

II. Hematology

I. Introduction

A. EMBRYOLOGY

1. Hematopoiesis begins in yolk sac during first month
2. At third month it begins in liver & spleen
3. Fourth month hematopoiesis begins in the bone marrow
4. At birth, liver & spleen hematopoiesis ↓↓

B. HEMATOPOIESIS

1. 3 stages: 1) proliferation of stem cells, 2) differentiation of blast cells, 3) maturation to final cell type
2. Common stem cell (preblast) expresses CD34 surface protein
3. CD34+ cells differentiate into 1) myeloid & 2) lymphoid blasts
4. Mutations in stem cell → myeloproliferative dz [see Section V]
5. Mutations in blast cell → acute leukemias [see Section VI]
6. Myelopoiesis
 - a. Myeloblast differentiates → progenitors of 1) erythrocyte, 2) megakaryocyte, 3) mast cell, 4) monocyte & 5) granulocyte
 - b. Granulocyte matures → neutrophil, eosinophil, basophil
 - c. 90% of neutrophils die within marrow, last 6 hr in circulation
 - d. Monocyte circulates for 6–10 hr, then matures in tissue
 - e. Megakaryocytes become multinucleate due to endomitotic reduplication (nucleus multiplies without cell division), matured cells split off platelets, which circulate for 7 days
 - f. Proerythrocyte nucleus shrinks & then is extruded, with Wright stain cytoplasm first → blue during RNA transcription, then → pink as hemoglobin is translated
 - g. Mature RBCs circulate for 120 days
7. Lymphoid blast matures → B cells, T cells, natural killer cells
(See Color Plate 14)

C. DISORDERS

1. ↑ risk infection if absolute neutrophil count $<1000/\text{mm}^3$
2. **All blood cell disorders are of 3 general types**
 - a. Altered production: clonal proliferation or bone marrow failure
 - b. Altered destruction: can be ↑ or ↓ (↓ apoptosis → cancer)
 - c. Qualitative (the cells don't work right)
3. Loss of adhesion allows cells to invade various anatomical sites, this is typical of leukemia/lymphoma
4. Myelodysplasia = preleukemic, increased numbers of abnormal myeloid blasts in marrow but not yet in peripheral blood
5. Blasts in periphery are typical of acute leukemias
6. Lymphocytic disorders are called "lymphocytic leukemia" if cells are in blood, "lymphoma" if they are parenchymal
7. **Acute leukemias onset 5–10 years after prior chemotherapy or radiation therapy given for other malignancies**

D. BIOPSIES

1. Marrow smear, clot section, bone marrow biopsy
2. Biopsy is the best for marrow architecture
3. % cellularity of marrow that should be found on normal biopsy can be estimated by the formula (100% – age)

II. Transfusion Medicine**A. BLOOD GROUPS—THE ABO SYSTEM**

1. ABO is one of 20 or so identified blood groups
2. Blood group O actually possess an antigen (Ag) called “H,” which can rarely induce antibody (Ab)
3. AB antigens are **polysaccharide moieties** on RBCs, endothelium, epidermal cells, intestinal cells, leukocytes & platelets
4. AB Ags elicit IgM antibodies, causing intravascular hemolysis
5. Group O cells & group AB plasma are universal donors (technically must be Rh negative, see below)
6. Incompatible donated plasma is quickly diluted while donated cells are exposed to high concentrations of Ab, so plasma donation is much less sensitive to reactions than cell donations
7. Group AB recipient is universal, since they do not make anti-AB antibody
8. If patient is O type, only O type blood can be safely given
9. If patient is AB, A or B can be used, as well as O packed cells
10. Rh is a **protein antigen** (contrast to AB Ags), determined by D & CcEe loci, but only D is measured to determine Rh positivity
11. Rh antigens elicit IgG antibodies, causing extravascular hemolysis

B. AGGLUTINATION

1. Direct Coombs’ test
 - a. Test for any autoimmune hemolysis
 - b. Pt’s RBCs tested with Coombs’ reagent = antihuman IgG
 - c. If the pt is hemolyzing, the Coombs’ reagent binds to the pt’s IgG that is attached to the pt’s own RBCs, causing agglutination
 - d. Cell’s zeta potential (negative) repels other cells, so the Coombs’ reagent is needed to bridge across the negative potential for agglutination to occur
 - e. Direct test looks for IgG, which crosses placenta, rarely agglutinates cells, is optimal at 37 °C, is not naturally occurring
2. Indirect Coombs’ test
 - a. The patient’s serum is added to foreign cells
 - b. Used to diagnose atypical, unexpected antibodies in the patient’s serum & for pretransfusion compatibility
 - c. Indirect looks for IgM, which cannot cross placenta, agglutinates cells, works at 4–20 °C & naturally occurs
 - d. Indirect also finds IgG directed at unusual epitopes
3. Reliability of compatibility following cross-match is 99.99%

C. BLOOD PRODUCTS

1. Whole blood is rarely given for volume loss
2. Packed red blood cells (PRBCs) are used for most transfusions

3. Fresh-frozen plasma contains all clotting factors except platelets
4. Cryoprecipitate has factors VIII, vWF, IX, fibrinogen: given for deficiencies of these factors, as well as for uremic bleeding
5. Rh immune globulin (RhoGAM): has IgG anti-Rh, given at 28 wk & within 72 hr of delivery to block sensitization in an Rh-negative woman who delivers an Rh-positive baby
6. Packed platelets given for thrombocytopenic bleeding

D. HAZARDS

1. **Intravascular hemolysis is invariably due to ABO incompatibility**
2. Si/Sx = fever, chills, facial flushing, chest/back pain, heat/pain at infusion site, dyspnea, hypotension, agitation, hemoglobinuria
3. Dx = free hemoglobin in urine/serum, Coombs' test, retest ABO match
4. Immediate reactions due to clerical errors, due to ABO incompatibility, can be life-threatening
5. Tx = STOP INFUSION, treat with diuretics plus fluid load to try to prevent acute tubular necrosis & oliguric renal failure
6. Nonhemolytic reactions include fever, urticaria, anaphylaxis, volume overload, citrate toxicity, hyperkalemia, acidosis, endotoxin, air embolism, hypothermia, hemosiderosis & DIC
7. Above often due to anticoagulants (citric acid) or to rapid infusion
8. Infectious diseases: **HCV is most frequent infection in blood transfusions, is now screened for**

III. Anemias

A. APLASTIC ANEMIA

1. Failure of hematopoiesis → ↓ counts of erythrocytes, neutrophils & platelets (lymphocytes spared due to long life)
2. Si/Sx = pancytopenia, petechiae/hemorrhage, pallor, weakness, infection
3. Labs = anemia, neutropenia, thrombocytopenia, hypocellular bone marrow
4. Causes
 - a. Usually idiopathic
 - b. Other = drugs (chloramphenicol), toxins (benzene, etc.), infections (parvovirus B19 is most common, also hepatitis B or C), radiation, paroxysmal nocturnal hemoglobinuria
5. Px = 90% die within 1 yr with transfusions & antibiotics
6. 50–70% of bone marrow transplant (BMT) patients will be cured of disease
7. In non-BMT candidates, can try antithymocyte globulin (ATG) with or without addition of growth factors (e.g., Neupogen, GM-CSF)

B. MEGALOBlastic ANEMIA

1. Impaired DNA synthesis with normal RNA & protein synthesis
2. Causes = B-12 deficiency, folate deficiency, chemotherapy
3. **Pathognomonic blood smear → hypersegmented neutrophils** (See Color Plate 15)
4. In cirrhosis blood smear → “spur cells” (acanthocytes), with large spikes protruding from membrane like cowboy spurs
5. Folic acid deficiency

- a. Look for megaloblastic anemia with glossitis
 - b. Causes can be dietary, ↑ requirements (pregnancy, hemolytic anemia, tumors), drugs (methotrexate, dilantin), or malabsorption due to intestinal resection
 - c. Dx: ↓ blood folate, along with characteristic changes in marrow & smear noted above
6. B₁₂ (cyanocobalamin) deficiency
- a. Si/Sx = megaloblastic anemia with neuropathies (2° to defective myelin synthesis)
 - b. Often due to lack of intrinsic factor (needed by mucosal cells in terminal ileum for B₁₂ absorption)
 - c. Causes include autoimmune (pernicious anemia), gastrectomy (chief cells secrete intrinsic factor), ileal resection (↓ uptake), enteritis (blocks uptake) & intestinal tapeworm (*Diphyllobothrium latum*) that metabolizes the B₁₂
 - d. Dx = megaloblastic marrow, macrocytic blood picture, ↓ serum B₁₂ levels, gastric analysis (achlorhydria is seen in pernicious anemia)
 - e. Serum methylmalonic acid & homocysteine levels are more sensitive than pure folate & B₁₂ levels
 - 1) Both methylmalonic & homocysteine ↑ in B₁₂ deficiency
 - 2) Only homocysteine elevated in folate deficiency
 - f. Schilling test
 - 1) Give radioactive B₁₂ orally, then nonradioactive B₁₂ intramuscularly, collect urine 24 hr
 - 2) Normal people will excrete 7–22% of the initial oral B₁₂
 - 3) Low urinary levels are seen in defective GI absorption
 - 4) If low, repeat test & give oral intrinsic factor with B₁₂ to assess change (this will ↑ urinary excretion of oral dose if problem is due to lack of intrinsic factor production)
 - 5) If this is also low give oral antibiotic with B₁₂ to assess change (this will ↑ urinary excretion if problem is parasitic)
 - 6) If antibiotics do not help either, the problem is likely one of absorption in the small bowel

C. MICROCYTIC ANEMIA

1. Result from ↓ hemoglobin production or impaired function
2. Iron deficiency anemia (most common anemia in the world)
 - a. Iron physiology
 - 1) 50 mg of iron/100 mL of blood, total body iron 50 mg/kg in males, 30 mg/kg in females
 - 2) Males require 1 mg/day, menstruating females require 2 mg/day
 - 3) Iron is transported via transferrin to marrow, used by developing RBCs to make hemoglobin & is stored in macrophages
 - 4) Amount of iron the plasma can bind at any one time is limited by plasma transferrin content = TIBC
 - 5) Ferritin is a measure of the total body iron stores
 - b. Peripheral smear shows hypochromia, microcytosis
 - c. Labs: ↓ iron, ↑ TIBC, ↓ ferritin, marrow stains show ↓↓ iron
 - d. **Iron deficiency anemia is not a final diagnosis: the cause of the iron deficiency MUST be found**

- e. **Iron deficiency anemia in the elderly is due to colon cancer until proven otherwise**
 - f. Blood loss must be ruled out in all adult cases, in children dietary causes are common
 - g. Most common cause worldwide is intestinal hookworm infection, suspect in immigrants from Third World
3. Anemia of chronic disease
- a. Idiopathic, may be result of aberrant cytokine patterns
 - b. Labs: ↓ iron, ↓ **TIBC**, ↑ **ferritin**, marrow iron increased, can be a normocytic/normochromic
 - c. Note that despite the ↓ iron, the body does not try to ↑ TIBC—this paradox is not readily explainable
 - d. **Characteristic laboratory finding is ↓ TIBC**
4. Sideroblastic anemia
- a. Problem is in accessing stored iron in mitochondria in the marrow
 - b. Look for ringed sideroblasts on iron stain of bone marrow
 - c. Labs: ↑ **iron**, N/↑ TIBC, ↑ ferritin
 - d. **Characteristic laboratory finding is elevated serum iron**
5. Lead poisoning
- a. Causes a hypochromic microcytic anemia due to lead inhibition of heme synthesis
 - b. Associated systemic Sx include encephalopathy (worse in children), seizures, ataxic gait, **wrist/foot drops**, renal tubular acidosis
 - c. Classic Dx findings
 - 1) **Bruton's lines** = blue/gray discoloration at gumlines
 - 2) **Basophilic stippling of red cells (blue dots in red cells)**
 - 3) X-rays show increased epiphyseal density of long bones
 - d. Tx = chelation with dimercaprol (BAL) &/or EDTA
6. Hemolytic anemias
- a. Intravascular hemolysis characterized by cell fragments on blood smear (See Color Plate 16), ↓ haptoglobin & ⊕ hemosiderin in urine
 - b. Extravascular hemolysis characterized by spherocytes on blood smear (haptoglobin can fall in severe dz)
 - c. Extrinsic (extracorporeal) hemolysis
 - 1) Coombs'⊕: antibodies to RBC due to incompatible blood transfusion or autoimmune hemolytic anemia (warm mediated by IgG, cold mediated by IgM)
 - 2) Mechanical destruction
 - a) Disseminated intravascular coagulation (DIC)
 - b) Thrombotic thrombocytopenic purpura (TTP)
 - c) Hemolytic-uremic syndrome (HUS)
 - d) Artificial heart valve
 - 3) Infectious agents—malaria, *Clostridium*
 - 4) Altered plasma components: lipids (see acanthocytes on smear), or hypophosphatemia
 - 5) Toxins & drugs (penicillin, α-methyl dopa, quinidine)
 - d. Intrinsic (intracorporeal) hemolysis
 - 1) Membrane defects include hereditary spherocytosis, hereditary elliptocytes, which are due to congenital defect in cytoskeleton proteins, resulting in very osmotically fragile cells
 - a) Tx = Folate supplementation & splenectomy

- 2) Paroxysmal nocturnal hemoglobinuria is caused by an acquired defect of the *PIG-A* gene, which inhibits GPI-anchoring of a variety of cell-surface proteins, including decay accelerating factor (DAF, or CD55) and membrane inhibitor of reactive lysis (MIRL, or CD59), both of which protect host cells from bystander destruction by activated complement cascade
- 3) Enzyme deficiency (e.g., G6PD, protein kinase deficiency)
- 7. Hemoglobinopathies
 - a. Thalassemias (quantitative hemoglobin defects)
 - 1) β -thalassemia: \downarrow production of β chains
 - a) Usually Mediterranean or black ethnicity
 - b) Homozygous β -/ β - = Thalassemia Major (Cooley's anemia)
 - i) Electrophoresis $\rightarrow \downarrow\downarrow\downarrow$ Hgb A, \uparrow Hgb A2, \uparrow **Hgb F**
 - ii) Si/Sx \rightarrow hepatosplenomegaly, anemia, frontal bossing due to extramedullary hematopoiesis, hypercellular marrow, iron overload (2° to transfusions), recurrent infxn, early death
 - iii) Smear \rightarrow marked anisocytosis & poikilocytosis with \uparrow reticulocytes, microcytic hypochromic RBCs, with many target cells
 - c) Heterozygous = Thalassemia Minor
 - i) Electrophoresis $\rightarrow \downarrow$ Hgb A, \uparrow Hgb A2(γ), **N Hgb F**
 - ii) Patients are often asymptomatic, can see silent anemia, smear shows target cells & microcytic/hypochromic RBC
 - 2) α -thalassemia: \downarrow production of α chains
 - a) Usually seen in Africans, Mediterraneans & Asians
 - b) **4** α -chain genes, 2 alleles on both chromosomes

TABLE 11-1 α -Thalassemias

| # ALLELES AFFECTED/ NAME OF DISEASE | CHARACTERISTIC | BLOOD SMEAR |
|--|---|---------------------------------------|
| 4 Hydrops fetalis | Fetal demise, total body edema | Bart's β_4 , Hgb precipitations |
| 3 Hgb H disease | Disease caused by precipitation of β -chain tetramers | Intraerythrocytic inclusions |
| 2 α -Thal. Minor | Usually clinically silent | Mild microcytic anemia |
| 1 Carrier state | No anemia, asymptomatic | No abnormalities |

- b. Sickle cell anemia (qualitative defect in hemoglobin)
 - 1) Sickle S type (the most common type)
 - a) HgS tetramer: single amino acid substitution of valine for glutamine
 - b) Exposes hydrophobic residue, which is then buried by hemoglobin polymerization
 - c) Polymerized tetrads cause the sickling of the cell (See Color Plate 17)
 - d) Sickle cells clog microcapillaries \rightarrow vaso-occlusive findings, pain crisis, myocardiopathy, infarcts of bone/CNS/lungs/kidneys, priapism & autosplenectomy due to splenic infarct

- e) Autosplenectomy → ↑susceptible to encapsulated bacteria
 - f) **Intravascular hemolysis episodes can cause gallstones in children, teens & young adults**
 - g) Heterozygotes may live approximately normal life spans, will have only rare sickle crises
- 2) Sickle C type
- a) Substitution of lysine for glutamine
 - b) Homozygous CC causes mild chronic anemia, less severe than sickle S

D. PERIPHERAL BLOOD SMEAR FINDINGS

TABLE 11-2 Peripheral Blood Smear in Anemia

| CONDITION | PERIPHERAL BLOOD SMEAR |
|-----------------------------------|--|
| Folate/B ₁₂ deficiency | Megaloblasts & hypersegmented neutrophils |
| Liver disease | Megaloblasts & target cells, cirrhosis → "spur cells" (acanthocytes) |
| Microcytic anemia | Microcytes, hypochromic |
| Lead poisoning | Microcytes, hypochromic, basophilic stippling of RBCs |
| Uremia | Burr cells (echinocytes) |
| Coombs'⊕ hemolysis | Microspherocytes |
| DIC/TTP/HUS | Schistocytes, helmet cells (PT/PTT ↑ only in DIC) |
| Thalassemia | Poikilocytosis, microcytic, hypochromic, ↑↑↑ target cells |
| Sickle cell | Sickle cells, rod-shaped sickle C crystals in sickle C disease |
| Abetalipoproteinemia | Spur cells (acanthocytes) |
| Asplenia | Howell-Jolly bodies |
| G6PD deficiency | Heinz bodies |

IV. Coagulation Disorders

A. THROMBOCYTOPENIA

1. Presents with petechiae, epistaxis, CNS bleeds, GI bleeds
 - a. Bleeding time elevated at counts <50,000
 - b. Clinically significant bleeds start at counts <20,000
 - c. CNS bleeds occur with counts <10,000
2. Caused by stem cell failure, increased destruction, splenic sequestration
3. Stem cell failure caused by leukemia, aplastic anemia, alcohol (can be mild intake), paroxysmal nocturnal hemoglobinuria
4. Destruction
 - a. Idiopathic thrombocytopenic purpura (ITP)
 - 1) An autoimmune disorder of autoantibody-mediated platelet destruction
 - 2) **In children follows URI & is self-limiting, in adults it is chronic**
 - 3) Si/Sx = petechiae, purpura, epistaxis, **with normal white & red cell morphology on peripheral blood smear**
 - 4) Tx = steroids (first line), splenectomy (second line) helps 50% of those who fail steroids, immunosuppressives (azathioprine, cyclophosphamide) are third line
 - b. Thrombotic thrombocytopenic purpura (TTP)
 - 1) An idiopathic systemic disease of acutely falling platelet counts that can be fatal

- 2) **Classic pentad of TTP**
 - a) Intravascular hemolytic anemia
 - b) Renal failure → proteinuria, hematuria, ↑ creatinine
 - c) Thrombocytopenia
 - d) Neurologic changes (focal & nonfocal)
 - e) Fever
- 3) Histopathology
 - a) **Characteristic pathology → platelet-fibrin thrombi in capillaries**
 - b) **Peripheral smears: fragmented RBCs (schistocytes)**
- 4) Tx = plasma exchange or intravenous immunoglobulin until dz abates, typically several days
- 5) Disease is fatal without treatment
- c. Drug-induced thrombocytopenia
 - 1) Heparin, sulfonamides, sulfonylureas, valproate, etc. can induce destruction
 - 2) Reverses within several days of ceasing drug intake
- d. Hemolytic-uremic syndrome (HUS)
 - 1) Usually in children, often caused by *E. coli* O157:H7
 - 2) Si/Sx
 - a) Glomerular sclerosis causing acute renal failure
 - b) Bloody diarrhea & abdominal pain, seizures
 - c) **Fulminant thrombocytopenia with hemolytic anemia is highly suggestive**
 - 3) Tx = dialysis helps children, but adults may be refractory & Px is much poorer
- e. Evan's syndrome
 - 1) IgG autoantibody mediated hemolytic anemia & thrombocytopenia
 - 2) Often have pancytopenia due to multiple autoantibodies
 - 3) Associated with collagen-vascular dz, TTP, hepatic cirrhosis, leukemia, sarcoidosis, Hashimoto's thyroiditis
 - 4) Tx = prednisone & intravenous immunoglobulin
- f. Lymphoma & leukemia
 - 1) Can produce antiplatelet antibodies
 - 2) Also induce splenic sequestration
- g. DIC
 - 1) Platelets trapped in fibrin mesh deposited in blood vessels
 - 2) Dx = ↑ fibrin-split products, ↓ fibrinogen, ↑ PT/PTT
- h.

TABLE 11-3 Differential Diagnosis of Platelet Destruction

| STUDY | AUTOANTIBODY (DRUG-INDUCED, EVAN'S SYNDROME, LYMPHOMA) | DIC | TTP/HUS |
|--------------|--|------------------|---------------------------|
| Blood smear | Microspherocytes | Schistocytes (+) | Schistocytes (+++) |
| Coombs' test | ⊕ | - | - |
| PT/PTT | Nml | ↑↑↑ | Nml / ↑ |

5. Splenic Sequestration
 - a. Trapping of platelets in reticuloendothelial cells of spleen
 - b. Caused by portal hypertension, lymphoma, leukemia, massive infection, chronic inflammation

B. PLATELET DYSFUNCTIONS

1. von-Willebrand factor (vWF) deficiency
 - a. **This is the most common inherited bleeding disorder (more common than hemophilia!!!)**
 - b. Three different types, most commonly autosomal dominant
 - 1) Type I due to ↓ secretion of functional vWF
 - 2) Type II due to secretion of dysfunctional vWF
 - 3) Type III is autosomal recessive, dysfunctional vWF
 - c. vWF secreted by endothelial cells, binds platelet surface receptor Gplb (see Bernard-Soulier syndrome below), bridging platelet to subendothelial matrix to initiate stasis
 - d. vWF deficiency presents with episodic ↑ **bleeding time & ecchymoses, with normal PT/PTT**
 - e. Stress affects vWF level & can exacerbate disease course
 - f. Due to mild, episodic nature of the disorder, it may go undiagnosed well into adult life
 - g. Dx = vWF levels & ristocetin-cofactor test (measures platelet aggregation induced by ristocetin binding of vWF)
 - h. Tx = DDAVP (↑ vWF secretion, only used in type I vWF, actually harmful in type II), or cryoprecipitate for pts with acute, severe dz
2. Bernard-Soulier syndrome
 - a. Autosomal recessive defect of platelet Gplb receptor (binds to vWF)
 - b. Presents with chronic, severe mucosal bleeds & **giant platelets on blood smear**
 - c. Tx = platelet transfusion
3. Glanzmann's thrombasthenia (GT)
 - a. Autosomal recessive defect in GpIIb/IIIa platelet receptor that binds fibrinogen, inhibiting platelet aggregation
 - b. Presents with chronic, severe mucosal bleeds
 - c. Tx = platelet transfusion
 - d. New anticoagulant drugs, called gpIIb/IIIa antagonists (abciximab, eptifibatid, tirofiban), mimic GT & cause anti-coagulation by inhibiting the gpIIb/IIIa receptor
4. Aspirin & uremia are acquired causes of platelet dysfunction

C. HEMOPHILIA

1. Hemophilia A
 - a. An X-linked deficiency in factor VIII, the most common hemophilia type
 - b. Many mutations, causing variable penetrance of the disease (variable disease severity)
 - c. Presents with hemarthroses (bleeding into joint), easy bruisability with minor trauma
 - d. **Labs → ↑ PTT, normal PT, normal bleeding time, ↓ factor VIII levels**
 - e. Can be acquired due to circulating antifactor VIII antibody

- 1) Differentiate genetic from acquired by adding patient's serum to control serum
- 2) If circulating antibody is present, mixed serum also has \uparrow PTT
- 3) If genetic, the mixed serum will have a normal PTT (control serum's factor VIII is enough despite dilution)
- f. Tx = recombinant factor VIII (first line), can use cryoprecipitate
2. Hemophilia B (Christmas disease)
 - a. X-linked factor IX deficiency, also with variable dz severity
 - b. **Lab shows \uparrow PTT, normal PT, normal bleeding time**, low factor IX levels, normal VIII levels
 - c. Disease presentation is identical to hemophilia A, must distinguish by specific factor levels
 - d. Tx = factor IX concentrate

D. CLOTTING FACTOR SYNTHESIS (FIGURE 11-1 CLOTTING CASCADE)

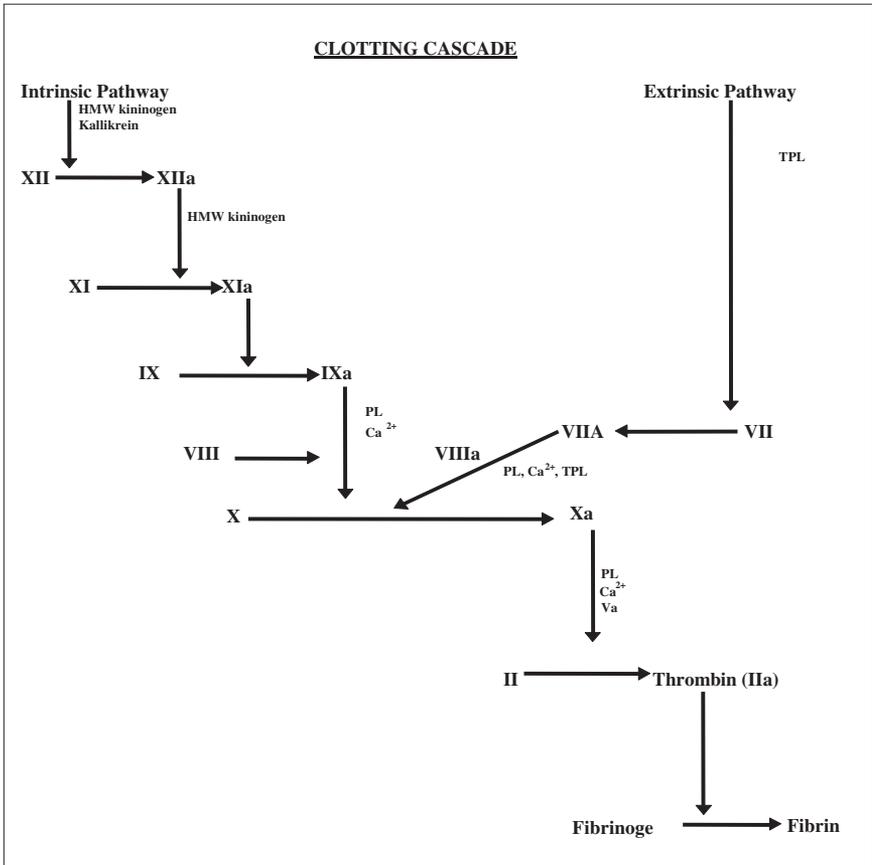


FIGURE 11-1 HMW = high molecular weight, TPL = tissue thromboplastin, PL = platelet phospholipid.

1. Disorder can be due to liver disease (liver makes all clotting factors) or vitamin K deficiency
2. Vitamin K necessary cofactor for γ -glutamyl-carboxylase, which carboxylates factors II, VII, IX, X, as well as protein C & S, so that they can interact with calcium (Figure 11-2)

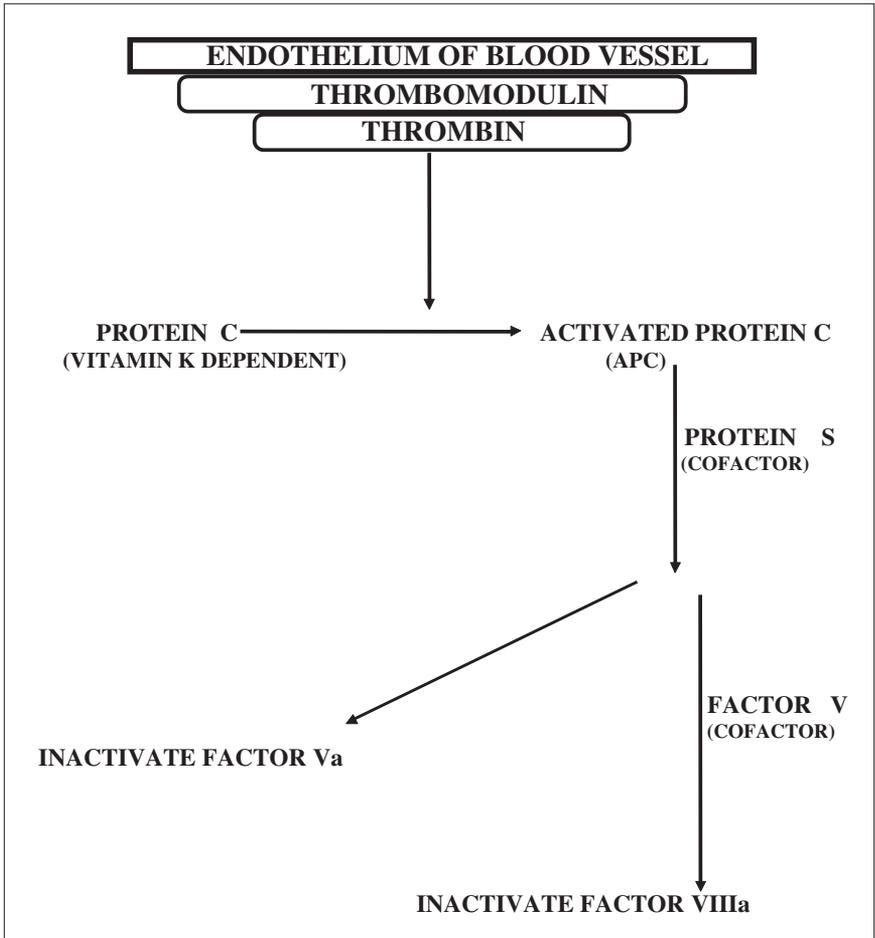


FIGURE 11-2 Schematic representation of vitamin K dependent mechanism of protein C inhibition of coagulation cascade.

3. Liver dz & vitamin K deficiency thus affect both intrinsic & extrinsic pathways, so PT & PTT will both be elevated (but PT more so)
4. Coumadin
 - a. Acts as a vitamin K analogue to inhibit carboxylation of factors II, VII, IX, X, as well as proteins C & S

- b. INR (pt's PT/control PT) should be >2 for Coumadin anticoagulation
- c. **Clinical Pearl: because Coumadin also interferes with protein C synthesis, & protein C has a very short half-life, initial administration of Coumadin can cause a fulminant skin necrosis 2° to capillary thrombosis**

E. CONGENITAL HYPERCOAGULABLE DISEASES

1. Factor V Leiden disease
 - a. Most common inherited hypercoagulable state
 - b. Due to amino acid substitution in factor V, causing it to be resistant to cleavage by activated protein C (APC)
 - c. Leads to dysregulated coagulation, ↑ risk of deep venous thrombosis &/or pulmonary embolism
2. Antithrombin deficiency
 - a. Antithrombin III binds to & inhibits coagulation proteins
 - b. Heparin works by stabilizing the antithrombin-coagulant complex, causing anti-coagulant effect
 - c. Deficiency of antithrombin III due to ↓ protein or mutation causing dysfunctional protein
3. Protein C & S deficiency
 - a. Liver γ-carboxylates proteins C & S (vitamin K-dependent)
 - b. Protein C is activated by thrombin, thrombomodulin complex then binds protein S (cofactor)
 - c. Activated protein C cleaves factors V & VIII, inhibiting further coagulation
 - d. Deficiency of protein C or S causes uninhibited coagulation
 - e. Coumadin may exacerbate, because it further lowers protein C levels by blocking vitamin K-dependent γ-carboxylation
4. List of hypercoagulable states

TABLE 11-4 Hypercoagulable States

| PRIMARY (INHERITED) | SECONDARY (ACQUIRED) | |
|------------------------------------|--------------------------|----------------------|
| Antithrombin III deficiency | Prolonged immobilization | L-asparaginase |
| Protein C deficiency | Pregnancy | Diabetes mellitus |
| Protein S deficiency | Surgery/Trauma | Hyperlipidemia |
| Factor V Leiden deficiency | Oral contraceptives | Anticardiolipin Ab |
| Dysfibrinogenemia | Homocystinuria | Lupus anticoagulant |
| Plasminogen (activator) deficiency | Malignancy | DIC |
| Heparin cofactor II deficiency | Smoking | Vitamin K deficiency |
| Homocystinemia | Nephrotic syndrome | |

V. Myeloproliferative Diseases

A. GENERAL CHARACTERISTICS

1. Caused by clonal proliferation of a myeloid stem cell → excessive production of mature, differentiated myeloid cell lines
2. There are 4 subtypes: 1) polycythemia vera, 2) thrombocythemia, 3) myelofibrosis, 4) chronic myeloid leukemia
3. All can transform into acute leukemias

B. POLYCYTHEMIA VERA

1. Rare disease, peak onset at 50–60yr, male predominance
2. Si/Sx = headache, vertigo, diplopia, retinal hemorrhages, strokes, angina, claudication (all due to vascular sludging), early satiety, splenomegaly, gout, **pruritus after showering**, plethora
3. Tx: phlebotomy to palliate, Px is good
4. **5% of pts progress to leukemia, 20% to myelofibrosis**
5. DDx for \uparrow hematocrit = 1° polycythemia & 2° erythrocytosis
 - a. 1° can be vera or relative (fluid loss), distinguish by normal RBC mass (radioactive test) & signs of hypovolemia (tenting, orthostatic changes, dry mucosa, etc.)
 - b. 2° due to high altitude, COPD, CHF, high-affinity hemoglobin, carbon monoxide poison (cigarettes), blood doping
 - c. 1° vs. 2° differentials

TABLE 11-5 Polycythemia Vera versus Reactive Polycythemia

| SIGN/TEST | POLYCYTHEMIA VERA | SECONDARY ERYTHROCYTOSIS |
|---------------------------|---------------------|--------------------------|
| O ₂ saturation | Normal | Decreased |
| Erythropoietin levels | Markedly diminished | Increased |
| Splenomegaly | + | – |
| Platelet count | Increased | Normal |
| Neutrophil count | Increased | Normal |
| Basophil count | Increased | Normal |

C. ESSENTIAL THROMBOCYTHEMIA (ET)

1. Clonal proliferation of megakaryocytes resulting \uparrow platelet counts
2. **Because there are numerous causes of 2° thrombocytosis, ET is a diagnosis of exclusion!**
3. Causes of 2° thrombocytosis include iron deficiency, any inflammatory disease (chronic infection, collagen-vascular, inflammatory bowel disease, etc.) & malignancy (common in chronic myelogenous leukemia, but can be seen in many cancers)
4. Si/Sx = platelet count $>5 \times 10^5$ cells/ μ L, splenomegaly, factitious hyperkalemia [see Nephrology, Hyperkalemia Algorithm], **ecchymoses/bleeding but not typically thrombosis**
5. Tx is only necessary if pt is symptomatic
 - a. Platelet exchange (apheresis) used in emergent setting
 - b. Hydroxyurea & interferon- α are longer-term options
 - c. Anagrelide is now the 1st line Tx for ET patients, mechanism is unknown but it somehow decreases platelet synthesis from megakaryocytes
6. Px is good unless dz progresses to myelofibrosis or acute leukemia (less than 5% \rightarrow leukemia)

D. IDIOPATHIC MYELOFIBROSIS

1. Typically affects patients ≥ 50 years old
2. Clonal proliferation of unknown cell type leading to fibrosis of bone marrow \rightarrow extramedullary hematopoiesis

3. Si/Sx = massive hepatomegaly, massive splenomegaly, blood smear → teardrop cells, nucleated red cells & immature white cells, gout, anemia often with ↑ white count & platelets (early)
4. Dx is by exclusion, but combination of extramedullary hematopoiesis & hypercellular marrow on Bx are keys
5. DDx = polycythemia vera, leukemia, myelophthistic disorders (invasion of bone marrow by multiple myeloma, lymphoma, metastatic carcinoma, sarcoidosis, tuberculosis, etc.)
6. Tx = symptomatic (splenectomy, antibiotics, allopurinol, etc.)
7. Px = very poor, median 5 yr before total marrow failure, can also progress to a refractory acute leukemia

E. CHRONIC MYELOGENOUS LEUKEMIA (SEE BELOW, SECTION VI.C)

VI. Leukemias

A. ACUTE LYMPHOBLASTIC LEUKEMIA

1. **Peak age 3–4yr**, most common neoplasm in children
2. Sx: fever, fatigue; Si: anemia, pallor, petechiae, infections
3. Lab: Leukocytosis, blasts in peripheral blood (PB), ↓ RBC count, ↓ platelets, **PAS+**, **CALLA+**, **TdT+**, marrow bx → ↑ blasts
4. Tx = chemotherapy: induction, consolidation, maintenance—intrathecal chemotherapy during consolidation
5. Px: 80% cure in children (lower in adults), therapy sequelae = growth defects, new cancers, increased rate of sterility

B. ACUTE MYELOGENOUS LEUKEMIA

1. **Most common leukemia in adults**
2. French American British (FAB) classification = M0 to M7

TABLE 11-6 Acute Myelogenous Leukemia Subtypes

| SUBTYPE | STAIN/KARYOTYPE | SPECIAL CHARACTERISTICS |
|---------------------------------------|---|---|
| M0: Minimal differentiated | | |
| M1: Myeloblastic | + Auer rod, + Sudan Black, + myeloperoxidase | |
| M2: Myeloblastic with differentiation | ++ Auer rod, + Sudan Black +++ myeloperoxidase | Prominent splenomegaly, ⊕ chloromas (green tumors made up of the blasts) |
| M3: Promyelocytic | +++ Auer rod, ↑ granular, +++ myeloperoxidase 15:17 translocation → retinoic acid receptor | DIC common-Tx with heparin Tx = all trans retinoic acid (ATRA) to induce blast differentiation, followed by consolidation chemotherapy |
| M4: Myelomonocytic | + myeloperoxidase | Subtype involves eosinophils |
| M5: Monocytic | | CNS, gingival involvement |
| M6: Erythroblastic | | Often preceded by myelodysplasia |
| M7: Megakaryoblastic | | |

3. Si/Sx = fever, fatigue, pallor, petechiae, infections, splenomegaly, lymphadenopathy
4. Lab: **Myeloperoxidase +, Sudan Black +, Auer Rods**, thrombocytopenia, peripheral blood & marrow Bx → myeloblasts
5. Tx = chemotherapy: induction, consolidation (no maintenance)
6. Px = depends on FAB type, but overall 30% cure, consider allogeneic bone marrow transplant (BMT) for better outcomes

C. CHRONIC MYELOGENOUS LEUKEMIA (CML)

1. Presents most commonly in the 50s, can present at any age
2. Sx = fatigue, anorexia, abdominal discomfort, early satiety, diaphoresis, arthritis, bone tenderness
3. Si = leukostasis ($WBC \geq 1 \times 10^5$) → dyspnea, dizzy, slurred speech, diplopia, confusion, retinal hemorrhage, papilledema
4. Lab: neutrophilia, thrombocytosis, **Philadelphia chromosome**⊕ [see below], peripheral blood → cells of all maturational stages
5. Tx in chronic phase = reduction of WBC count with hydroxyurea or interferon (IFN)- α , or brand new Tx with drug-designed tyrosine kinase inhibitor, signal transduction inhibitor (STI)-571, which specifically blocks the oncogenic tyrosine kinase protein formed by the *bcr:abl* translocation
6. **Blast crisis = acute phase, leads to death in 3–6 mo, mean time to onset = 3–4 yr, only BMT can prevent**
7. Must differentiate from a “leukemoid” reaction to a severe infection

TABLE 11-7 Differential for CML versus Leukemoid Reaction

| TEST/SIGN | CML | LEUKEMOID REACTION |
|---------------------------------------|--------------------------------------|---|
| Philadelphia chromosome | ⊕ | – |
| Maturation of peripheral cells | Blasts with marked left shift | Left shift with fewer blasts |
| WBC count | Very high | High (usually less than 1×10^5) |
| Leukocyte alkaline phosphatase | Low | High |
| Basophilia | ⊕ | – |
| Platelet counts | Very high | High |
| Splenomegaly | Present | Absent |
| Arthritis/Uricemia | ⊕ | – |
| Myeloid:Erythroid marrow ratio | Greater than 10:1 | Less than 10:1 |
| Serum B_{12} | Increased | Normal |
| Malaise | +/- | +++ |

8. Philadelphia chromosome (Ph chromosome)
 - a. Present in >90% of CML patients, **it is pathognomonic**
 - b. Shortened chromosome 22—translocation of *abl* from 9 to *bcr* on 22
 - c. *bcr:abl* alters growth regulation, fusion protein has constitutive tyrosine kinase activity that acts to promote cell cycling
 - d. Translocation ALSO present in lymphocytes (except for long-lived memory cells)
 - e. **Even pts without Ph chromosome invariably have *bcr:abl* translocation on a scale too small to be seen by karyotype**

D. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

1. Increasing incidence with age, causes 30% of leukemias in US
2. 95% are memory B-cell types (a form of blood-borne lymphoma) **expressing the CD5 protein as a surface marker**
3. Si: organomegaly, +/- anemia, later stages see thrombocytopenia due to autoimmunity
4. Lab: normal morphology lymphocytosis of blood & marrow, monoclonal antibodies (check lambda vs. kappa light chain to determine monoclonality), autoimmune hemolysis (Coombs'⊕, ↑ indirect bilirubin, ↓ haptoglobin, spherocytosis)
5. Anemia occurs due to autoimmunity, splenomegaly, bone marrow infiltration, chemotherapy
6. **Tx: early therapy does NOT prolong life, infection is #1 cause of death, treatment is palliative**
7. Two staging systems, Rai & Binet, involving number of nodes involved & associated organomegaly
8. Chromosome 12 & 14 abnormalities noted
9. *bcl-1* translocated from 11 next to Ig heavy chain promoter on 14
10. Differential: viral infxn, but leukocytes won't be small, resting cells
11. Other presentations of similar leukemias
 - a. Hairy cell leukemia (B-cell subtype)
 - 1) Si/Sx = pancytopenia, erythema nodosum, characteristic hairy cell morphology
 - 2) Tx: IFN- α , splenectomy
 - b. T-cell leukemias
 - 1) T-cell subtype of CLL is rare & tends to be less aggressive, not associated with HTLV
 - 2) Human T-cell leukemia virus (HTLV)
 - a) HTLV is endemic to Japan & the Caribbean, transmitted like HIV, via placenta, body fluids & sex
 - b) Causes endemic T-cell leukemia, different from T-cell CLL
 - c) HTLV also causes tropical spastic paraparesis
 - i) Insidious paresis in lower extremities only
 - ii) Minimal to mild changes in sensation
 - iii) Marked lower extremity hyperreflexia, paralysis & urinary incontinence
 - 3) $\gamma\delta$ T-cell [see Appendix C, Section II.B.1.c] leukemias can occur in the gut
 - 4) Large granular lymphocyte leukemia (T-cell subtype)
 - a) Cells have mature CD8 or NK cell morphology
 - b) Si/Sx = neutropenia, splenomegaly, arthritis, mild leukocytosis, lymphadenopathy, ↑ blood Ca^{2+}
 - 5) Generally T-cell leukemias involve skin, often present with erythematous rashes

Most Common Leukemias by Age:

Up to age 15 = ALL; age 15–39 = AML; age 40–59 = AML & CML, age 60 & over = CLL

VII. Lymphoma

A. GENERAL CHARACTERISTICS

1. Lymphomas are solid tumors of the lymphoid system (lymph node, tonsils, GI tract, spleen & liver)
2. Present with large nontender, firm, fixed lymph nodes
3. These are differentiated from reactive lymph nodes, which are tender, soft, moveable & smaller
4. Typically lymphoma is not found in bone marrow like leukemia
5. 2 major types of lymphoma are Hodgkin's & non-Hodgkin's

B. NON-HODGKIN'S LYMPHOMA (NHL)

1. Description
 - a. Histology → diffuse or follicular (nodular)
 - b. Grade → low, intermediate, or high, related to degree of differentiation of cell type
 - c. Morphology → large or small cell with multiple variants (e.g., cleaved or non-cleaved)
2. Follicular vs. diffuse type
 - a. Follicular (nodular) type
 - 1) Rare in children, better Px than diffuse counterpart
 - 2) Is a B-cell type
 - 3) Those with small cells do better than large cells
 - b. Diffuse type
 - 1) More aggressive than nodular
 - 2) Either B-cell or T-cell type
 - 3) Highly aggressive (high grade) are always diffuse
3. Grade
 - a. Low grade → small lymphocytic, follicular small cleaved cell, follicular mixed small cleaved
 - b. Intermediate grade → follicular large cell, diffuse small cleaved cell, diffuse mixed/small/large cell types
 - c. High grade
 - 1) The most aggressive NHLs; all are histologically diffuse types
 - 2) Types
 - a) Immunoblastic type seen in immunocompromised
 - b) Lymphoblastic involves mediastinum & bone marrow, is TdT positive & has T-cell markers
 - 3) **Small Noncleaved cell = Burkitt's lymphoma**
 - i) B-cell type, closely linked to Epstein-Barr virus
 - ii) African Burkitt's (endemic) involves jaw bones
 - iii) US form involves abdomen more commonly
 - iv) **Classic histologic description is the "starry sky pattern,"** caused by dark background of densely packed lymphocytes (sky) with light colored spots in them caused by scattered macrophages (the stars)
 - v) Translocation of *c-myc* from chromosome 8 to chromosome 14 Ig heavy chain locus

4. Cutaneous T-cell lymphoma (CTCL, mycosis fungoides)
 - a. Slowly progressive CD4+ T-cell lymphoma of the skin, usually occurring in elderly
 - b. **Classic histologic description** → **cells contain cerebriform nuclei** (nucleus looks like cerebral gyri)
 - c. Often presents with systemic erythroderma, a total body erythematous & pruritic rash, which can precede clinically apparent malignancy by years
 - d. Leukemic phase of this disease is called “Sézary syndrome”
5. Angiocentric T-cell lymphoma
 - a. 2 subtypes = nasal T-cell lymphoma (lethal midline granuloma) & pulmonary angiocentric lymphoma (Wegener’s granulomatosis)
 - b. Nasal T-cell lymphoma is EBV associated
 - c. Both are highly lethal, nonresponsive to chemotherapy
 - d. Classic presentation = large mass that when biopsied is nondiagnostic due to large areas of necrosis within mass
 - e. Can cause airway compromise by local compression/edema
 - f. Tx = palliative radiation therapy

C. HODGKIN’S LYMPHOMA

1. Occurs in a bimodal age distribution, young men (women for nodular sclerosis type, see below) & geriatric population
2. EBV infection is present in up to 50% of cases
3. Si/Sx resemble inflammatory disorder, **classic Pel-Epstein fevers** (fevers wax & wane over weeks), chills, night sweats, weight loss, leukocytosis, **in some pts Sx worsen with alcohol intake**
4. Reed-Sternberg (RS) cells
 - a. Possibly the malignant cell of Hodgkin’s
 - b. **Classically appear as binucleated giant cells (“owl eyes”) with eosinophilic inclusions** (See Color Plate 18)
 - c. **One variation is Lacunar cell, a mononucleated giant cell**
 - d. Dz severity is proportional to number of R-S cells seen in tumor
5. Rye classification contains 4 variants
 - a. Lymphocytic predominance is least frequently occurring, a B-cell type
 - b. Mixed cellularity
 - 1) Most frequently occurring type
 - 2) Histology → lymphocytes, eosinophils, RS cells, plasma cells
 - c. Nodular sclerosis
 - 1) More frequent in women
 - 2) Histology
 - a) **Nodular division of lymph nodes by fibrous bands**
 - b) **Lacunar cell RS variant**
 - d. Lymphocyte depletion
 - 1) Poorest prognosis
 - 2) Histology → frequent necrosis, many RS cells
6. Clinical staging more closely linked to Px than histologic type
 - a. Stage I = 1 lymph node involved

- b. Stage II = 2 or more lymph nodes on same side of diaphragm
- c. Stage III = involvement on both sides of diaphragm
- d. Stage IV = disseminated, ≥ 1 organ or extranodal tissue involved
- e. Type A = systemic symptoms absent
- f. Type B = systemic symptoms present (e.g., fever, night sweats, unexpected weight loss $>10\%$)