

HIGH-YIELD SYSTEMS

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 .

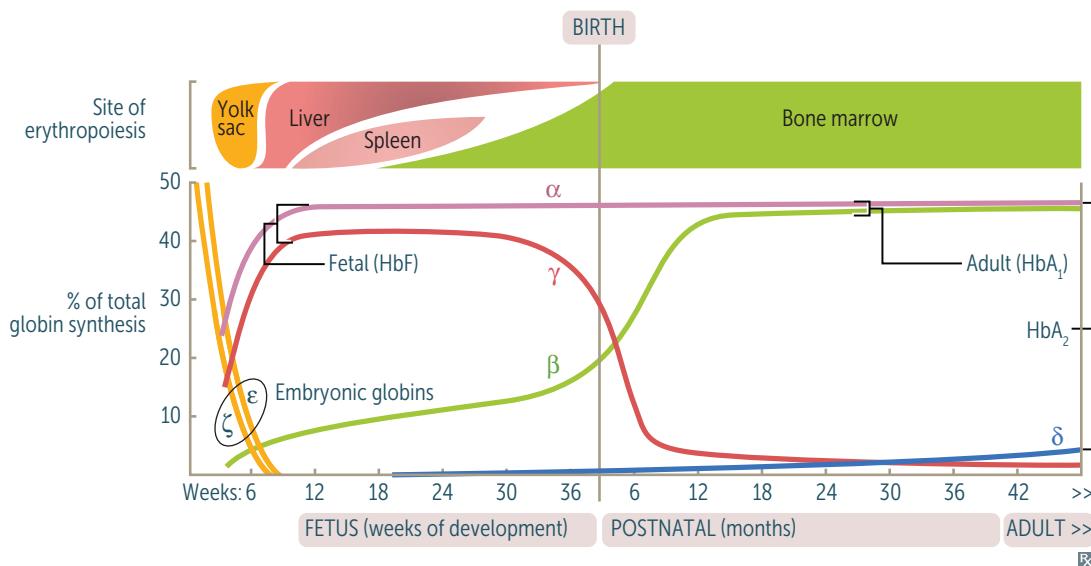
Fetal hemoglobin (HbF) = $\alpha_2\gamma_2$.

Adult hemoglobin (HbA₁) = $\alpha_2\beta_2$.

HbF has higher affinity for O₂ because it binds to 2,3-BPG with relatively lower affinity, allowing HbF to capture O₂ from maternal hemoglobin (HbA₁ and HbA₂) across the placenta. HbA₂ ($\alpha_2\delta_2$) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:

Alpha always; gamma goes, beta becomes beta.



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 | NONE | Anti-D |
| Clinical relevance | A, O | B, O | AB, A, B, O | O | Rh+, Rh- | Rh- |
| Compatible RBC types to receive | A, AB | B, AB | AB | A, B, AB, O | Rh+ | Rh+, Rh- |
| Compatible RBC types to donate to | | | | | | |

Rx

Hemolytic disease of the fetus and newborn

Also called erythroblastosis fetalis. Most commonly involves the antigens of the major blood groups (eg, Rh and ABO), but minor blood group incompatibilities (eg, Kell) can also result in disease, ranging from mild to severe.

ABO hemolytic disease

INTERACTION Type O pregnant patient; type A or B fetus.

MECHANISM Preexisting pregnant patient anti-A and/or anti-B IgG antibodies cross the placenta → attack fetal and newborn RBCs → hemolysis.

PRESENTATION 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 Treatment: phototherapy or exchange transfusion.

Rh hemolytic disease

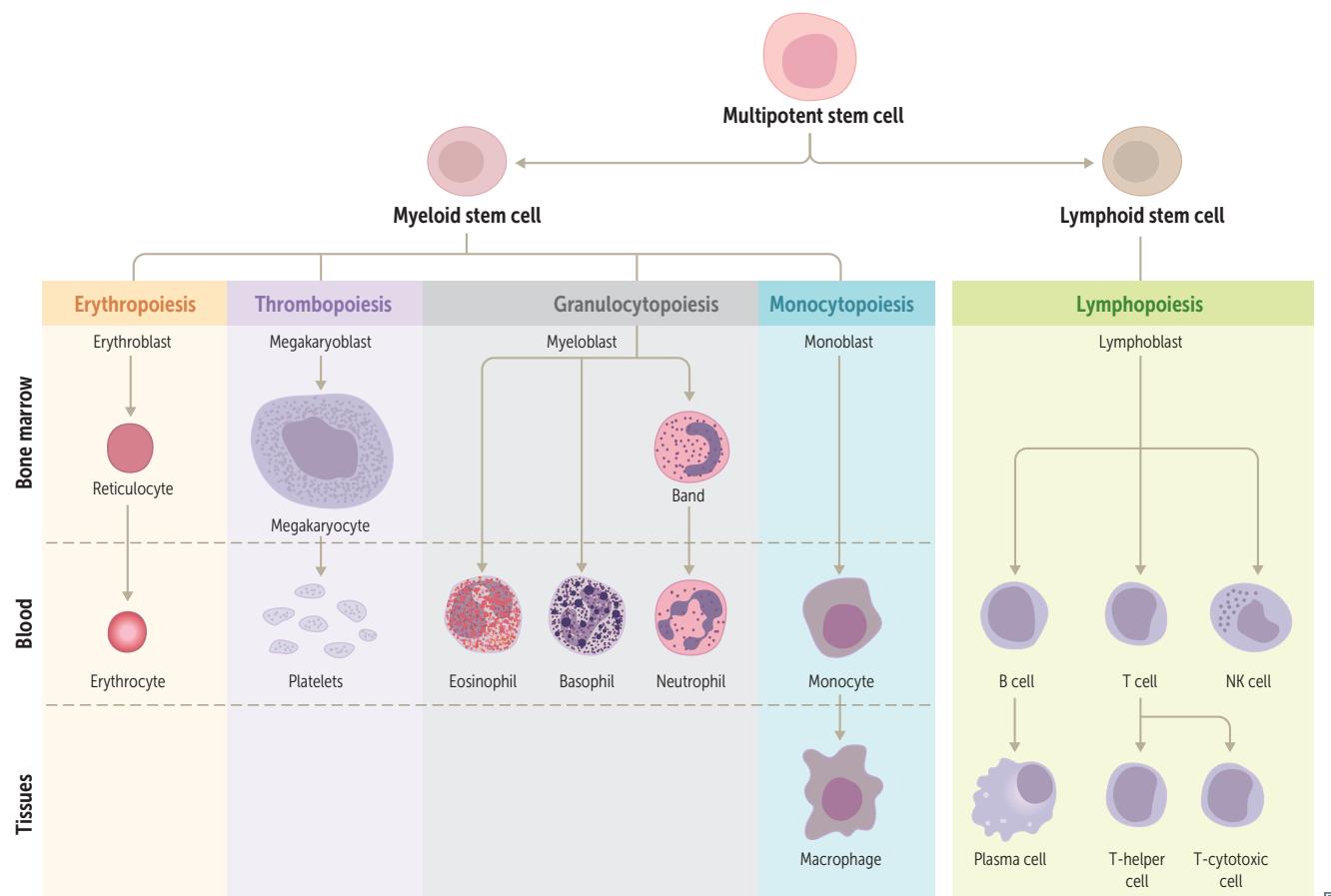
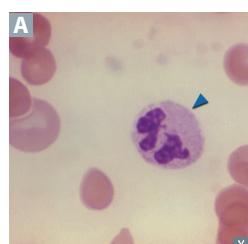
Rh- pregnant patient; Rh+ fetus.

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.

Hydrops fetalis, jaundice shortly after birth, kernicterus.

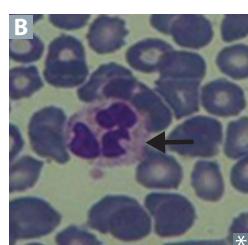
Prevent by administration of anti-D IgG to Rh- pregnant patients during third trimester and early postpartum period as well as in cases of ectopic pregnancy, miscarriage, abdominal trauma, and antepartum hemorrhage (if fetus Rh+). Prevents maternal anti-D IgG production.

▶ HEMATOLOGY AND ONCOLOGY—ANATOMY

Hematopoiesis**Neutrophils**

Acute inflammatory response cells. Phagocytic.

Multilobed nucleus **A**. Specific granules contain leukocyte alkaline phosphatase (LAP), collagenase, lysozyme, and lactoferrin. Azurophilic granules (lysosomes) contain proteinases, acid phosphatase, myeloperoxidase, and β -glucuronidase. Inflammatory states (eg, bacterial infection) cause neutrophilia and changes in neutrophil morphology, such as left shift, toxic granulation (dark blue, coarse granules), Döhle bodies (light blue, peripheral inclusions, arrow in **B**), and cytoplasmic vacuoles.



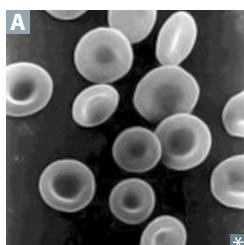
Neutrophil chemotactic agents: C5a, IL-8,

LTB_4 , 5-HETE (leukotriene precursor), kallikrein, platelet-activating factor, N-formylmethionine (bacterial proteins).

Hypersegmented neutrophils (nucleus has 5–6+ lobes) are seen in vitamin B₁₂/folate deficiency.

Left shift—↑ neutrophil precursors (eg, band cells, metamyelocytes) in peripheral blood. Reflects states of ↑ myeloid proliferation (eg, inflammation, CML).

Leukoerythroblastic reaction—left shift accompanied by immature RBCs. Suggests bone marrow infiltration (eg, myelofibrosis, metastasis).

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.

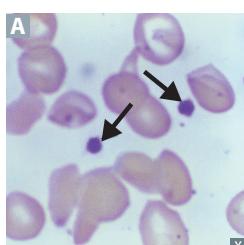
Erythrocytosis = polycythemia = ↑ Hct.

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.

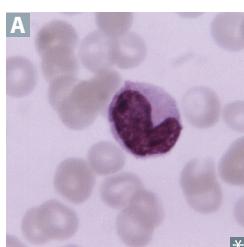
Thrombocytopenia or ↓ platelet function results in petechiae.

vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

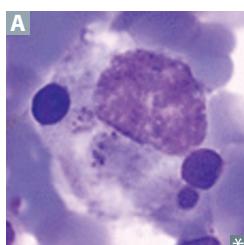
Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor four.

Monocytes

Found in blood, differentiate into macrophages or dendritic cells in tissues.

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

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

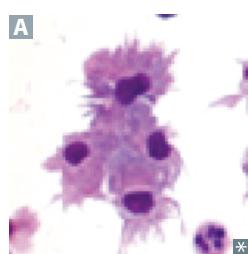
Macrophages

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.

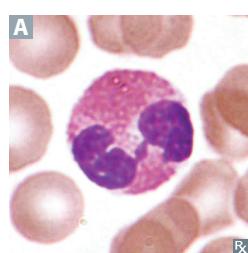
Macro = large; *phage* = eater.

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**A**

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**A**

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 cationic protein, eosinophil-derived neurotoxin, and IL-5, which promotes eosinophilic activation and proliferation.

Eosin = pink dye; *philic* = loving.

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

Parasites

Asthma

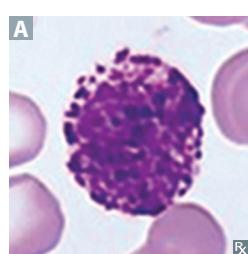
Chronic adrenal insufficiency

Myeloproliferative disorders

Allergic processes

Neoplasia (eg, Hodgkin lymphoma)

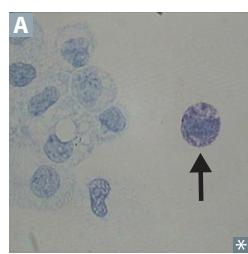
Eosinophilic granulomatosis with polyangiitis

Basophils**A**

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**A**

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.

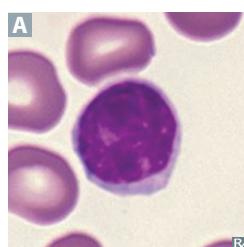
Involved in type I hypersensitivity reactions.

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

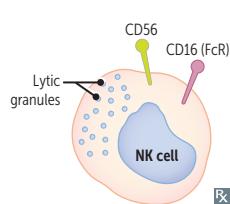
Vancomycin, opioids, and radiocontrast dye can elicit IgE-independent mast cell degranulation.

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

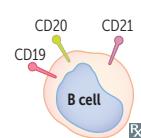
↑ histamine → flushing, pruritus, hypotension, abdominal pain, diarrhea, peptic ulcer disease.

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**.

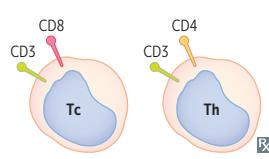
Natural killer cells

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.

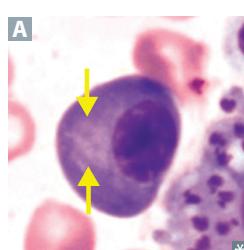
T cells

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.

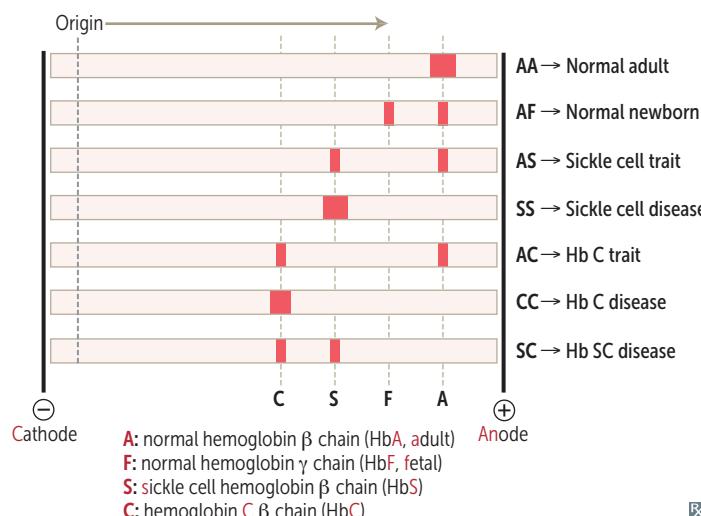
Rule of 8: MHC **II** × CD**4** = 8;
MHC **I** × CD**8** = 8.

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.

► HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

Hemoglobin electrophoresis

During gel electrophoresis, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid \ominus with valine (neutral) and lysine \oplus , respectively, making HbC and HbS more positively charged than HbA.

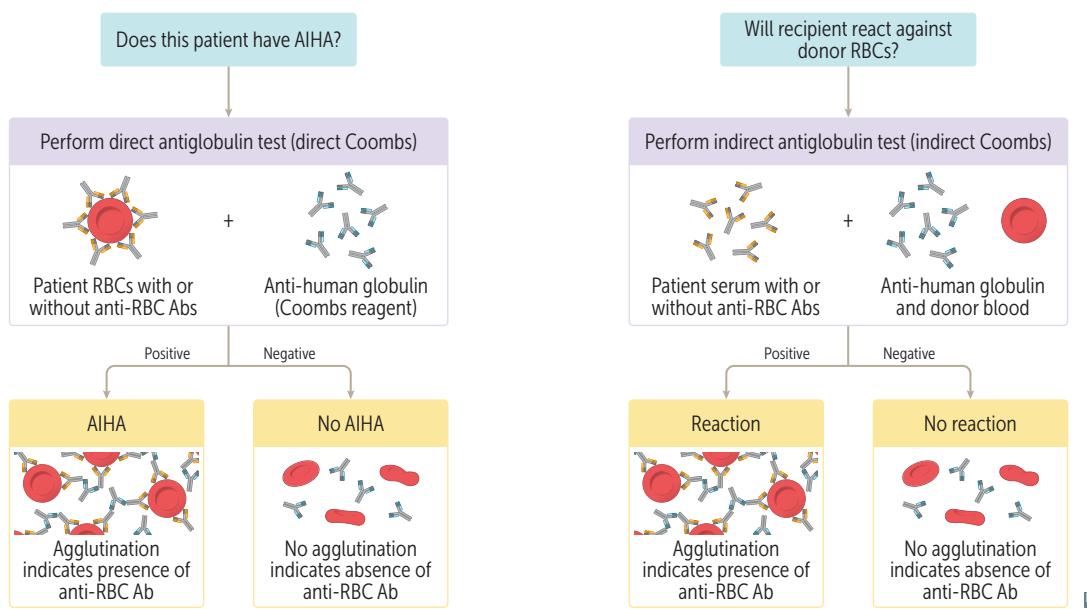
A Fat Santa Claus can't go far.
 HbC is closest to the **Cathode**. HbA is closest to the **Anode**.

Antiglobulin test

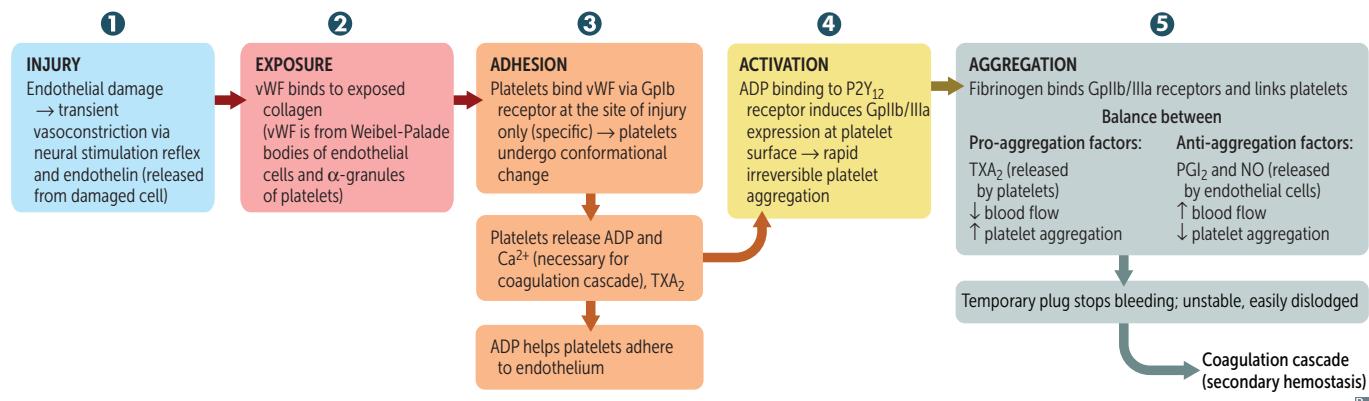
Also called Coombs test. Detects the presence of antibodies against circulating RBCs.

Direct antiglobulin test—anti-human globulin (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are (**directly**) coated with anti-RBC Abs. Used for AIHA diagnosis.

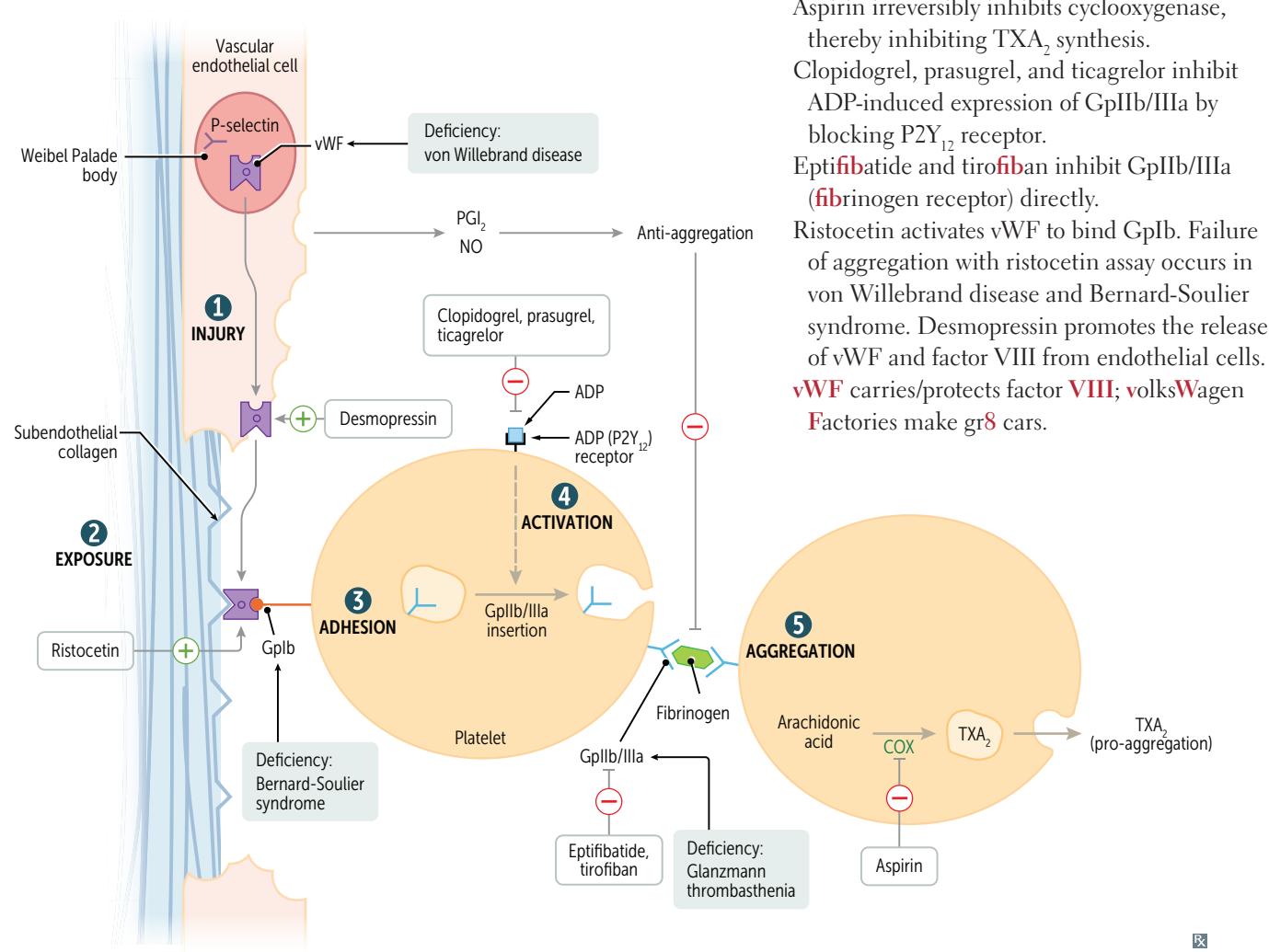
Indirect (not direct) antiglobulin test—normal RBCs added to patient's serum. If serum has anti-RBC Abs, RBCs agglutinate when Coombs reagent is added. Used for pretransfusion testing.



Platelet plug formation (primary hemostasis)

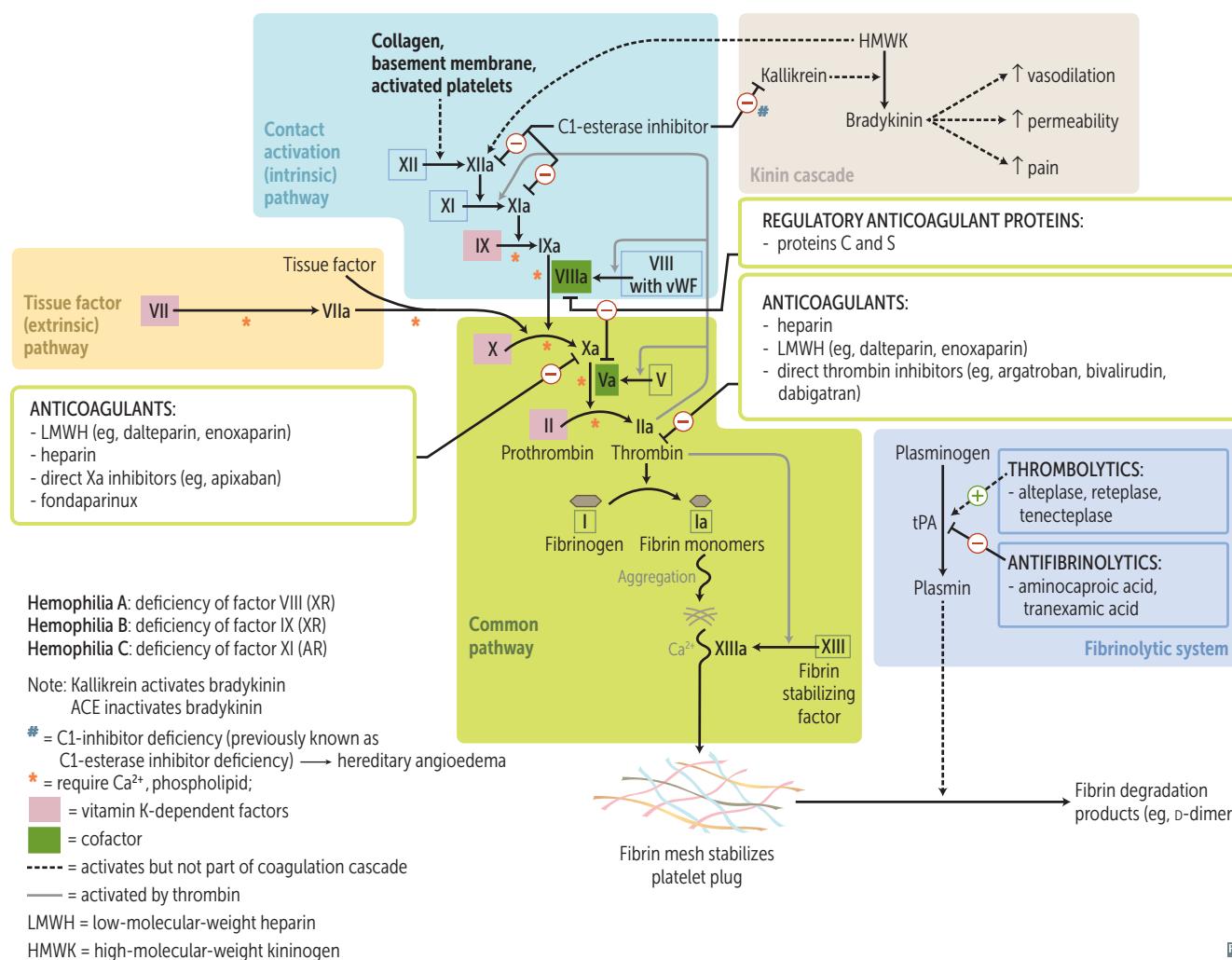


Thrombogenesis



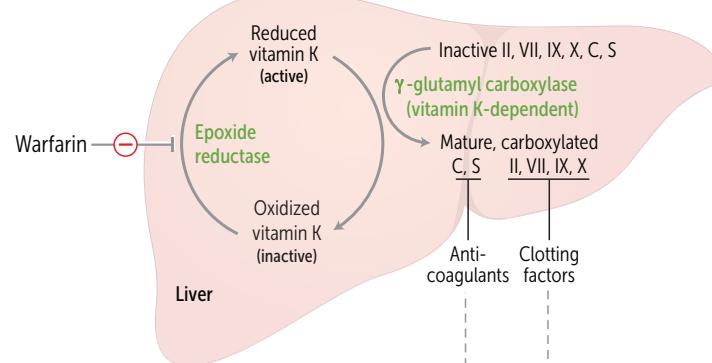
Coagulation and kinin pathways

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.

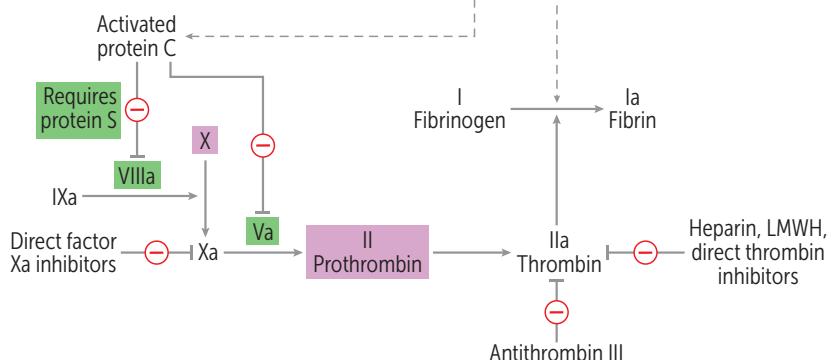


Vitamin K-dependent coagulation

Procoagulation



Anticoagulation



■ = vitamin K-dependent factors
■ = cofactor

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

Vitamin K deficiency → ↓ carboxylation and maturation 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.

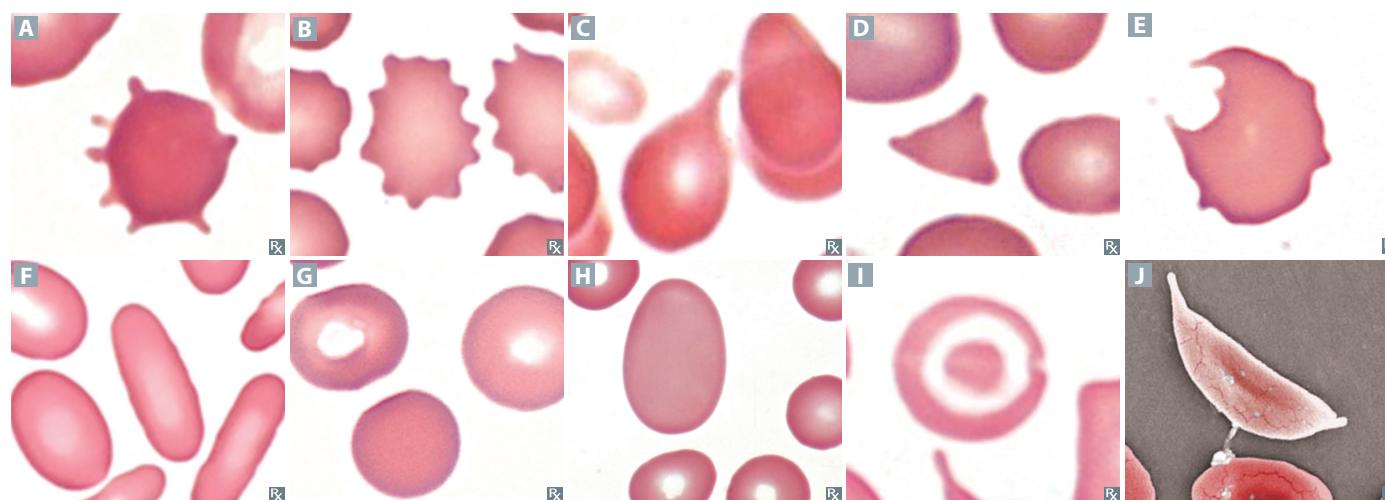
Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

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

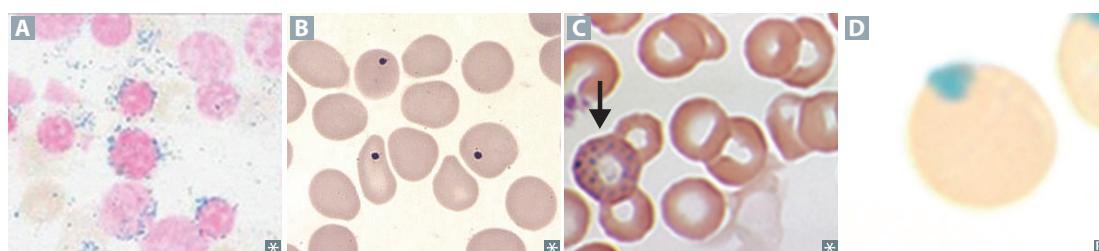
RBC morphology

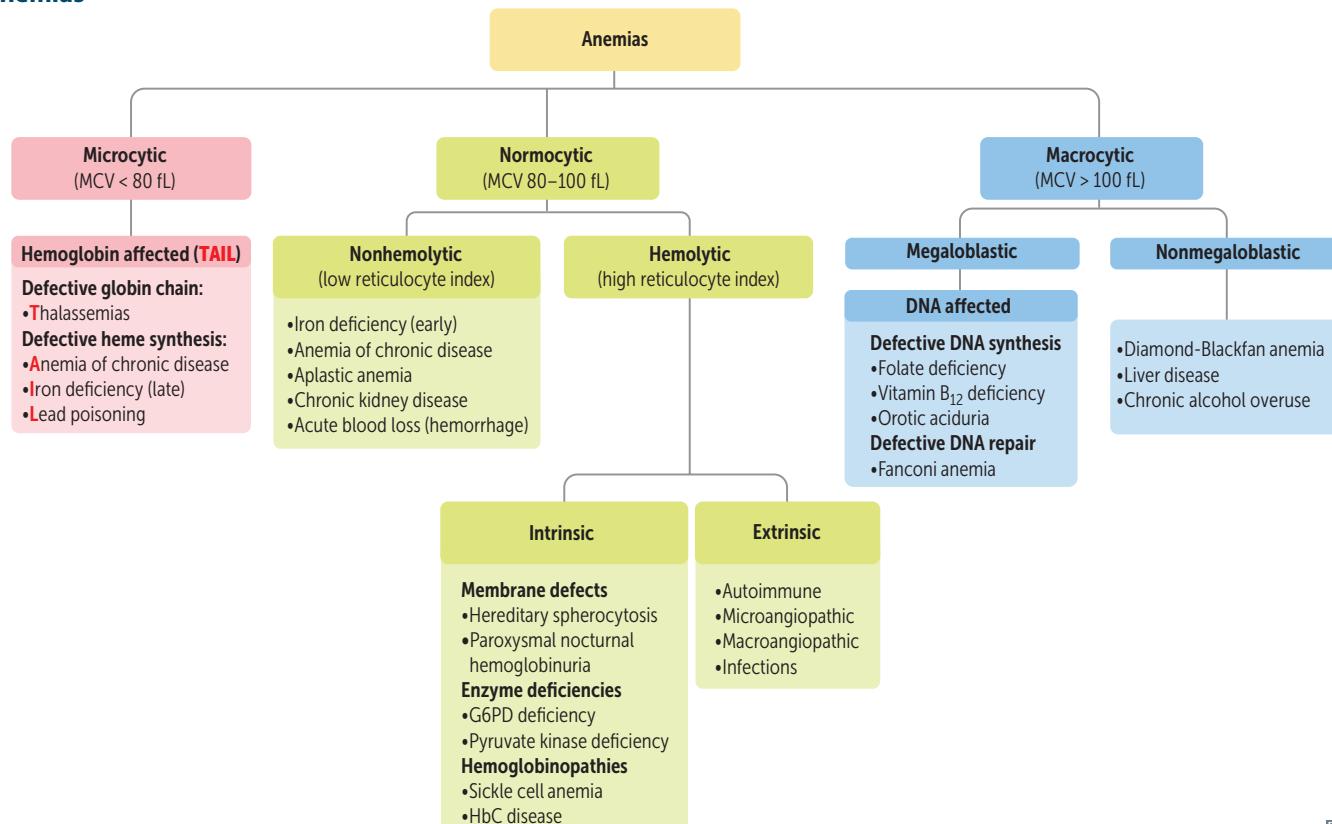
| TYPE | ASSOCIATED PATHOLOGY | NOTES |
|---|---|--|
| Acanthocytes A ("spur cells") | Liver disease, abetalipoproteinemia, vitamin E deficiency | Projections of varying size at irregular intervals (acanthocytes are asymmetric) |
| Echinocytes B ("burr cells") | Liver disease, ESRD, pyruvate kinase deficiency | Smaller and more uniform projections than acanthocytes (echinocytes are even) |
| Dacrocytes C ("teardrop cells") | Bone marrow infiltration (eg, myelofibrosis) | RBC "sheds a tear " because it's mechanically squeezed out of its home in the bone marrow |
| Schistocytes D ("helmet" cells) | Microangiopathic hemolytic anemia (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis) | Fragmented RBCs |
| Degmacytes E ("bite cells") | G6PD deficiency | Due to removal of Heinz bodies by splenic macrophages (they " deg " them out of/bite them off of RBCs) |
| Elliptocytes F | Hereditary elliptocytosis | Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin) |
| Spherocytes G | Hereditary spherocytosis, autoimmune hemolytic anemia | Small, spherical cells without central pallor ↓ surface area-to-volume ratio |
| Macro-ovalocytes H | Megaloblastic anemia (also hypersegmented PMNs) | |
| Target cells I | HbC disease, Asplenia, Liver disease, Thalassemia | " HALT ," said the hunter to his target ↑ surface area-to-volume ratio |
| Sickle cells J | Sickle cell anemia | Sickling occurs with low O ₂ conditions (eg, high altitude, acidosis), high HbS concentration (ie, dehydration) |



RBC inclusions

| TYPE | ASSOCIATED PATHOLOGY | NOTES |
|-------------------------------|--|--|
| Bone marrow | | |
| Iron granules A | 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 B | Functional hyposplenia (eg, sickle cell disease), asplenia | Basophilic nuclear remnants (do not contain iron) Usually removed by splenic macrophages |
| Basophilic stippling C | Sideroblastic anemias, thalassemias | Basophilic ribosomal precipitates (do not contain iron) |
| Pappenheimer bodies | Sideroblastic anemias | Basophilic granules (contain iron) “Pappen- hammer ” bodies |
| Heinz bodies D | G6PD deficiency | Denatured and precipitated hemoglobin (contain iron) Phagocytic removal of Heinz bodies → bite cells (take a bite of Heinz [ketchup]) Requires supravital stain (eg, crystal violet) to be visualized |



Anemias

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:

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

Mentzer index

Used to differentiate between thalassemia trait and iron deficiency anemia. An index of **less** than 13 suggests **thalassemia** trait. An **increased** index (> 13) suggests **iron deficiency anemia**.

$$\text{Mentzer index} = \frac{\text{MCV}}{\text{RBC count}}$$

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.

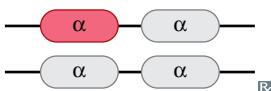
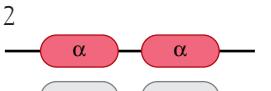
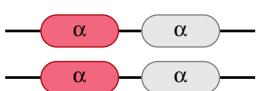
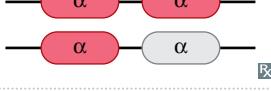
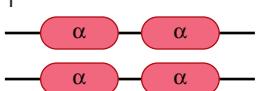
Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and hypochromasia (↑ central pallor) **A**.

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 | DISEASE | CLINICAL OUTCOME |
|-------------------------------------|--|--|
| 1 | α -thalassemia minima | No anemia (silent carrier) |
| |  | |
| 2 | α -thalassemia minor | Mild microcytic, hypochromic anemia |
| |  Cis or  | |
| 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 |
| |  | |

Microcytic, hypochromic anemias (continued)**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 Mediterranean populations.

| # OF β-GLOBIN GENES MUTATED | DISEASE | CLINICAL OUTCOME |
|--|-------------------------------------|---|
| 1 (β^+/β or β^0/β) | 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^0/β^0) | β-thalassemia major (Cooley anemia) | Severe microcytic anemia with target cells and ↑ anisopoikilocytosis requiring blood transfusions (↑ risk of 2° hemochromatosis), marrow expansion (“crew cut” on skull x-ray D) → skeletal deformities, extramedullary hematopoiesis → HSM. ↑ risk of parvovirus B19-induced aplastic crisis. ↑ HbF and HbA ₂ , becomes symptomatic after 6 months when HbF declines (HbF is protective). Chronic hemolysis → pigmented gallstones. |
| 1 (β^+/HbS or β^0/HbS) | Sickle cell β-thalassemia | Mild to moderate sickle cell disease depending on whether there is ↓ (β^+/HbS) or absent (β^0/HbS) β-globin synthesis. |

Lead poisoning

Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).

Symptoms of LLEEAAD poisoning:

- **L**ead **L**ines on gingivae (Burton lines) and on metaphyses of long bones E on x-ray.
- **E**ncephalopathy and **E
- **A**bdominal colic and sideroblastic **A**nemia.
- **D**rugs—wrist and foot drop.**

Treatment: chelation with succimer, EDTA, dimercaprol.

↑ exposure risk: children—chipped paint in old houses (built before 1978); adults—workplace (eg, batteries, ammunition).

Sideroblastic anemia

Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B₆ deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).

Lab findings: ↑ iron, normal/↓ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue-stained mitochondria) seen in bone marrow. Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

Treatment: pyridoxine (B₆, cofactor for ALA synthase).



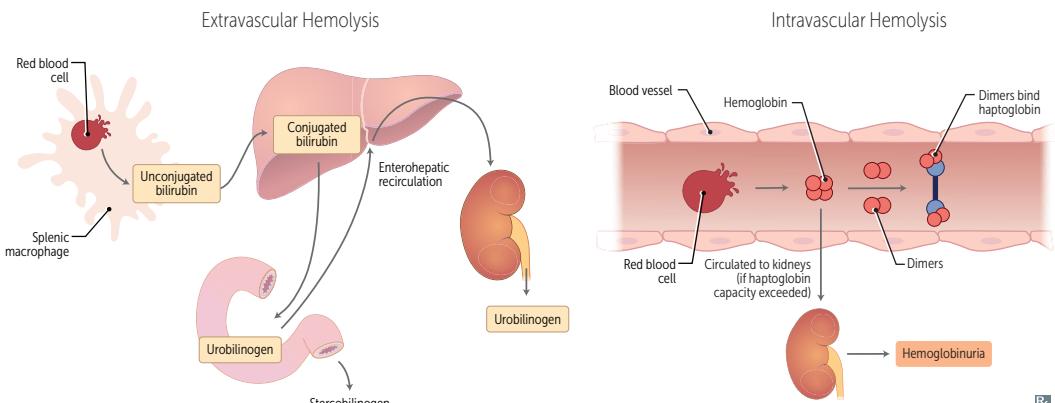
Macrocytic anemias

MCV > 100 fL.

| | DESCRIPTION | FINDINGS |
|--|--|---|
| Megaloblastic anemia | Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm. Causes: vitamin B ₁₂ deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs). | RBC macrocytosis, hypersegmented neutrophils (arrow in A), glossitis. |
| Folate deficiency | Causes: malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy). | ↑ homocysteine, normal methylmalonic acid. No neurologic symptoms (vs B ₁₂ deficiency). |
| Vitamin B₁₂ (cobalamin) deficiency | Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), <i>Diphyllobothrium latum</i> (fish tapeworm). | ↑ 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 | Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B ₁₂ . No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia). | 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. A pure Diamond causes pure red cell aplasia. |

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 (↑ adipose tissue in bone marrow in aplastic anemia). 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.</p> <p>→ ↓ surface area/dehydration → ↑ MCHC</p> <p>→ premature removal by spleen (extravascular hemolysis).</p> | <p>Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection).</p> <p>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.</p> <p>Treatment: splenectomy.</p> |
| Paroxysmal nocturnal hemoglobinuria | <p>Hematopoietic stem cell mutation</p> <p>→ ↑ complement-mediated intravascular hemolysis, especially at night. Acquired <i>PIGA</i> 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).</p> <p>Pink/red urine in morning. Associated with aplastic anemia, acute leukemias.</p> <p>Labs: CD55/59 ⊖ RBCs on flow cytometry.</p> <p>Treatment: eculizumab (targets terminal complement protein C5).</p> |
| G6PD deficiency | <p>X-linked recessive. G6PD defect</p> <p>→ ↓ NADPH → ↓ reduced glutathione</p> <p>→ ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, fava beans)</p> <p>→ hemolysis.</p> <p>Causes extravascular and intravascular hemolysis.</p> | <p>Back pain, hemoglobinuria a few days after oxidant stress.</p> <p>Labs: ↓ G6PD activity (may be falsely normal during acute hemolysis), blood smear shows RBCs with Heinz bodies and bite cells.</p> <p>“Stress makes me eat bites of fava beans with Heinz ketchup.”</p> |
| Pyruvate kinase deficiency | <p>Autosomal recessive. Pyruvate kinase defect</p> <p>→ ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG</p> <p>→ ↓ hemoglobin affinity for O₂.</p> | <p>Hemolytic anemia in a newborn.</p> <p>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</p> <p>→ aggregation of hemoglobin. Causes extravascular and intravascular hemolysis.</p> <p>Pathogenesis: ↓ O₂, ↑ 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). ▪ Autosplenectomy (Howell-Jolly bodies) → ↑ 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.</p> <p>Treatment: hydroxyurea (↑ HbF), hydration.</p> |
| HbC disease | Glutamic acid-to-lysine (lysine) mutation in β-globin. Causes extravascular hemolysis. | HbSC (1 of each mutant gene) milder than HbSS. Blood smear in homozygotes: hemoglobin crystals inside RBCs, target cells. |

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 >> intravascular 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 >> intravascular 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. | Schisto cytes (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>). | |

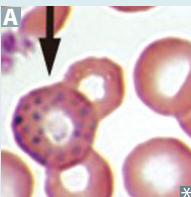
Leukopenias

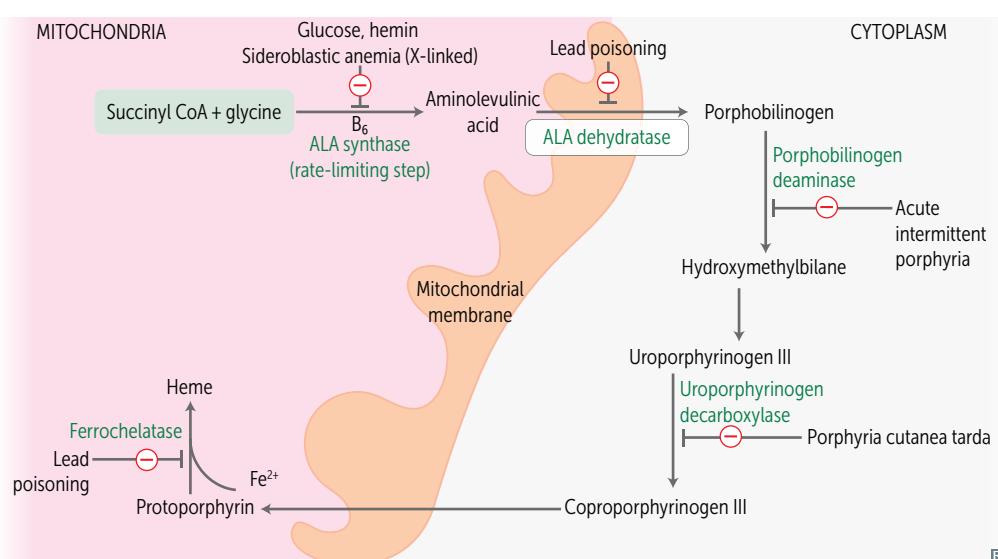
| CELL TYPE | CELL COUNT | CAUSES |
|--------------------|--|--|
| Neutropenia | Absolute neutrophil count $< 1500 \text{ cells/mm}^3$ Severe infections typical when $< 500 \text{ cells/mm}^3$ | Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, autoimmunity (eg, SLE), radiation, 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. |
| Acute intermittent porphyria | Porphobilinogen deaminase (autosomal dominant mutation) | Porphobilinogen, ALA | Symptoms (5 P's): ▪ 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 | Occurs via free radical formation and membrane lipid peroxidation → cell death. | |
| FINDINGS | Acute | Chronic |
| | ↑ 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. |
| SYMPTOMS/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. | Chelation, regular therapeutic phlebotomy (unless contraindicated, eg, anemia) |

| | |
|------------------------------|--|
| Coagulation disorders | PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT (Play Tennis outside [extrinsic 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 intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT (Play Table Tennis inside). 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. Most commonly due to 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 and aggregation. |

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: ↓ quantity/function of 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: vWF concentrates, desmopressin (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 Stroke, Snake bites, Sepsis (gram ⊖), Trauma, Obstetric complications, acute Pancreatitis, malignancy, nephrotic syndrome, transfusion (SSSTOP making new thrombi). Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII. |

| DISEASE | DESCRIPTION |
|-------------------------------------|--|
| Hereditary thrombophilias | Autosomal dominant disorders resulting in hypercoagulable state (↑ tendency to develop thrombosis). |
| Antithrombin deficiency | 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 deficiency | ↓ ability to inactivate factors Va and VIIIa. ↑ 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

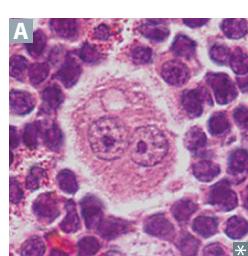
| COMPONENT | DOSAGE EFFECT | CLINICAL USE |
|---|---|---|
| Packed RBCs | ↑ Hb and O ₂ binding (carrying) capacity, ↑ hemoglobin ~1 g/dL per unit, ↑ hematocrit ~3% per unit | Acute blood loss, severe anemia |
| Platelets | ↑ platelet count ~30,000/microL per unit (↑ ~5000/mm ³ /unit) | Stop significant 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). |

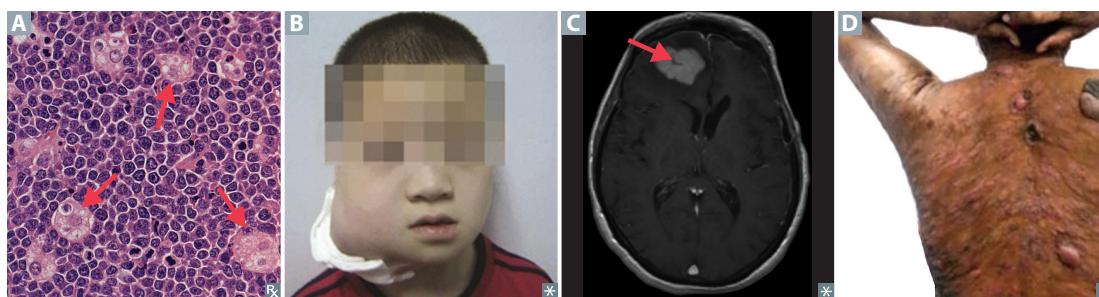
Hodgkin lymphoma

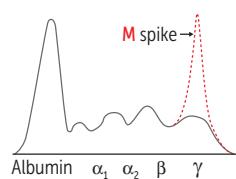
Contains Reed-Sternberg cells: distinctive tumor giant cells; bilobed nucleus with the **2** halves as mirror images (“owl eyes” **A**). RS cells are CD15+ and CD30+ B-cell origin. **2 owl eyes × 15 = 30.**

| 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

| TYPE | OCCURS IN | GENETICS | COMMENTS |
|--|--|--|--|
| Neoplasms of mature B cells | | | |
| Burkitt lymphoma | Adolescents or young adults “Burkid” lymphoma (more common in kids) | t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14) | “Starry sky” appearance (StarBurst), sheets of lymphocytes with interspersed “tingible body” macrophages (arrows in A). Associated with EBV. Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form. |
| Diffuse large B-cell lymphoma | Usually older adults, but 20% in children | Mutations in <i>BCL-2</i> , <i>BCL-6</i> | Most common type of non-Hodgkin lymphoma in adults. |
| Follicular lymphoma | Adults | t(14;18)—translocation of heavy-chain Ig (14) and <i>BCL-2</i> (18) | Indolent course with painless “waxing and waning” lymphadenopathy. Bcl-2 normally inhibits apoptosis. |
| Mantle cell lymphoma | Adult males >> adult females | t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+ | Very aggressive, patients typically present with late-stage disease. |
| Marginal zone lymphoma | Adults | t(11;18) | Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma; may regress with <i>H pylori</i> eradication]). |
| Primary central nervous system lymphoma | Adults | EBV related; associated with HIV/AIDS | Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests. |
| Neoplasms of mature T cells | | | |
| Adult T-cell lymphoma | Adults | Caused by HTLV (associated with IV drug use) | Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia. |
| Cutaneous T-cell lymphoma | Adults | | Heterogenous group of T-cell neoplasms affecting the skin ± blood, lymph nodes, or viscera. Most common subtype is mycosis fungoides D characterized by erythematous patches favoring sun-protected areas that progress to plaques, then eventually tumors. |



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

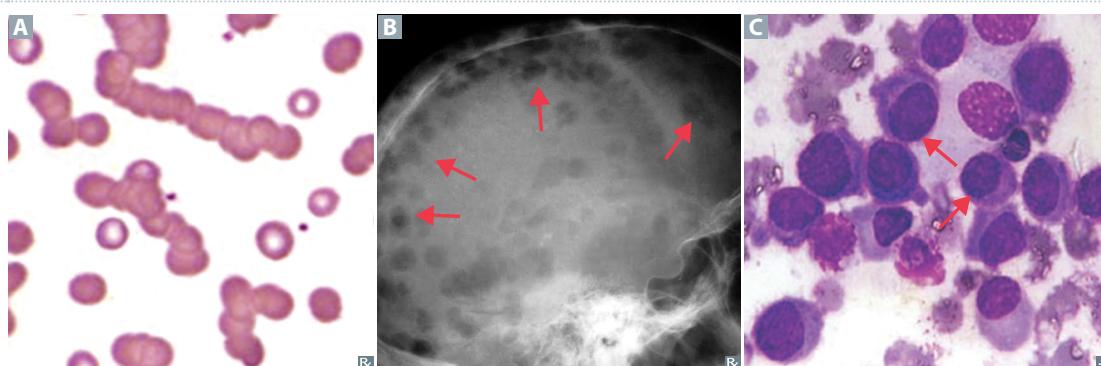
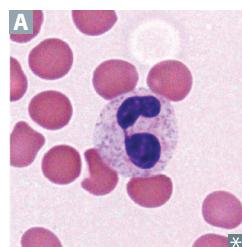
Overproduction of IgG (most common) > IgA > Ig light chains. Clinical features (**CRAB**): hyper**C**alcemia (\uparrow cytokine secretion [eg, IL-1, TNF- α , RANK-L] by malignant plasma cells \rightarrow \uparrow osteoclast activity), **R**enal insufficiency, **A**nemia, **B**one lytic lesions (“punched out” on x-ray **B** \rightarrow back pain, pathologic fractures). 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 (**macro**globulinemia 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 examination 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**

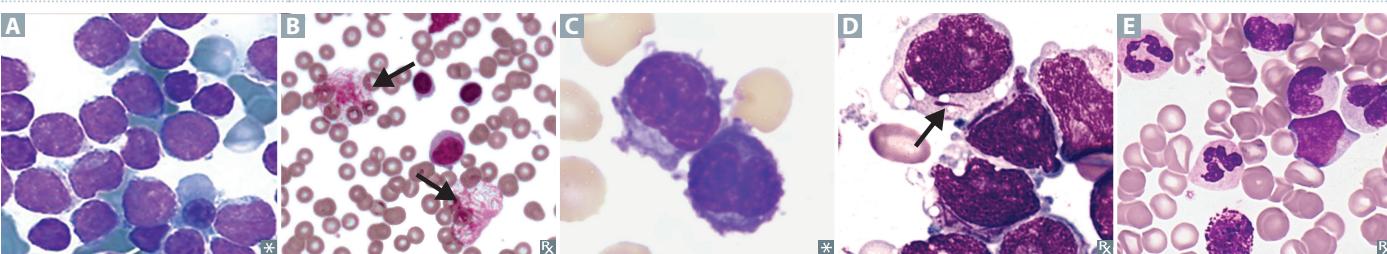
Stem cell disorders involving ineffective hematopoiesis \rightarrow defects in cell maturation of nonlymphoid lineages. Bone marrow blasts $<20\%$ (vs $>20\%$ in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML. More common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

Pseudo-Pelger-Huët 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 (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood), although some cases present with normal/↓ 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).</p> <p>Most responsive to therapy.</p> <p>May spread to CNS and testes.</p> <p>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).</p> <p>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.</p> <p>Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia.</p> <p>Stains TRAP (Tartrate-Resistant Acid Phosphatase) ⊕ (TRAPped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with BRAF mutations.</p> <p>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).</p> <p>Risk factors: prior exposure to alkylating chemotherapy, radiation, benzene, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]).</p> <p>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”).</p> <p>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 blood cell under a microscope. Panel A shows a dense cluster of dark purple-stained cells. Panel B shows a peripheral blood smear with several pinkish-purple cells, some of which have black arrowheads pointing to them. Panel C shows a light-colored background with a few dark purple-stained cells. Panel D shows a cluster of dark purple-stained cells with one cell containing a prominent purple rod-shaped structure (Auer rod). Panel E shows a variety of pinkish-purple and dark purple-stained cells.</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).

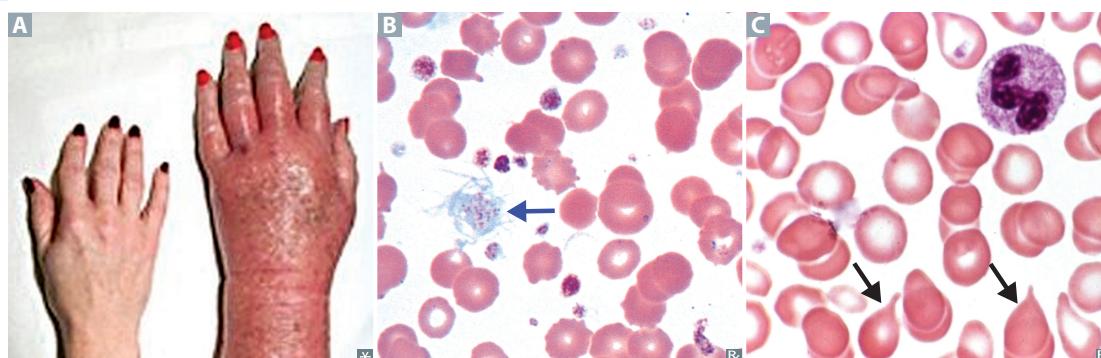
Essential thrombocythemia

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/mm ³ | 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 | ↑ |

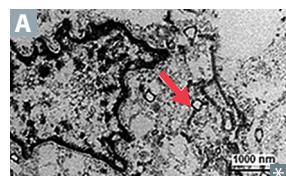
Polycythemia

| | 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. |

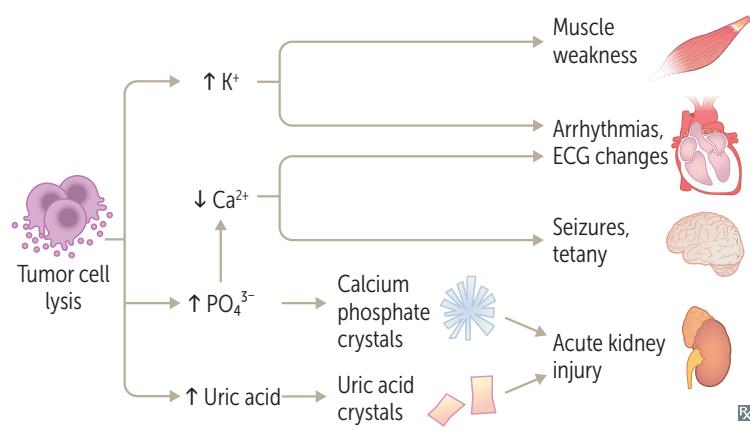
↑↓ = 1° disturbance

Chromosomal translocations

| TRANSLOCATION | ASSOCIATED DISORDER | NOTES |
|-----------------------------------|--|--|
| t(8;14) | Burkitt (Burk-8) lymphoma (c-myc activation) | |
| t(11;14) | Mantle cell lymphoma (cyclin D1 activation) | |
| t(11;18) | Marginal zone lymphoma | |
| t(14;18) | Follicular lymphoma (BCL-2 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**.

Tumor lysis syndrome

Oncologic emergency triggered by massive tumor cell lysis, seen most often with lymphomas/leukemias. Usually caused by treatment initiation, but can occur spontaneously with fast-growing cancers. Release of K⁺ → hyperkalemia, release of PO₄³⁻ → hyperphosphatemia, hypocalcemia due to Ca²⁺ sequestration by PO₄³⁻. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Prevention and treatment include aggressive hydration, allopurinol, rasburicase. Tumor cell breakdown causes ↑ K⁺, ↓ Ca²⁺, ↑ Uric acid, and ↑ PO₄³⁻ (BreaK the CUP).

▶ HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

Heparin

| | |
|-----------------|---|
| MECHANISM | Activates antithrombin, which ↓ action primarily of factors IIa (thrombin) and Xa. Short half-life. |
| CLINICAL USE | Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta; low-molecular-weight heparin [eg, enoxaparin] preferred). Monitor PTT. |
| ADVERSE EFFECTS | Bleeding (reverse with protamine sulfate), heparin-induced thrombocytopenia (HIT), osteoporosis (with long-term use), drug-drug interactions, type 4 renal tubular acidosis. <ul style="list-style-type: none"> ▪ HIT type 1—mild (platelets > 100,000/mm³), transient, nonimmunologic drop in platelet count that typically occurs within the first 2 days of heparin administration. Not clinically significant. ▪ HIT type 2—development of IgG antibodies against heparin-bound platelet factor 4 (PF4) that typically occurs 5–10 days after heparin administration. Antibody-heparin-PF4 complex binds and activates platelets → removal by splenic macrophages and thrombosis → ↓ platelet count. Highest risk with unfractionated heparin. Treatment: discontinue heparin, start alternative anticoagulant (eg, argatroban). Fondaparinux safe to use (does not interact with PF4). |
| NOTES | Low-molecular-weight heparins (eg, enoxaparin, dalteparin) act mainly on factor Xa. Longer half-life. Fondaparinux acts only on factor Xa. Both are not easily reversible. Unfractionated heparin used in patients with renal insufficiency (low-molecular-weight heparins should be used with caution because they undergo renal clearance). |

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 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

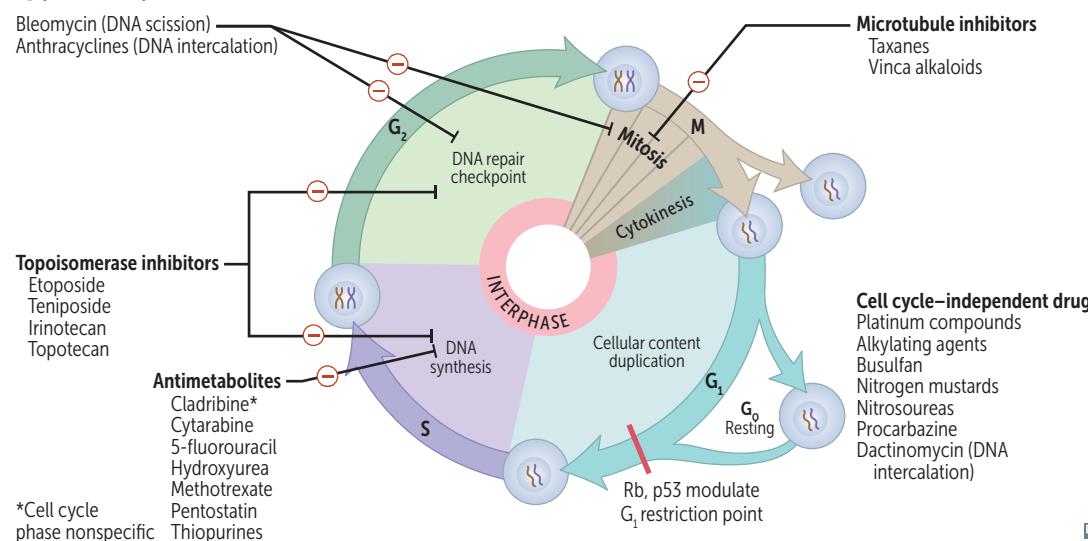
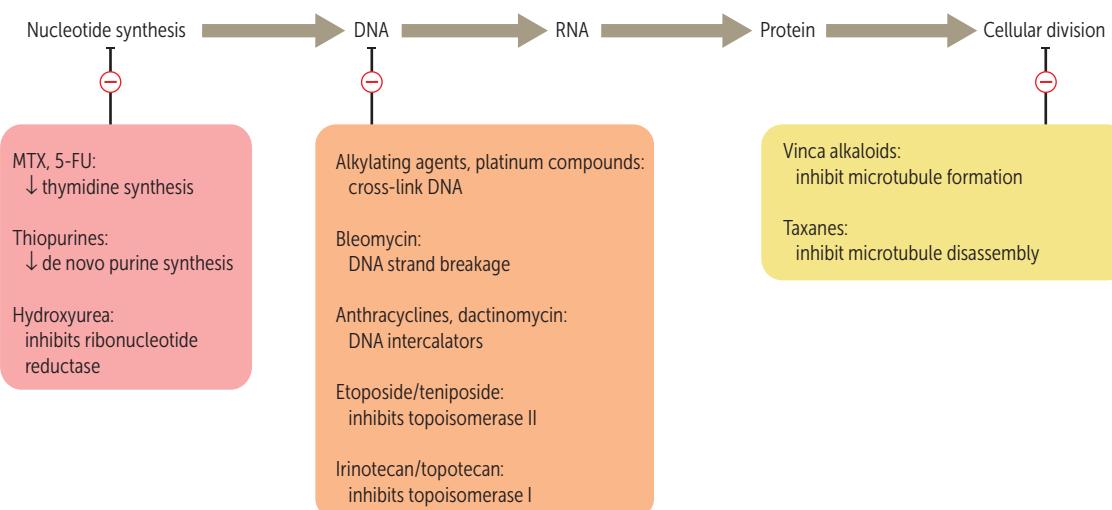
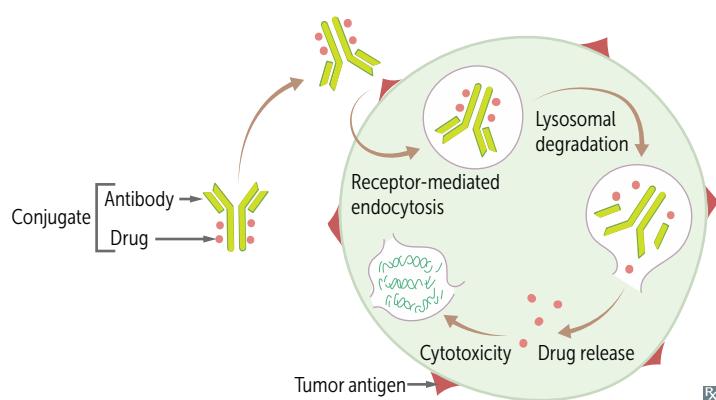
| ANTICOAGULANT | REVERSAL AGENT | NOTES |
|--|---|--|
| Heparin | Protamine sulfate | ⊕ charged peptide that binds ⊖ charged heparin |
| Warfarin | Vitamin K (slow) +/- FFP or PCC (rapid) | |
| Dabigatran | Idarucizumab | Monoclonal antibody Fab fragments |
| Direct factor Xa inhibitors (eg, apixaban, rivaroxaban) | 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 |
| Eptifibatide, tirofiban, abciximab | 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 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**Cancer therapy—targets****Antibody-drug conjugates**

Formed by linking monoclonal antibodies with cytotoxic chemotherapeutic drugs. Antibody selectivity against tumor antigens allows targeted drug delivery to tumor cells while sparing healthy cells → ↑ efficacy and ↓ toxicity.
Example: ado-trastuzumab emtansine (T-DM1) for HER2 + breast cancer.

Antitumor antibiotics Dactinomycin is cell cycle nonspecific; bleomycin and anthracycline are G₂/M phase specific.

| DRUG | MECHANISM | CLINICAL USE | ADVERSE EFFECTS |
|---|--|--|---|
| Bleomycin | Generates free radicals → DNA strand breaks | 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 into DNA → DNA strand breaks → ↓ replication Inhibit topoisomerase II | Solid tumors, leukemias, lymphomas | Dilated cardiomyopathy (often irreversible; prevent with dexrazoxane), 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 thiopurine S-methyltransferase (genetic polymorphism) and xanthine oxidase (↑ toxicity with allopurinol or febuxostat) |
| Cladribine, pentostatin | Purine nucleoside analogs → unable to be processed by ADA, interfering with DNA synthesis | Hairy cell leukemia | Myelosuppression |
| Cytarabine (arabinofuranosyl cytidine) | Pyrimidine nucleoside 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 <i>Cyclophosphamide, ifosfamide</i> | 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 <i>Carmustine, lomustine</i> | 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 (risk of hypertensive crisis with tyramine ingestion) | 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 <i>Docetaxel, paclitaxel</i> | Hyper stabilize polymerized microtubules → prevent mitotic spindle breakdown | Various tumors (eg, ovarian and breast carcinomas) | Myelosuppression, neuropathy, hypersensitivity Taxes stabilize society |
| Vinca alkaloids <i>Vincristine, vinblastine</i> | Bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation | Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas | Vin cripine (crisps the nerves): neurotoxicity (axonal neuropathy), constipation (including ileus) Vin blastine (blasts the marrow): myelosuppression |

Topoisomerase inhibitorsAll cause ↑ DNA strand breaks, 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), endometrial cancer, uterine sarcoma. |

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).

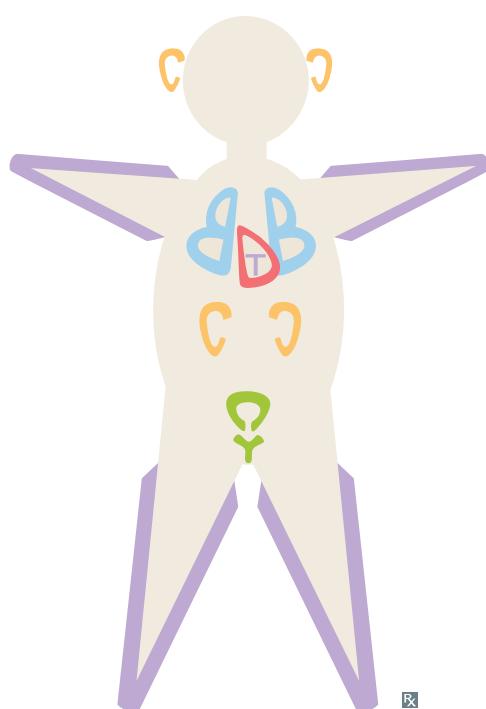
| AGENT | TARGET | CLINICAL USE | ADVERSE EFFECTS |
|--------------------------------------|---|---|---|
| Alemtuzumab | CD52 | Chronic lymphocytic leukemia (CLL), multiple sclerosis. | \uparrow risk of infections and autoimmunity (eg, ITP) |
| Bevacizumab | VEGF (inhibits blood vessel formation) | Colorectal 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 Don't Trast HER , she will break your heart | 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, gefitinib, 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 (induces 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 | Sulphydryl 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.