysis.</p> <p>Pathogenesis: low O₂, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → vaso-occlusive disease.</p> <p>Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS.</p> <p>Heterozygotes (sickle cell trait) have resistance to malaria.</p> <p>Sickle cells are crescent-shaped RBCs A. "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).</p>	<p>Complications:</p> <ul style="list-style-type: none"> ■ Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19). ■ Autoimmunity (Howell-Jolly bodies) <ul style="list-style-type: none"> → ↑ risk of infection by encapsulated organisms (eg, <i>Salmonella</i> osteomyelitis). ■ Splenic infarct/sequestration crisis. ■ Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke. ■ Sickling in renal medulla (↓ Po₂) → renal papillary necrosis → hematuria (also seen in sickle cell trait). <p>Hb electrophoresis: ↓ HbA, ↑ HbF, ↑ HbS. Treatment: hydroxyurea (↑ HbF), hydration.</p>
HbC disease	<p>Glutamic acid-to-lysine (lysine) mutation in β-globin. Causes extravascular hemolysis.</p>	<p>HbSC (1 of each mutant gene) milder than HbSS. Blood smear in homozygotes: hemoglobin crystals inside RBCs, target cells.</p>



Extrinsic hemolytic anemias

	DESCRIPTION	FINDINGS
Autoimmune hemolytic anemia	A normocytic anemia that is usually idiopathic and Coombs \oplus . Two types: <ul style="list-style-type: none"> ▪ Warm AIHA—chronic anemia in which primarily IgG causes extravascular hemolysis. Seen in SLE and CLL and with certain drugs (eg, β-lactams, α-methyldopa). “Warm weather is Good.” ▪ Cold AIHA—acute anemia in which primarily IgM + complement cause RBC agglutination and extravascular hemolysis upon exposure to cold \rightarrow painful, blue fingers and toes. Seen in CLL, <i>Mycoplasma pneumoniae</i> infections, infectious mononucleosis. 	Spherocytes and agglutinated RBCs A on peripheral blood smear. Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory). Cold AIHA treatment: cold avoidance, rituximab.
Drug-induced hemolytic anemia	Most commonly due to antibody-mediated immune destruction of RBCs or oxidant injury via free radical damage (may be exacerbated in G6PD deficiency). Common causes include antibiotics (eg, penicillins, cephalosporins), NSAIDs, immunotherapy, chemotherapy.	Spherocytes suggest immune hemolysis. Bite cells suggest oxidative hemolysis. Can cause both extravascular and intravascular hemolysis.
Microangiopathic hemolytic anemia	RBCs are damaged when passing through obstructed or narrowed vessels. Causes intravascular hemolysis. Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency.	Schistocytes (eg, “helmet cells”) are seen on peripheral blood smear due to mechanical destruction (<i>schisto</i> = to split) of RBCs.
Macroangiopathic hemolytic anemia	Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.	Schistocytes on peripheral blood smear.
Hemolytic anemia due to infection	\uparrow destruction of RBCs (eg, malaria, <i>Babesia</i>).	

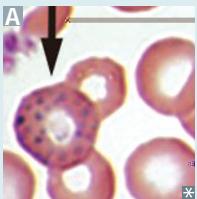
Leukopenias

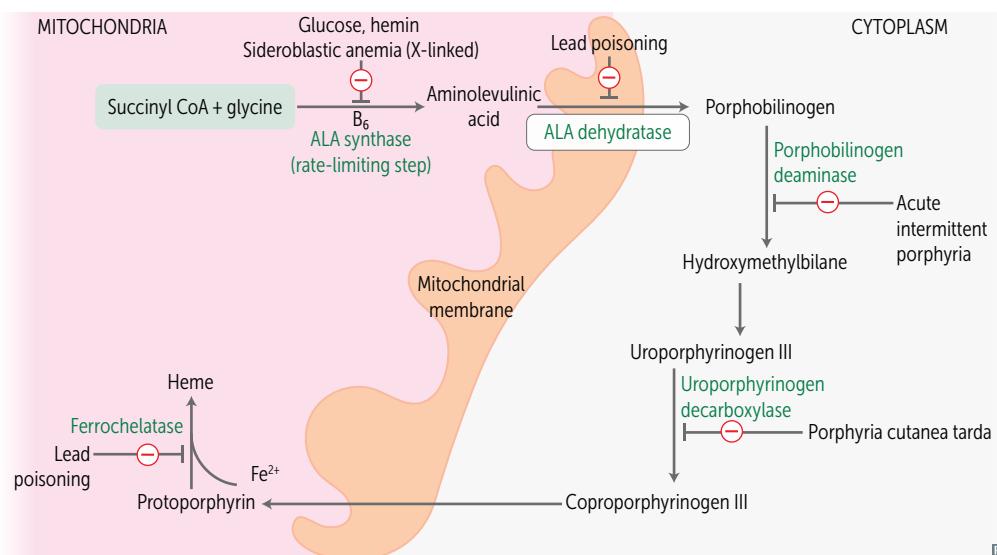
CELL TYPE	CELL COUNT	CAUSES
Neutropenia	Absolute neutrophil count $< 1500 \text{ cells/mm}^3$ Severe infections typical when $< 500 \text{ cells/mm}^3$	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation, congenital
Lymphopenia	Absolute lymphocyte count $< 1500 \text{ cells/mm}^3$ ($< 3000 \text{ cells/mm}^3$ in children)	HIV, DiGeorge syndrome, SCID, SLE, glucocorticoids ^a , radiation, sepsis, postoperative
Eosinopenia	Absolute eosinophil count $< 30 \text{ cells/mm}^3$	Cushing syndrome, glucocorticoids ^a

^aGlucocorticoids cause neutrophilia, despite causing eosinopenia and lymphopenia. Glucocorticoids \downarrow activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, glucocorticoids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

Heme synthesis, porphyrias, and lead poisoning

The porphyrias are hereditary or acquired conditions of defective heme synthesis that lead to the accumulation of heme precursors. Lead inhibits specific enzymes needed in heme synthesis, leading to a similar condition.

CONDITION	AFFECTED ENZYME	ACCUMULATED SUBSTRATE	PRESENTING SYMPTOMS
Lead poisoning 	Ferrochelatase and ALA dehydratase	Protoporphyrin, ALA (blood)	Microcytic anemia (basophilic stippling in peripheral smear A , ringed sideroblasts in bone marrow), GI and kidney disease. Children—exposure to lead paint → mental deterioration. Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination (peripheral neuropathy).
Acute intermittent porphyria	Porphobilinogen deaminase (autosomal dominant mutation)	Porphobilinogen, ALA	Symptoms (5 P's): <ul style="list-style-type: none">▪ Painful abdomen▪ Port wine-colored Pee▪ Polyneuropathy▪ Psychological disturbances▪ Precipitated by factors that ↑ ALA synthase (eg, drugs [CYP450 inducers], alcohol, starvation) Treatment: hemin and glucose.
Porphyria cutanea tarda 	Uroporphyrinogen decarboxylase	Uroporphyrin (tea-colored urine)	Blistering cutaneous photosensitivity and hyperpigmentation B . Most common porphyria. Exacerbated with alcohol consumption. Causes: familial, hepatitis C . Treatment: phlebotomy, sun avoidance, antimalarials (eg, hydroxychloroquine).



Iron poisoning

	Acute	Chronic
FINDINGS	High mortality rate associated with accidental ingestion by children (adult iron tablets may look like candy).	Seen in patients with 1° (hereditary) or 2° (eg, chronic blood transfusions for thalassemia or sickle cell disease) hemochromatosis.
MECHANISM	Cell death due to formation of free radicals and peroxidation of membrane lipids.	
SYMPOMS/SIGNS	Abdominal pain, vomiting, GI bleeding. Radiopaque pill seen on x-ray. May progress to anion gap metabolic acidosis and multiorgan failure. Leads to scarring with GI obstruction.	Arthropathy, cirrhosis, cardiomyopathy, diabetes mellitus and skin pigmentation (“bronze diabetes”), hypogonadism.
TREATMENT	Chelation (eg, deferoxamine, deferasirox), gastric lavage.	Phlebotomy (patients without anemia) or chelation.

Coagulation disorders

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ **PT** (**P**lay **T**ennis **o**utside [**e**xtrinsic pathway]).
 INR (international normalized ratio) = patient PT/control PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin, which prolongs INR.
 PTT—tests function of common and **i**ntrinsic pathway (all factors except VII and XIII). Defect → ↑ **PTT** (**P**lay **T**able **T**ennis **i**nside).
 TT—measures the rate of conversion of fibrinogen → fibrin. Prolonged by anticoagulants, hypofibrinogenemia, DIC, liver disease.
 Coagulation disorders can be due to clotting factor deficiencies or acquired factor inhibitors (most commonly against factor VIII). Diagnosed with a mixing study, in which normal plasma is added to patient’s plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

DISORDER	PT	PTT	MECHANISM AND COMMENTS
Hemophilia A, B, or C	—	↑	Intrinsic pathway coagulation defect (↑ PTT). <ul style="list-style-type: none"> ▪ A: deficiency of factor VIII; X-linked recessive. Pronounce “hemophilia Ate (eight).” ▪ B: deficiency of factor IX; X-linked recessive. ▪ C: deficiency of factor XI; autosomal recessive. Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures). Treatment: desmopressin, factor VIII concentrate, emicizumab (A); factor IX concentrate (B); factor XI concentrate (C).
Vitamin K deficiency	↑	↑	General coagulation defect. Bleeding time normal. ↓ activity of factors II, VII, IX, X, protein C, protein S.

Platelet disorders

All platelet disorders have ↑ bleeding time (BT), mucous membrane bleeding, and microhemorrhages (eg, petechiae, epistaxis). Platelet count (PC) is usually low, but may be normal in qualitative disorders.

DISORDER	PC	BT	NOTES
Bernard-Soulier syndrome	-/↓	↑	Autosomal recessive defect in adhesion. ↓ GpIb → ↓ platelet-to-vWF adhesion. Labs: ↓ platelet aggregation, Big platelets.
Glanzmann thrombasthenia	-	↑	Autosomal recessive defect in aggregation. ↓ GpIIb/IIIa (↓ integrin $\alpha_{IIb}\beta_3$) → ↓ platelet-to-platelet aggregation and defective platelet plug formation. Labs: blood smear shows no platelet clumping.
Immune thrombocytopenia	↓	↑	Destruction of platelets in spleen. Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets. May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions. Labs: ↑ megakaryocytes on bone marrow biopsy, ↓ platelet count. Treatment: glucocorticoids, IVIG, rituximab, TPO receptor agonists (eg, eltrombopag, romiplostim), or splenectomy for refractory ITP.
Uremic platelet dysfunction	-	↑	In patients with renal failure, uremic toxins accumulate and interfere with platelet adhesion.

Thrombotic microangiopathies

Disorders overlap significantly in symptomatology. May resemble DIC, but do not exhibit lab findings of a consumptive coagulopathy (eg, ↑ PT, ↑ PTT, ↓ fibrinogen), as etiology does not involve widespread clotting factor activation.

	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome
EPIDEMIOLOGY	Typically females	Typically children
PATHOPHYSIOLOGY	Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease) → ↓ degradation of vWF multimers → ↑ large vWF multimers → ↑ platelet adhesion and aggregation (microthrombi formation)	Predominately caused by Shiga toxin-producing <i>Escherichia coli</i> (STEC) infection (serotype O157:H7), which causes profound endothelial dysfunction.
PRESENTATION	Triad of thrombocytopenia (↓ platelets), microangiopathic hemolytic anemia (↓ Hb, schistocytes, ↑ LDH), acute kidney injury (↑ Cr)	
DIFFERENTIATING SYMPTOMS	Triad + fever + neurologic symptoms	Triad + bloody diarrhea
LABS	Normal PT and PTT helps distinguish TTP and HUS (coagulation pathway is not activated) from DIC (coagulation pathway is activated)	
TREATMENT	Plasma exchange, glucocorticoids, rituximab	Supportive care

Mixed platelet and coagulation disorders

DISORDER	PC	BT	PT	PTT	NOTES
von Willebrand disease	—	↑	—	—/↑	Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF carries/protects factor VIII). Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion. Most are autosomal dominant. Mild but most common inherited bleeding disorder. Commonly presents with menorrhagia or epistaxis. Treatment: desmopressin, which releases vWF stored in endothelium.
Disseminated intravascular coagulation	↓	↑	↑	↑	Widespread clotting factor activation → thromboembolic state with excessive clotting factor consumption → ↑ thromboses, ↑ hemorrhages (eg, blood oozing from puncture sites). May be acute (life-threatening) or chronic (if clotting factor production can compensate for consumption). Causes: heat S troke, S nake bites, S eptis (gram ⊖), T rauma, O bstetric complications, acute P ancreatitis, m alignancy, n ephrotic syndrome, t ransfusion (SSSTOP making n ew t hrombi). Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.

Hereditary thrombophilias Autosomal dominant disorders resulting in hypercoagulable state (↑ tendency to develop thrombosis).

DISEASE	DESCRIPTION
Antithrombin de ciency	Has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following standard heparin dosing. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.
Factor V Leiden	Production of mutant factor V (guanine → adenine DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Complications include DVT, cerebral vein thrombosis, recurrent pregnancy loss.
Protein C or S de ciency	↓ ability to inactivate factors Va and VIIa. ↑ risk of warfarin-induced skin necrosis. Together, protein C Cancels, and protein S Stops, coagulation.
Prothrombin G20210A mutation	Point mutation in 3' untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.

Blood transfusion therapy

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O ₂ binding (carrying) capacity, ↑ hemoglobin ~1 g/dL per unit, ↑ hematocrit ~3% per unit	Acute blood loss, severe anemia
Platelets	↑ platelet count ~30,000/microL per unit (↑ ~5000/mm ³ /unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S	Cirrhosis, immediate anticoagulation reversal
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII
Albumin	↑ intravascular volume and oncotic pressure	Post-paracentesis, therapeutic plasmapheresis

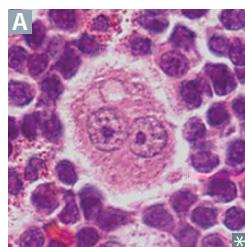
Blood transfusion risks include infection transmission (low), transfusion reactions, transfusion-associated circulatory overload (TACO; volume overload → pulmonary edema, hypertension), transfusion-related acute lung injury (TRALI; hypoxia and inflammation → noncardiogenic pulmonary edema, hypotension), iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca²⁺ chelator), and hyperkalemia (RBCs may lyse in old blood units).

Leukemia vs lymphoma

Leukemia	Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
Lymphoma	Discrete tumor mass arising from lymph nodes. Variable clinical presentation (eg, arising in atypical sites, leukemic presentation).

**Hodgkin vs
non-Hodgkin
lymphoma**

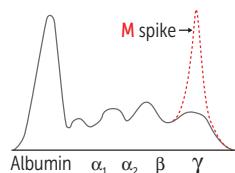
Hodgkin	Non-Hodgkin
Both may have constitutional (“B”) signs/symptoms: low-grade fever, night sweats, weight loss.	
Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
Characterized by Reed-Sternberg cells.	Majority involve B cells; rarely of T-cell lineage.
Bimodal distribution: young adults, > 55 years.	Can occur in children and adults.
Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

Hodgkin lymphoma

Contains Reed-Sternberg cells: distinctive tumor giant cells; bilobed nucleus with the **2** halves as mirror images (“owl eyes” **A**). RS cells are CD15+ and CD30+ B-cell origin. **2** owl eyes × **15 = 30**.

SUBTYPE	NOTES
Nodular sclerosis	Most common
Mixed cellularity	Eosinophilia; seen in immunocompromised patients
Lymphocyte rich	Best prognosis (the rich have better bank accounts)
Lymphocyte depleted	Worst prognosis (the poor have worse bank accounts); seen in immunocompromised patients

Non-Hodgkin lymphoma

Plasma cell dyscrasias

Group of disorders characterized by proliferation of a single plasma cell clone, typically overproducing a monoclonal immunoglobulin (also called paraprotein). Seen in older adults. Screening with serum protein electrophoresis (**M** spike represents overproduction of **Monoclonal Ig**), serum immunofixation, and serum free light chain assay. Urine protein electrophoresis and immunofixation required to confirm urinary involvement (urine dipstick only detects albumin). Diagnostic confirmation with bone marrow biopsy. Peripheral blood smear may show rouleaux formation **A** (RBCs stacked like poker chips).

Multiple myeloma

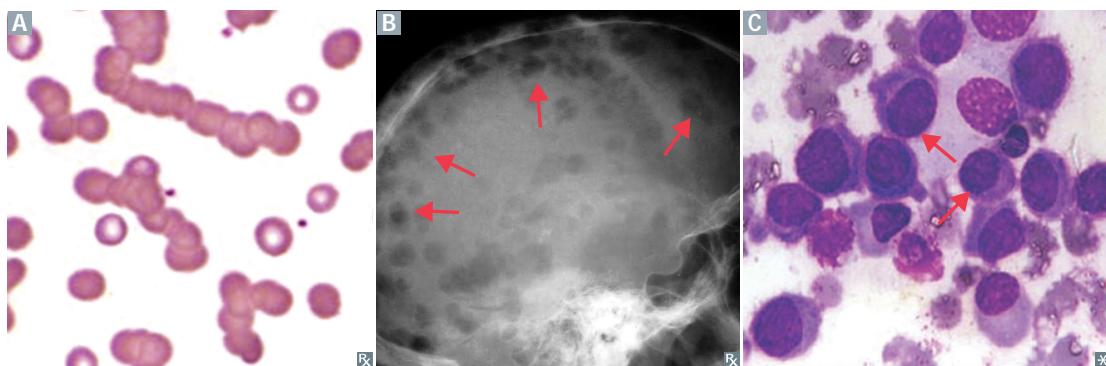
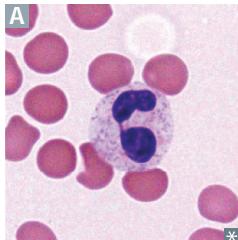
Overproduction of IgG (most common) > IgA > Ig light chains. Clinical features (**CRAB**): hyper**C**alcemia (\uparrow cytokine secretion [eg, IL-1, TNF- α , RANK-L] by malignant plasma cells $\rightarrow \uparrow$ osteoclast activity), **R**enal insufficiency, **A**nemia, **B**one lytic lesions (“punched out” on x-ray **B** \rightarrow back pain). Complications: \uparrow infection risk, 1° amyloidosis (AL). Urinalysis may show Ig light chains (Bence Jones proteinuria) with \ominus urine dipstick. Bone marrow biopsy shows $>10\%$ monoclonal plasma cells with clock-face chromatin **C** and intracytoplasmic inclusions containing Ig.

Waldenström macroglobulinemia

Overproduction of IgM (**macroglobulinemia** because IgM is the **largest** Ig). Clinical features include anemia, constitutional (“B”) signs/symptoms, lymphadenopathy, hepatosplenomegaly, hyperviscosity (eg, headache, bleeding, blurry vision, ataxia), peripheral neuropathy. Funduscopic shows dilated, segmented, and tortuous retinal veins (sausage link appearance). Bone marrow biopsy shows $>10\%$ monoclonal B lymphocytes with plasma cell features (lymphoplasmacytic lymphoma) and intranuclear pseudoinclusions containing IgM.

Monoclonal gammopathy of undetermined significance

Overproduction of any Ig type (M spike <3 g/dL). Asymptomatic (no CRAB findings). 1%–2% risk per year of progressing to multiple myeloma. Bone marrow biopsy shows $<10\%$ monoclonal plasma cells.

**Myelodysplastic syndromes**

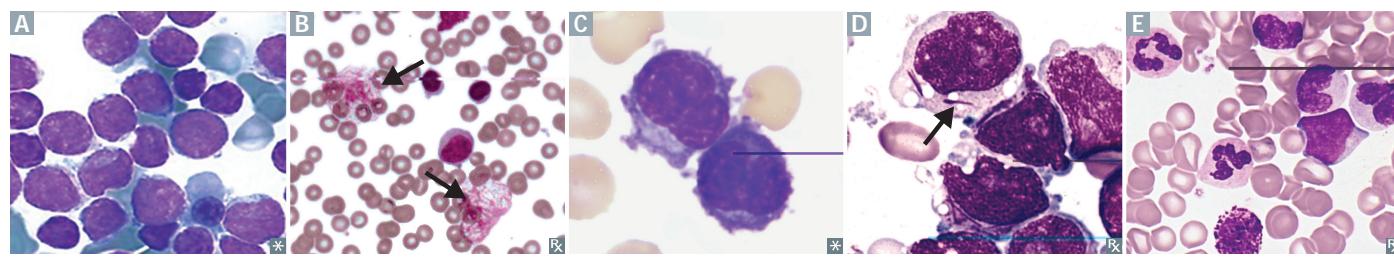
Stem cell disorders involving ineffective hematopoiesis \rightarrow defects in cell maturation of nonlymphoid lineages. Bone marrow blasts $<20\%$ (vs $>20\%$ in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML. More common in older adults.

Pseudo-Pelger-Hüet anomaly—neutrophils with bilobed (“duet”) nuclei **A**. Associated with myelodysplastic syndromes or drugs (eg, immunosuppressants).

Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (\downarrow RBCs), infections (\downarrow mature WBCs), and hemorrhage (\downarrow platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood), although some cases present with normal/ \downarrow WBCs.

Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

TYPE	NOTES
Lymphoid neoplasms	
Acute lymphoblastic leukemia/lymphoma	<p>Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis.</p>
Chronic lymphocytic leukemia/small lymphocytic lymphoma	<p>Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).</p>
Hairy cell leukemia	<p>Adult males. Mature B-cell tumor. Cells have filamentous, hairlike projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon. Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia. Stains TRAP (Tartrate-Resistant Acid Phosphatase) + (TRAPped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with BRAF mutations. Treatment: purine analogs (cladribine, pentostatin).</p>
Myeloid neoplasms	
Acute myelogenous leukemia	<p>Median onset 65 years. Auer rods D; myeloperoxidase + cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear. May present with leukostasis (capillary occlusion by malignant, nondistensible cells → organ damage). Risk factors: prior exposure to alkylating chemotherapy, radiation, benzene, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-trans retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation.</p>
Chronic myelogenous leukemia	<p>Peak incidence: 45–85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], BCR-ABL) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL (“blast crisis”). Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib).</p>
 <p>The figure consists of five panels labeled A through E, each showing a different type of leukemic cell under a microscope. Panel A shows a dense cluster of dark purple-stained cells. Panel B shows a peripheral blood smear with several white blood cells; two specific cells are highlighted with black arrows. Panel C shows a low-magnification view of a tissue sample with various cell types. Panel D shows a high-magnification view of a cell with prominent purple-stained rod-shaped inclusions (Auer rods). Panel E shows a cluster of cells with distinct purple-stained granules.</p>	

Myeloproliferative neoplasms

Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

Polycythemia vera

Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired JAK2 mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities **A**. Associated with hyperviscosity and thrombosis (eg, PE, DVT, Budd-Chiari syndrome).

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

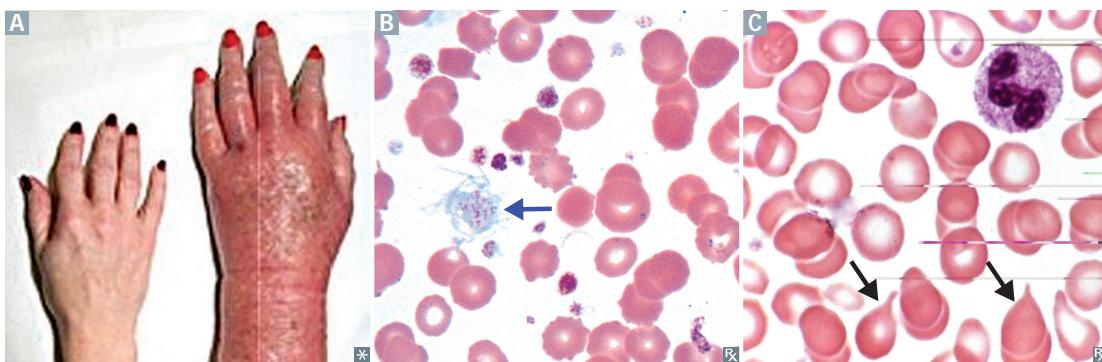
Essential thrombocythemia

Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed **B**. Erythromelalgia may occur.

Myelofibrosis

Atypical megakaryocyte hyperplasia → ↑ TGF-β secretion → ↑ fibroblast activity → obliteration of bone marrow with fibrosis. Associated with massive splenomegaly and “teardrop” RBCs **C**. “Bone marrow **cries** because it’s fibrosed and is a dry tap.”

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	JAK2 MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖

**Leukemoid reaction vs chronic myelogenous leukemia**

	Leukemoid reaction	Chronic myelogenous leukemia
DEFINITION	Reactive neutrophilia > 50,000 cells/mm³	Myeloproliferative neoplasm ⊕ for BCR-ABL
NEUTROPHIL MORPHOLOGY	Toxic granulation, Döhle bodies, cytoplasmic vacuoles	Pseudo-Pelger-Huët anomaly
LAP SCORE	↑	↓ (LAP enzyme ↓ in malignant neutrophils)
EOSINOPHILS AND BASOPHILS	Normal	↑

Polycythemia

	PLASMA VOLUME	RBC MASS	O ₂ SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	—	—	—	Dehydration, burns.
Appropriate absolute	—	↑	↓	↑	Lung disease, congenital heart disease, high altitude, obstructive sleep apnea.
Inappropriate absolute	—	↑	—	↑	Exogenous EPO (athlete misuse, also called “blood doping”), androgen supplementation. Inappropriate EPO secretion: malignancy (eg, RCC, HCC).
Polycythemia vera	↑	↑↑	—	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

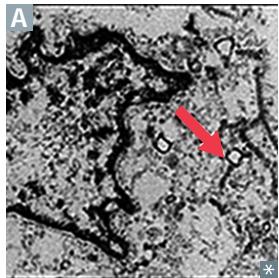
↑↓ = 1° disturbance

Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	NOTES
t(8;14)	Burkitt (Burk-8) lymphoma (<i>c-myc</i> activation)	
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(11;18)	Marginal zone lymphoma	
t(14;18)	Follicular lymphoma (<i>BCL-2</i> activation)	
t(15;17)	APL (formerly M3 type of AML)	
t(9;22) (Philadelphia chromosome)	CML (BCR-ABL hybrid), ALL (less common); Philadelphia CreaML cheese	The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, <i>c-myc</i> and <i>BCL-2</i>) are translocated next to this heavy chain gene region, they are overexpressed.

Langerhans cell histiocytosis

Collective group of proliferative disorders of Langerhans cells (antigen-presenting cells normally found in the skin). Presents in a child as lytic bone lesions and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 and CD1a. Birbeck granules (“tennis rackets” or rod shaped on EM) are characteristic **A**.



Warfarin

MECHANISM	Inhibits vitamin K epoxide reductase by competing with vitamin K → inhibition of vitamin K-dependent γ -carboxylation of clotting factors II, VII, IX, and X and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (VKORC1). In laboratory assay, has effect on extrinsic pathway and ↑ PT. Long half-life. “The ex-President T went to war(farin).”
CLINICAL USE	Chronic anticoagulation (eg, venous thromboembolism prophylaxis and prevention of stroke in atrial fibrillation). Not used in pregnant patients (because warfarin, unlike heparin, crosses placenta). Monitor PT/INR.
ADVERSE EFFECTS	Bleeding, teratogenic effects, skin/tissue necrosis A , drug-drug interactions (metabolized by cytochrome P-450 [CYP2C9]). Initial risk of hypercoagulation: protein C has shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production → hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis. Heparin “bridging”: heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis. For reversal of warfarin, give vitamin K. For rapid reversal, give FFP or PCC.



Heparin vs warfarin

	Heparin	Warfarin
ROUTE OF ADMINISTRATION	Parenteral (IV, SC)	Oral
SITE OF ACTION	Blood	Liver
ONSET OF ACTION	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
DURATION OF ACTION	Hours	Days
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
CROSSES PLACENTA	No	Yes (teratogenic)

Direct coagulation factor inhibitors

Do not usually require lab monitoring.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Bivalirudin, argatroban, dabigatran	Directly inhibit thrombin (factor IIa)	Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is BAD for the patient	Bleeding (idarucizumab can be used to inhibit dabigatran)
Apixaban, edoxaban, rivaroxaban	Directly inhibit (ban) factor Xa	Oral agents. DVT/PE treatment and prophylaxis; stroke prophylaxis in patients with atrial fibrillation	Bleeding (reverse with andexanet alfa)

Anticoagulation reversal

ANTICOAGULANT	REVERSAL AGENT	NOTES
Heparin	Protamine sulfate	⊕ charged peptide that binds ⊖ charged heparin
Warfarin	Vitamin K (slow) +/- FFP or PCC (rapid)	
Dabigatran	Idarucizumab	Monoclonal antibody Fab fragments
Direct factor Xa inhibitors	Andexanet alfa	Recombinant modified factor Xa (inactive)

Antiplatelets

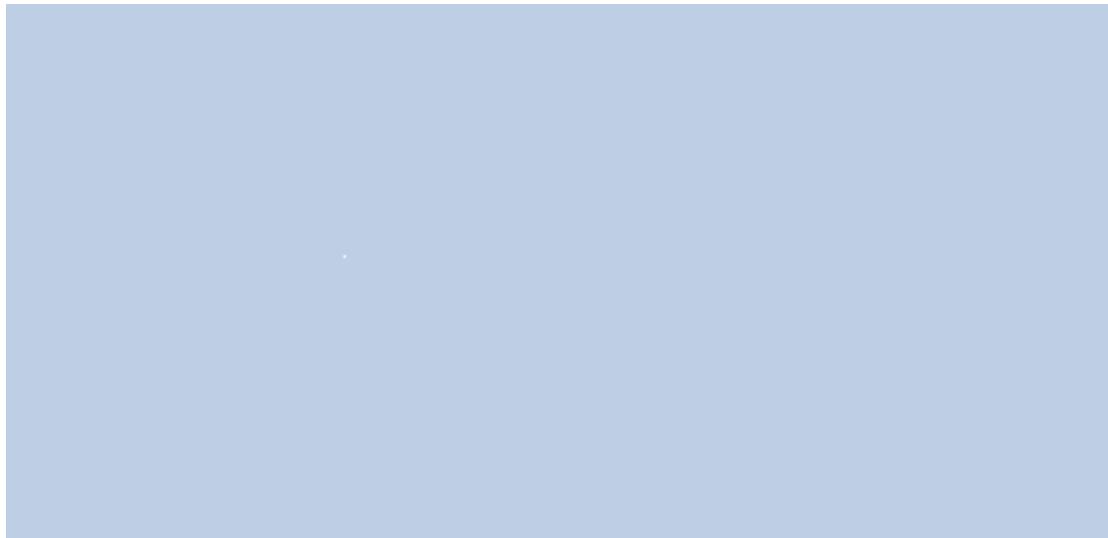
All work by ↓ platelet aggregation.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Aspirin	Irreversibly blocks COX → ↓ TXA ₂ release	Acute coronary syndrome; coronary stenting, ↓ incidence or recurrence of thrombotic stroke	Gastric ulcers, tinnitus, allergic reactions, renal injury, Reye syndrome (in children)
Clopidogrel, prasugrel, ticagrelor	Block ADP (P2Y ₁₂) receptor → ↓ ADP-induced expression of GpIIb/IIIa	Same as aspirin; dual antiplatelet therapy	Bleeding
Epti batide, tiro ban	Block GpIIb/IIIa (fibrinogen receptor) on activated platelets	Unstable angina, percutaneous coronary intervention	Bleeding, thrombocytopenia
Cilostazol, dipyridamole	Block phosphodiesterase → ↓ cAMP hydrolysis → ↑ cAMP in platelets	Intermittent claudication, stroke prevention, cardiac stress testing, prevention of coronary stent restenosis	Nausea, headache, facial flushing, hypotension, abdominal pain

Thrombolytics

Alteplase (tPA), reteplase (rPA), tenecteplase (TNK-tPA).

MECHANISM	Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count.
CLINICAL USE	Early MI, early ischemic stroke, direct thrombolysis of high-risk PE.
ADVERSE EFFECTS	Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC).

Cancer therapy—cell cycle

Antitumor antibioticsAll are cell cycle nonspecific, except bleomycin which is G₂/M phase specific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Bleomycin	Induces free radical formation → breaks in DNA strands	Testicular cancer, Hodgkin lymphoma	Pulmonary fibrosis, skin hyperpigmentation
Dactinomycin (actinomycin D)	Intercalates into DNA, preventing RNA synthesis	Wilms tumor, Ewing sarcoma, rhabdomyosarcoma	Myelosuppression
Anthracyclines Doxorubicin, daunorubicin	Generate free radicals Intercalate in DNA → breaks in DNA → ↓ replication Inhibit topoisomerase II	Solid tumors, leukemias, lymphomas	Dilated cardiomyopathy (often irreversible; prevent with dextrazoxane), myelosuppression

Antimetabolites

All are S-phase specific except cladribine, which is cell cycle nonspecific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Thiopurines Azathioprine, 6-mercaptopurine	Purine (thiol) analogs → ↓ de novo purine synthesis AZA is converted to 6-MP, which is then activated by HGPRT	Rheumatoid arthritis, IBD, SLE, ALL; steroid-refractory disease Prevention of organ rejection Weaning from glucocorticoids	Myelosuppression; GI, liver toxicity 6-MP is inactivated by xanthine oxidase (↑ toxicity with allopurinol or febuxostat)
Cladribine, pentostatin	Purine analogs → unable to be processed by ADA, interfering with DNA synthesis	Hairy cell leukemia	Myelosuppression
Cytarabine (arabinofuranosyl cytidine)	Pyrimidine analog → DNA chain termination Inhibits DNA polymerase	Leukemias (AML), lymphomas	Myelosuppression
5-Fluorouracil	Pyrimidine analog bioactivated to 5-FdUMP → thymidylate synthase inhibition → ↓ dTMP → ↓ DNA synthesis Capecitabine is a prodrug	Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical) Effects enhanced with the addition of leucovorin	Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome)
Hydroxyurea	Inhibits ribonucleotide reductase → ↓ DNA synthesis	Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease (↑ HbF)	Severe myelosuppression, megaloblastic anemia
Methotrexate	Folic acid analog that competitively inhibits dihydrofolate reductase → ↓ dTMP → ↓ DNA synthesis	Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas Nonneoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis	Myelosuppression (reversible with leucovorin “rescue”), hepatotoxicity, mucositis (eg, mouth ulcers), pulmonary fibrosis, folate deficiency (teratogenic), nephrotoxicity

Alkylating agents

All are cell cycle nonspecific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Busulfan	Cross-links DNA	Used to ablate patient's bone marrow before bone marrow transplantation	Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation
Nitrogen mustards Cyclophosphamide, ifosfamide	Cross-link DNA Require bioactivation by liver	Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis)	Myelosuppression, SIADH, Fanconi syndrome (ifosfamide), hemorrhagic cystitis and bladder cancer (prevent with mesna)
Nitrosoureas Carmustine, lomustine	Cross-link DNA Require bioactivation by liver Cross blood-brain barrier → CNS entry	Brain tumors (including glioblastoma multiforme) Put nitro in your Must ang and travel the globe	CNS toxicity (convulsions, dizziness, ataxia)
Procarbazine	Mechanism unknown Weak MAO inhibitor	Hodgkin lymphoma, brain tumors	Myelosuppression, pulmonary toxicity, leukemia, disulfiram-like reaction

Platinum compounds

Cisplatin, carboplatin, oxaliplatin.

MECHANISM	Cross-link DNA. Cell cycle nonspecific.
CLINICAL USE	Solid tumors (eg, testicular, bladder, ovarian, GI, lung), lymphomas.
ADVERSE EFFECTS	Nephrotoxicity (eg, Fanconi syndrome; prevent with amifostine), peripheral neuropathy, ototoxicity.

Microtubule inhibitors

All are M-phase specific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Taxanes Docetaxel, paclitaxel	Hyperstabilize polymerized microtubules → prevent mitotic spindle breakdown	Various tumors (eg, ovarian and breast carcinomas)	Myelosuppression, neuropathy, hypersensitivity Taxes stabilize society
Vinca alkaloids Vincristine, vinblastine	Bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation	Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas	Vincristine (crisps the nerves): neurotoxicity (axonal neuropathy), constipation (including ileus) Vinblastine (blasts the marrow): myelosuppression

Topoisomerase inhibitorsAll cause ↑ DNA degradation resulting in cell cycle arrest in S and G₂ phases.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Irinotecan, topotecan	Inhibit topoisomerase I “-tecone”	Colon, ovarian, small cell lung cancer	Severe myelosuppression, diarrhea
Etoposide, teniposide	Inhibit topoisomerase II “-bothside”	Testicular, small cell lung cancer, leukemia, lymphoma	Myelosuppression, alopecia

Tamoxifen

MECHANISM	Selective estrogen receptor modulator with complex mode of action: antagonist in breast tissue, partial agonist in endometrium and bone. Blocks the binding of estrogen to ER in ER \oplus cells.
CLINICAL USE	Prevention and treatment of breast cancer, prevention of gynecomastia in patients undergoing prostate cancer therapy.
ADVERSE EFFECTS	Hot flashes, \uparrow risk of thromboembolic events (eg, DVT, PE) and endometrial cancer.

Anticancer monoclonal antibodies Work against extracellular targets to neutralize them or to promote immune system recognition (eg, ADCC by NK cells). Eliminated by macrophages (not cleared by kidneys or liver).

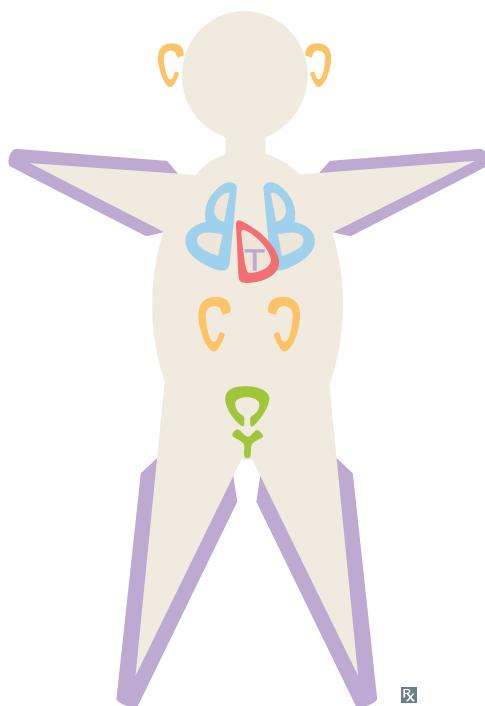
AGENT	TARGET	CLINICAL USE	ADVERSE EFFECTS
Alemtuzumab	CD52	Chronic lymphocytic leukemia (CLL), multiple sclerosis.	\uparrow risk of infections and autoimmunity (eg, ITP)
Bevacizumab	VEGF (inhibits blood vessel formation)	Colorectal cancer (CRC), renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), angioproliferative retinopathy	Hemorrhage, blood clots, impaired wound healing
Cetuximab, panitumumab	EGFR	Metastatic CRC (wild-type RAS), head and neck cancer	Rash, elevated LFTs, diarrhea
Rituximab	CD20	Non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP, TTP, AIHA, multiple sclerosis	Infusion reaction due to cytokine release following interaction of rituximab with its target on B cells
Trastuzumab	HER2 (“trust HER”)	Breast cancer, gastric cancer	Dilated cardiomyopathy (often reversible)
Pembrolizumab, nivolumab, cemiplimab	PD-1	Various tumors (eg, NSCLC, RCC, melanoma, urothelial carcinoma)	\uparrow risk of autoimmunity (eg, dermatitis, enterocolitis, hepatitis, pneumonitis, endocrinopathies)
Atezolizumab, durvalumab, avelumab	PD-L1		
Ipilimumab	CTLA-4		

Anticancer small molecule inhibitors

AGENT	TARGET	CLINICAL USE	ADVERSE EFFECTS
Alectinib, crizotinib	ALK	Non–small cell lung cancer	Edema, rash, diarrhea
Erlotinib, ge tinib, afatinib	EGFR	Non–small cell lung cancer	Rash, diarrhea
Imatinib, dasatinib, nilotinib	BCR-ABL (also other tyrosine kinases [eg, c-KIT])	CML, ALL, GISTS	Myelosuppression, ↑ LFTs, edema, myalgias
Ruxolitinib	JAK1/2	Polycythemia vera	Bruises, ↑ LFTs
Bortezomib, ixazomib, carfilzomib	Proteasome (induce arrest at G2-M phase via accumulation of abnormal proteins → apoptosis)	Multiple myeloma, mantle cell lymphoma	Peripheral neuropathy, herpes zoster reactivation (↓ T-cell activation → ↓ cell-mediated immunity)
Vemurafenib, encorafenib, dabrafenib	BRAF	Melanoma Often co-administered with MEK inhibitors (eg, trametinib)	Rash, fatigue, nausea, diarrhea
Palbociclib	Cyclin-dependent kinase 4/6 (induces arrest at G1-S phase → apoptosis)	Breast cancer	Myelosuppression, pneumonitis
Olaparib	Poly(ADP-ribose) polymerase (↓ DNA repair)	Breast, ovarian, pancreatic, and prostate cancers	Myelosuppression, edema, diarrhea

Chemotoxicity amelioration

DRUG	MECHANISM	CLINICAL USE
Amifostine	Free radical scavenger	Nephrotoxicity from platinum compounds
Dexrazoxane	Iron chelator	Cardiotoxicity from anthracyclines
Leucovorin (folinic acid)	Tetrahydrofolate precursor	Myelosuppression from methotrexate (leucovorin “rescue”); also enhances the effects of 5-FU
Mesna	Sulfhydryl compound that binds acrolein (toxic metabolite of cyclophosphamide/ifosfamide)	Hemorrhagic cystitis from cyclophosphamide/ifosfamide
Rasburicase	Recombinant uricase that catalyzes metabolism of uric acid to allantoin	Tumor lysis syndrome
Ondansetron, granisetron	5-HT ₃ receptor antagonists	Acute nausea and vomiting (usually within 1-2 hr after chemotherapy)
Prochlorperazine, metoclopramide	D ₂ receptor antagonists	
Aprepitant, fosaprepitant	NK ₁ receptor antagonists	Delayed nausea and vomiting (>24 hr after chemotherapy)
Filgrastim, sargramostim	Recombinant G(M)-CSF	Neutropenia
Epoetin alfa	Recombinant erythropoietin	Anemia

Key chemotoxicities

Cisplatin, Carboplatin → ototoxicity

Vincristine → peripheral neuropathy
Bleomycin, Busulfan → pulmonary fibrosis
Doxorubicin, Daunorubicin → cardiotoxicity
Trastuzumab → cardiotoxicity
Cisplatin, Carboplatin → nephrotoxicity

Cyclophosphamide → hemorrhagic cystitis

Nonspecific common toxicities of nearly all cytotoxic chemotherapies include myelosuppression (neutropenia, anemia, thrombocytopenia), GI toxicity (nausea, vomiting, mucositis), alopecia.