Hematology & Oncology
Part 1

Ashlee Crawley
Outline

- Blood Cell Differentiation
- Platelet Plug Formation
- Coagulation Cascade
- Thrombogenesis
- ANEMIAS:
  - microcytic,
  - macrocytic
  - Normocytic
- Heme Synthesis
- Leukemia
- Lymphoma
- Pharmacology
Normal Lab Values

- MCV: average volume of the RBC; 82-96
- MCH: mean cell hemoglobin 27-33
- MCHC: mean cell hemoglobin concentration; 33-37
- RDW: coefficient of variation of MCV; range of sizes; 11.5-14.5
- Prothrombin Time: PT 11-14 seconds
  - Tests the function of the common and extrinsic pathway:
    - factors I, II, V, VII, and X
- Partial Thromboplastin Time: PTT 25-35 seconds
  - Tests the function of the common and intrinsic pathway
    - All factors EXCEPT VII and XIII
- International Normalized Ratio: INR 0.8-1.2
Primary Hemostasis

1. Injury
   - vWF binds to exposed collagen on endothelial damage

2. Platelet Adhesion:
   - Platelet receptor GPIb bind to endothelial receptor vWF

3. Platelet Activation:
   - Platelets degranulate and release:
     - ADP: promotes exposure of GPIIb/IIIa receptors on platelets
     - TXA2 promotes platelet aggregation

4. Platelet Aggregation:
   - Fibrinogen links GPIIb/IIIa and links platelets
   - forms temporary plug and the coagulation cascade begins....
Hemostatic Disorders:

Symptoms:
- Mucosal bleeding: epistaxis, hemoptysis, GI bleeding, hematuria, and menorrhagia.
  - Severe thrombocytopenia can lead to intracranial bleeding.
- Skin bleeding: petechiae, Purpura, ecchymosis.
  - Petechiae is specifically a sign up thrombocytopenia, so low platelet count*
Disorders of Primary Hemostasis

- **Immune Thrombocytopenic Purpura**
  - Autoimmune production of IgG against platelet antigens GpIIb/IIIa
  - Platelets are consumed by splenic macrophages -> thrombocytopenia
  - Acute form occurs in children after a viral infection. It is self-limited and resolves within weeks
  - Chronic form occurs in middle-aged women. It can be primary or associated with autoimmune disorder (SLE)
  - Labs:
    - Thrombocytopenia
    - Normal PT/PTT
  - Histological Finding:
    - Increased megakaryocytes
Disorders of Primary Hemostasis

- Microangiopathic Hemolytic Anemia: formation of microthrombi in small blood vessels
  - Clinical Findings: skin and mucosal bleeding, hemolytic anemia, fever
  - Thrombotic Thrombocytopenia Purpura
    - ADAMTS13, the enzyme that cleaves vWF, is decreased
    - The clots do not adhere properly, creating microthrombi
    - Can see CNS abnormalities
  - Hemolytic Uremic Syndrome
    - Seen in children with E. coli 0157:H7 diarrhea
    - E. coli toxin causes damage to endothelial cells, causing microthrombi
    - Renal insufficiency
  - Labs:
    - Thrombocytopenia
    - Normal PT/PTT
    - Anemia with schistocytes
    - Increased megakaryocytes on bone marrow
Other Disorders

- Bernard-Soulier Syndrome
  - Genetic GPIb deficiency, so platelet adhesion is impaired

- Glanzmann’s Thrombasthenia:
  - Genetic GPIIb/IIIa deficiency, so platelet aggregation is impaired
The Coagulation Cascade generates thrombin, which converts fibrinogen to fibrin. Fibrin is cross-linked to stabilize the platelet clot.

**PT:** factors I, II, V, VII, and X

**PTT:** All factors EXCEPT VII and XIII
Disorders of The Coagulation Cascade

- **Hemophilia A**
  - Factor VIII Deficiency
  - X-linked recessive (predominately affects males)
  - Presents with deep tissue and joint bleeding
  - Labs:
    - Increased PTT but normal PT
    - Decreased Factor VIII levels
    - Normal Platelet Count

- **Hemophilia B**
  - Factor IX Deficiency
Other Hemostasis Disorders

Von Willebrand Disease
- Most common inherited coagulation disorder; Autosomal Dominant
- Low vWF impairs platelet adhesion
- Labs:
  - Increased bleeding time
  - Increased PTT but normal PT
  - Ristocetin Test

Vitamin K Deficiency
- Vitamin K is responsible for carboxylating factors II, VII, IX, X, protein C, and protein S.
- The Deficiency occurs in:
  - Newborns due to the lack of colonization of bacteria in their GI tract
  - Long-Term Antibiotic Therapy
  - Malabsorption

PT: factors I, II, V, VII, and X
PTT: All factors EXCEPT VII and XIII
DIC

- Pathologic activation of coagulation cascade causes consumption of platelets and clotting factors, resulting in bleeding

- Causes:
  - Sepsis
  - Trauma
  - Obstetric Complications
  - Malignancy
  - Nephrotic Syndrome
  - Post-Transfusion

- Labs:
  - Thrombocytopenia
  - Increased PT/PTT
  - Decreased Fibrinogen
  - Elevated D-Dimer

PT: factors I, II, V, VII, and X
PTT: All factors EXCEPT VII and XIII
Anticoagulation Pharmacology

**Warfarin:**
- interferes with the normal synthesis of Vitamin K dependent factors: II, VII, IX, and X, as well as Proteins C and S.
- Used for DVT prophylaxis, prevention of stroke
- Can have an ↑ PT
- Should not be used in pregnant women
- Toxicity: bleeding, teratogenic, drug-interactions
- To reverse its effects, give Vitamin K

PT: factors I, II, V, VII, and X
PTT: All factors EXCEPT VII and XIII
Anemias

Megaoblastic

Non-Megaloblastic

Iron deficiency

ACD

ACD

Iron deficiency

Thalassemias

Lead poisoning

Sideroblastic anemia

ADP

Aplastic anemia

Chronic kidney disease

RBC membrane defect: hereditary spherocytosis

RBC enzyme deficiency: G6PD, PK

HbC

Sickle cell anemia

Paroxysmal nocturnal hemoglobinuria

ACD may first present as a normocytic anemia and then progress to a microcytic anemia.
Microcytic Anemias

- MCV < 80
- Usually a production problem, causing decreased hemoglobin:
  - Iron Deficiency:
  - Anemia of Chronic Disease***
  - Thalassemia
  - Lead Poisoning
  - Sideroblastic

• Iron Deficiency:
  - Anemia of Chronic Disease***
  - Thalassemia
  - Lead Poisoning
  - Sideroblastic
Microcytic Anemia Smear
Iron Deficiency Anemia

- Most common type of anemia
- Microcytic, hypochromic anemia
- Causes:
  - Chronic bleeding
  - Malnutrition/absorption
  - Pregnancy
- Lab Values:
  - ↓ serum Fe
  - ↓ Ferritin
  - ↑ transferrin
  - ↓ TIBC
Anemia of Chronic Disease

- Can present as normocytic or hypochromic
- Chronic inflammation causes an increase in acute phase proteins, which increase hepcidin production
- Iron is locked away in macrophages and not able to be used
- ↓ serum Fe
- ↑ ferritin
- ↓ TIBC

[Diagram showing the pathway of iron absorption and metabolism, with a note on hepcidin regulation]
**Thalassemias**

**α – Thalassemia**
- Prevalent in Asian and African Populations
- Defect in the α globin gene DELETION, causing ↓ α globin synthesis

**β - Thalassemia**
- Prevalent in Mediterranean Populations
- Gene MUTATIONS
- β Thalassemia minor
  - β chain is underproduced and is usually asymptomatic
- β Thalassemia major
  - β chain is absent, leading to a severe anemia that requires blood transfusions
- Target Cells: buildup of hemoglobin in the center of the RBC
Heme Synthesis

Sideroblastic Anemia:

- Defect in heme synthesis
- Hereditary: defect in δ-aminolevulinic acid synthase
- **Lead Poisoning:** lead inhibits ferrochelatase and ALA dehydrogenase, leading to ↓ heme synthesis
- Other etiologies: Alcohol, Isoniazid Therapy

Labs:

- ↑ iron
- ↑ transferrin
- ↑ ferritin

Histology:

- Ringed Sideroblast
Macrocytic Megaloblastic Anemia

MCV > 100
Vitamin B12 Deficiency
Folate Deficiency
Folate Deficiency

- **Causes:**
  - Malnutrition (alcoholics)
  - Impaired metabolism (TMP/SMX)
  - Pregnancy

- **Labs:**
  - ↑ homocysteine
  - Normal methylmalonic acid
Vitamin B12 Deficiency

- Causes:
  - Insufficient intake (vegan diet)
  - Malabsorption (Crohn’s)
  - Pernicious Anemia
  - Diphyllobothrium latum

- Labs:
  - ↑ homocysteine
  - ↑ methylmalonic acid

- Neurologic Symptoms: peripheral neuropathy, change in sensation, spasticity, dementia
Nonmegaloblastic Macrocytic Anemia

- DNA synthesis is not impaired
- Causes include alcoholism and other liver diseases, drugs (5-FU, AZT)
Normocytic Anemia

- MCV = 80-100
- Divided into:
  - Hemolytic
    - Extravascular
      - Hereditary Spherocytosis
      - Sickle Cell Anemia
    - Intravascular
      - Paroxysmal Nocturnal Hemoglobinuria (PNH)
      - G6PD Deficiency
      - Immune Hemolytic Anemia
      - Microangiopathic Hemolytic Anemia
      - Malaria
  - Non-Hemolytic
    - Aplastic Anemia
    - Anemia of Chronic Disease***
Hereditary Spherocytosis

- Defect in the Ankyrin protein interacting with RBC membrane skeletons, so there is less membrane and the RBCs are removed prematurely by the spleen
- Findings:
  - Splenomegaly
  - Jaundice
  - Spherocytes on peripheral smear
- Dx: + osmotic fragility test
- Tx: Splenectomy
  - Spherocytes will still be present but the anemia will resolve
**Sickle Cell Anemia**

- HbS point mutation
- Pathogenesis: low O2 or dehydration precipitates sickling/polymerization
- Sickled (crescent-shaped) RBCs that get destroyed in the spleen and damage the capillaries
- Homozygotic Complications:
  - Some get autosplenectomies, which can cause an increased risk of encapsulated organism infections
  - Salmonella Osteomyelitis
  - Renal Papillary Necrosis
  - Aplastic Crisis due to Parvo Infection
- Heterozygotes have resistance to malaria
Other Extravascular Hemolytic Anemias

- Pyruvate Kinase Deficiency: autosomal recessive
  - ↓ ATP leads to rigid RBCs

- HbC Defect:
  - Autosomal Recessive mutation in the beta chain of hemoglobin
    - Glutamic acid is replaced by lysine
  - MUCH less common than sickle cell anemia
  - Mild anemia due to extravascular hemolysis
  - HbC crystals are seen in RBCs
G6PD Deficiency

- X-linked
- Defect in G6PD -> decreased glutathione -> ↑ RBC susceptibility to oxidant stress
- Triggered by: infection, sulfa drugs, fava beans
- Labs:
  - RBCs with Heinz Bodies (precipitated Hemoglobin)
  - Bite Cells
Paroxysmal Nocturnal Hemoglobinuria

- Acquired mutation of PIGA gene that causes impaired synthesis of GPI, the factor that protects the RBC membrane from complement
- Intravascular, complement-mediated RBC lysis that occurs periodically, especially during sleep when there is a mild respiratory acidosis
- Triad of Findings:
  - Hemolytic Anemia
  - Pancytopenia
  - Venous Thrombosis
- Dx: CD55/59 of RBCs is Absent
Autoimmune Hemolytic Anemia

- IgG: chronic anemia due to SLE, CLL, and some drugs (penicillins and cephalosporins)
  - IgG binds to RBCs in the warm temperature of the central body
- IgM: seen in CLL, Mycoplasma pneumonia infections, infectious Mononucleosis
- Erythroblastosis fetalis: Rh antigen incompatibility, seen in newborns
- Coomb’s Test positive
  - Direct Coombs test confirms the presence of antibody-coated RBCs
Microangiopathic Hemolytic Anemia

- RBCs are damaged when passing through an obstructed or narrowed vessel.
- Seen in DIC, TTP, HUS, SLE, malignant hypertension
- Shistocytes (helmet cells) are seen on smear due to mechanical destruction
Malaria

- Infection of RBCs and liver with Plasmodium, transmitted by the female Anopheles mosquito
- During the plasmodium life cycle, RBCs are rupture, resulting in intravascular hemolysis and a cyclic fever
- There can be mild extravascular hemolysis and splenomegaly as the spleen consumes some infected RBCs

Ring stage of *P. falciparum*
Aplastic Anemia

- Caused by destruction of myeloid stem cells:
  - Radiation or drugs: benzene, chloramphenicol, animetabolites, alkylating agents
  - Viruses: Parvovirus B19, EBV, HIV, HCV
  - Fanconi’s Anemia: DNA repair defect; short stature, increased incidence of tumors/leukemia
  - Idiopathic

- Characteristics:
  - Pancytopenia
  - Cell morphology will be normal but hypocellular bone marrow
  - Fatigue, malaise, pallor, Purpura, mucosal bleeding, infection
References:

- Pathoma
- First Aid
- Robbins and Cotran Review of Pathology, Fourth Edition
  - https://www-clinicalkey-com.libproxy.unm.edu/#!/content/book/3-s2.0-B9781455751556000143
A 3-year-old boy from Sicily has a poor appetite and is underweight for his age and height. Physical examination shows hepatosplenomegaly. The hemoglobin concentration is 6 g/dL, and the peripheral blood smear shows severely hypochromic and microcytic RBCs. The total serum iron level is normal, and the reticulocyte count is 10%. A radiograph of the skull shows maxillofacial deformities and expanded marrow spaces. Which of the following is the most likely cause of this child’s illness?

- A Imbalance in α-globin and β-globin chain production
- B Increased fragility of erythrocyte membranes
- C Reduced synthesis of hemoglobin F
- D Relative deficiency of vitamin B₁₂
- E Sequestration of iron in reticuloendothelial cells
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- B Increased fragility of erythrocyte membranes
- C Reduced synthesis of hemoglobin F
- D Relative deficiency of vitamin B\(_{12}\)
- E Sequestration of iron in reticuloendothelial cells
A This patient of Mediterranean descent has β-thalassemia major. In this condition, there is a severe reduction in the synthesis of β-globin chains without impairment of α-globin synthesis. The free, unpaired α-globin chains form aggregates that precipitate within normoblasts and cause them to undergo apoptosis. The death of RBC precursors in the bone marrow is called “ineffective erythropoiesis.” Not only does this cause anemia, but it also increases the absorption of dietary iron, giving rise to iron overload, which results in hemochromatosis with infiltrative cardiomyopathy, hepatic cirrhosis, and “bronze diabetes” from pancreatic islet dysfunction. The severe anemia triggers erythropoietin synthesis, which expands the erythropoietic marrow. The marrow expansion encroaches on the bones, causing maxillofacial deformities. Extramedullary hematopoiesis causes hepatosplenomegaly. In comparison, the hemolytic anemia is mild in β-thalassemia minor, and there is very little ineffective erythropoiesis. Hemochromatosis is particularly detrimental to the liver and heart. Patients with chronic anemia may require RBC transfusions, which adds even more iron to body stores. The other listed options do not lead to a marked expansion of hematopoiesis.
Question 2

A 23-year-old African-American man passes dark reddish brown urine 3 days after taking an anti-inflammatory medication that includes phenacetin. He is surprised, because he has been healthy all his life and has had no major illnesses. On physical examination, he is afebrile, and there are no remarkable findings. CBC shows a mild normocytic anemia, but the peripheral blood smear shows precipitates of denatured globin (Heinz bodies) with supravital staining and scattered “bite cells” in the population of RBCs. Which of the following is the most likely diagnosis?

- A α-Thalassemia minor
- B β-Thalassemia minor
- C Glucose-6-phosphate dehydrogenase deficiency
- D Sickle cell trait
- E Abnormal ankyrin in RBC cytoskeletal membrane
- F Warm antibody autoimmune hemolytic anemia
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C Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder that affects about 10% of African-American males. The lack of this enzyme subjects hemoglobin to damage by oxidants, including drugs such as primaquine, sulfonamides, nitrofurantoin, phenacetin, and aspirin (in large doses). Infection can also cause oxidative damage to hemoglobin. Heinz bodies are denatured hemoglobin, and they damage the RBC membrane, giving rise to intravascular hemolysis. The “bite cells” result from the attempts of overeager splenic macrophages to pluck out the Heinz bodies, adding an element of extravascular hemolysis. Heterozygotes with α-thalassemia (1 or 2 abnormal genes out of 4 total α-globin genes) have no major problems, but in cases of α-thalassemia major, perinatal death is the rule. Likewise, β-thalassemia minor and sickle cell trait are conditions usually with no major problems and no relation to drug usage. RBC membrane abnormalities, such as hereditary spherocytosis (caused by abnormal spectrin), typically produce a mild anemia without significant hemolysis, and there is no drug sensitivity. Some autoimmune hemolytic anemias can be drug related, but the hemolysis is predominantly extravascular.
A 37-year-old woman has experienced abdominal pain and intermittent low-volume diarrhea for the past 3 months. On physical examination, she is afebrile. A stool sample is positive for occult blood. A colonoscopy is performed, and biopsy specimens from the terminal ileum and colon show microscopic findings consistent with Crohn disease. She does not respond to medical therapy, and part of the colon and terminal ileum are removed. She is transfused with 2 U of packed RBCs during surgery. Three weeks later, she appears healthy, but complains of easy fatigability. On investigation, CBC findings show hemoglobin of 10.6 g/dL, hematocrit of 31.6%, RBC count of 2.69 million/μL, MCV of 118 μm³, platelet count of 378,000/mm³, and WBC count of 9800/mm³. The reticulocyte count is 0.3%. Which of the following is most likely to produce these hematologic findings?

- A Anemia of chronic disease
- B Chronic blood loss
- C Hemolytic anemia
- D Myelophthisic anemia
- E Vitamin B₁₂ deficiency
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Question 3 Explanation

The high MCV indicates a marked macrocytosis, greater than expected from reticulocytosis alone. The two best-known causes for such an anemia (also known as megaloblastic anemia when characteristic megaloblastic precursors are seen in the bone marrow) are vitamin B<sub>12</sub> and folate deficiency. Because vitamin B<sub>12</sub> complexed with intrinsic factor is absorbed in the terminal ileum, its removal can cause vitamin B<sub>12</sub> deficiency. Anemia of chronic disease is generally a normocytic anemia. Chronic blood loss and iron deficiency produce a microcytic pattern of anemia, as does dietary iron deficiency. Hemolytic anemia is unlikely several weeks after blood transfusion. Inflammatory bowel diseases (e.g., Crohn disease) increase the risk of malignancy, but myelophthisic anemias (from space-occupying lesions of the marrow) are usually normocytic to mildly macrocytic (from reticulocytosis).
A 42-year-old woman has had nosebleeds, easy bruising, and increased bleeding with her menstrual periods for the past 4 months. On physical examination, her temperature is 37°C, pulse is 88/min, and blood pressure is 90/60 mm Hg. She has scattered petechiae over the distal extremities. There is no organomegaly. Laboratory studies show hemoglobin of 12.3 g/dL, hematocrit of 37%, platelet count of 21,500/mm$^3$, and WBC count of 7370/mm$^3$. A bone marrow biopsy specimen shows a marked increase in megakaryocytes. The prothrombin and partial thromboplastin times are within the reference range. What is the most likely diagnosis?

- A Disseminated intravascular coagulation
- B Hemophilia B
- C Immune thrombocytopenic purpura
- D Metastatic breast carcinoma
- E Thrombotic thrombocytopenic purpura
- F Vitamin K deficiency
- G Von Willebrand disease
Question 4

A 42-year-old woman has had nosebleeds, easy bruising, and increased bleeding with her menstrual periods for the past 4 months. On physical examination, her temperature is 37° C, pulse is 88/min, and blood pressure is 90/60 mm Hg. She has scattered petechiae over the distal extremities. There is no organomegaly. Laboratory studies show hemoglobin of 12.3 g/dL, hematocrit of 37%, platelet count of 21,500/mm $^3$, and WBC count of 7370/mm $^3$. A bone marrow biopsy specimen shows a marked increase in megakaryocytes. The prothrombin and partial thromboplastin times are within the reference range. What is the most likely diagnosis?

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- C Immune thrombocytopenic purpura
- D Metastatic breast carcinoma
- E Thrombotic thrombocytopenic purpura
- F Vitamin K deficiency
- G Von Willebrand disease
C Reduced numbers of platelets can result from decreased production or increased destruction. Marrow examination in this case shows numerous megakaryocytes, which excludes decreased production. Accelerated destruction can be caused by hypersplenism, but there is no splenomegaly in this case. Peripheral platelet destruction is often immunologically mediated and can result from well-known autoimmune diseases such as systemic lupus erythematosus, or it can be idiopathic. When all known causes of thrombocytopenia are excluded, a diagnosis of idiopathic (immune) thrombocytopenic purpura (ITP) can be made. This patient seems to have no other symptoms or signs and has no history of drug intake or infections that can cause thrombocytopenia. ITP is most likely. Thrombotic thrombocytopenic purpura (TTP) is another entity to be considered, but TTP produces a microangiopathic hemolytic anemia (MAHA) that typically is associated with fever, neurologic symptoms, and renal failure. Disseminated intravascular coagulation (DIC) is another form of MAHA. Hemophilia B, similar to hemophilia A, leads to soft tissue bleeding, and the partial thromboplastin time is prolonged, but the platelet count is normal. Metastases can act as a space-occupying lesion in the marrow to reduce hematopoiesis, but this is unlikely to be selective with megakaryocytes, and in this case, there is a megakaryocytic hyperplasia. Vitamin K deficiency prolongs the prothrombin time initially and the partial thromboplastin time if severe, but does not affect platelets. In von Willebrand disease, bleeding is due to abnormal platelet adhesion, but platelet numbers are normal.
A clinical study is performed involving adult patients diagnosed with microangiopathic hemolytic anemia. A subgroup of patients who had fever or diarrhea preceding the initial diagnosis of anemia were excluded. The patients had schistocytes present on peripheral blood smears. Some of these patients were found to have a deficiency of a metalloproteinase known as ADAMTS13. Which of the following conditions were the patients with this deficiency most likely to have?

- A Disseminated intravascular coagulation (DIC)
- B Hemolytic-uremic syndrome (HUS)
- C Heparin-induced thrombocytopenia (HIT)
- D Idiopathic thrombocytopenic purpura (ITP)
- E Thrombotic thrombocytopenic purpura (TTP)
A clinical study is performed involving adult patients diagnosed with microangiopathic hemolytic anemia. A subgroup of patients who had fever or diarrhea preceding the initial diagnosis of anemia were excluded. The patients had schistocytes present on peripheral blood smears. Some of these patients were found to have a deficiency of a metalloproteinase known as ADAMTS13. Which of the following conditions were the patients with this deficiency most likely to have?

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C. Heparin-induced thrombocytopenia (HIT)
D. Idiopathic thrombocytopenic purpura (ITP)
E. Thrombotic thrombocytopenic purpura (TTP)
54 E A deficiency of ADAMTS13, from an acquired antibody to this metalloproteinase or a genetic mutation in the encoding gene, can lead to accumulation of large von Willebrand multimers that promote platelet microaggregate formation, resulting in TTP that is marked by a pentad of microangiopathic hemolytic anemia, fever, neurologic changes, thrombocytopenia, and renal failure. DIC results from acquired conditions that promote consumption of coagulation factors, not a metalloproteinase deficiency. HUS is very similar to TTP, but is more likely related to a preceding infectious gastroenteritis with diarrhea. HIT occurs in about 5% of individuals receiving heparin, and the most serious complication is widespread arterial and venous thrombosis. ITP is mainly complicated by bleeding from thrombocytopenia.
Hematopoietic and Lymphoreticular Systems Part 1

The hematology and Oncology section of first aid is comprised of topics we have covered in multiple blocks: It touches on blood cell differentiation, platelet plug formation, the coagulation cascade, Thrombogenesis, Anemias, heme syntheses, leukemia, lymphoma, and pharmacology. I am going to be covering the platelet plug formation and coagulation cascade, and their associated pathologies, as well as all of the anemias and some of the disorders of heme synthesis. There will also be five questions from the Robbins Review of Pathology Book to test your knowledge.

Normal Values:

- **MCV:** average volume of the RBC; 82-96
  - This determines whether the anemia is classified as microcytic, normocytic, or macrocytic
- **MCH:** mean cell hemoglobin 27-33
- **MCHC:** mean cell hemoglobin concentration; 33-37
- **RDW:** coefficient of variation of MCV; range of sizes; 11.5-14.5
- **Prothrombin Time:** PT 11-14 seconds
  - Tests the function of the common and extrinsic pathway:
    - Factors I, II, V, VII, and X
- **Partial Thromboplastin Time:** PTT 25-35 seconds
  - Tests the function of the common and intrinsic pathway
    - All factors EXCEPT VII and XIII
- **International Normalized Ratio:** INR 0.8-1.2

**Primary Hemostasis:** When there is injury to a blood vessel, that vessel will vasoconstrict and express endothelin. Then Von Willebrand Factor will come to attach to the subepithelial receptors that have been exposed.

1. **Platelet Adhesion:** Platelet receptor GPIb binds to vWF
2. **Platelets degranulate and release:**
   - ADP: promotes exposure of GPIIb/IIIa receptors on platelets
   - TXA2 promotes platelet aggregation
3. **Platelets link together with fibrinogen to form a platelet plug because the platelet plug is very weak at this point.**
4. **Coagulation cascade begins to stabilize that clot that was formed.**

**Disorders of Primary Hemostasis:** The platelet plugs are not being formed correctly, so there is some sort of increased bleeding

**Symptoms:**

- **Mucosal bleeding:** epistaxis, hemoptysis, GI bleeding, hematuria, and menorrhagia.
  - Severe thrombocytopenia can lead to intracranial bleeding.
- **Skin bleeding:** petechiae, Purpura, ecchymosis.
  - Petechiae is specifically a sign up thrombocytopenia, so low platelet count*

There are some examples of that below
Immune Thrombocytopenic Purpura
- Autoimmune production of IgG against platelet antigens GpIIb/IIIa
- Platelets are consumed by splenic macrophages, leading to thrombocytopenia
- Acute form occurs in children after a viral infection
- Chronic form occurs in middle-aged women. It can be secondary to an autoimmune disease like SLE
- Labs:
  - Thrombocytopenia
  - Normal PT/PTT because it is not affecting the coagulation cascade
- Histological Finding:
  - Increased megakaryocytes: Since there are low circulating platelet numbers, the bone marrow is trying to compensate.

Microangiopathic Hemolytic Anemia: There is formation of microthrombi in the blood
For both of the conditions below, patients present with skin/mucosal bleeding, hemolytic anemia because those microthrombi are lysing RBCs, and a fever in response to the lysing.
  - Thrombotic Thrombocytopenia Purpura
    - ADAMTS13, the enzyme that cleaves vWF, is decreased
    - The clots do not adhere properly, creating microthrombi
    - Can see CNS abnormalities
  - Hemolytic Uremic Syndrome
    - Seen in children with E. coli 0157:H7 diarrhea
    - E. coli directly causes damage to endothelial cells, causing microthrombi
    - Renal insufficiency
  - Labs:
    - Thrombocytopenia: platelets are being used up in those microthrombi
    - Normal Pt/PTT because it is not affecting the coagulation cascade
    - Anemia with schistocytes

Other Disorders
  - Bernard-Soulier Syndrome: genetic GP1b deficiency
  - Glanzmann’s Thrombasthenia: Genetic GpIIb/IIIa deficiency

Coagulation Cascade: The function of the coagulation cascade is to generate thrombin, which converts fibrinogen to fibrin. Then the fibrin can cross-link to stabilize the platelet clot

Disorders of the Coagulation Cascade
Hemophilia A
  - Factor VIII Deficiency: Without this factor, Prothrombin cannot be converted to Thrombin, and fibrinogen cannot be converted to fibrin.
  - X-linked recessive (predominately affects males)
  - Presents with deep tissue and joint bleeding. The clots formed are weak and not stabilized by fibrin
  - Labs:
    - Increased PTT but normal PT because PT only tests the function of 1, 2, 5, 7, and 10
Decreased Factor VIII levels
- Normal Platelet Count
- Tx: Recombinant Factor VIII

**Hemophilia B**
- Factor IX Deficiency: presents very similarly with the same labs

**Other Hemostasis Disorders**

**Von Willebrand Disease:** This is considered a kind of combined primary and secondary hemostatic disorder. Von Willebrand factor helps with platelet adhesion, but it also carries and protects factor VIII.
- Most common inherited coagulation disorder
- Autosomal Dominant
- Labs:
  - Increased bleeding time because the wound bleeds longer before a clot can be formed.
  - Increased PTT but normal PT because there is a problem with factor 8.
  - Ristocetin Test: induces platelet agglutination by causing vWF to bind to GP1B. Test is abnormal

**Vitamin K Deficiency:** Remember from GI, some of our Vitamin K comes from our diet, but almost half of it most likely is made from out intestinal microbiome. That helps to explain who is at risk for getting a Vitamin K deficiency:
- Vitamin K is responsible for carboxylating factors II, VII, IX, X, protein C, and protein S.
- The Deficiency occurs in:
  - Newborns due to the lack of colonization of bacteria in their GI tract
  - Long-Term Antibiotic Therapy, where the microbiota has been wiped out.
  - Malabsorption

**DIC**
- Pathologic activation of coagulation cascade causes consumption of platelets and clotting factors, resulting in bleeding
- Causes:
  - Sepsis: the endotoxin can activate the coagulation cascade
  - Trauma: Rattlesnake Bite
  - Obstetric Complications
  - Malignancy: Adenocarcinoma and Acute Promyelocytic Leukemia
  - Nephrotic Syndrome
  - Post-Transfusion
- Labs:
  - Decreased platelet count
  - Increased PT/PTT
  - Decreased Fibrinogen
  - Elevated D-Dimer
**Anticoagulation Pharmacology**

**Warfarin:**
- Interferes with the normal synthesis of Vitamin K dependent factors: II, VII, IX, and X, as well as Proteins C and S.
- Used for DVT prophylaxis, prevention of stroke
- Can have an ↑ PT
- Should not be used in pregnant women
- Toxicity: bleeding, teratogenic, drug-interactions
- To reverse its effects, give Vitamin K

**Anemias:** Anemias are a decrease in RBC mass, number, hemoglobin, etc. They are usually separated by the MCV that is present, which can help us to distinguish the causes of the anemia. Microcytic Anemias are usually a problem with production: either the iron that is needed, the globin chain, or with the heme synthesis. Macrocytic Anemias are either a problem with DNA synthesis (making the cells large without dividing), or related to liver function. Finally, Normocytic anemias are either a problem with the RBCs getting lysed, or a hemolytic anemia, or a nonhemolytic anemia, which includes CKD and aplastic anemia.

**Microcytic Anemias:** MCV <80
The cells are microcytic (smaller than the lymphocytes), as well as hypochromic, meaning they have more of a white pallor in the center

**Iron Deficiency Anemia:**
Most common anemia

Microcytic, Hypochromic Anemia
In normal iron uptake, the iron is absorbed into the luminal cells of the duodenum. There, the iron is transported into the blood by ferroportin transporters. The protein transferrin carries the iron in the blood to various sites, like the liver or macrophages. Another protein, ferritin binds to iron to prevent it from forming free radicals. Chronic bleeds in the GI tract, malabsorption, or pregnancy can all lead to decreased iron absorption. This decrease in iron causes less ferritin to be made because there is less free iron that needs to be bound and stored. Transferrin levels increase it try to pick up any iron, but the saturation remains low.

Causes:
- Chronic bleeding
- Malnutrition/absorption
- Pregnancy

Lab Values:
- ↓ serum Fe
- ↓ Ferritin
- ↑ transferrin
- ↓ TIBC

***Plummer-Vision Syndrome: dysphagia (esophageal webbing), glossitis, iron deficiency anemia***
Anemia of Chronic Disease
Can present as normocytic or hypochromic***
Chronic inflammation causes an increase acute phase proteins, which increase hepcidin production
Iron is locked away in macrophages and not able to be used
  • ↓ serum Fe
  • ↑ ferritin: ferritin is storing the iron so that it cannot be used
  • ↓ TIBC: there is more transferrin to try to take up the free iron
Treat the underlying cause

Thalassemias: One way to remember it is: thala“sea”mia because it was originally discovered as the Mediterranean variant. These disorders are a problem with the globin chain production of the hemoglobin, causing a microcytic anemia.

α – Thalassemia
Prevalent in Asian and African Populations
Defect in the α-globin gene DELETION, causing ↓ α globin synthesis.

β - Thalassemia
Prevalent in Mediterranean Populations
Caused by gene MUTATIONS
β Thalassemia minor
  β chain is under produced and is usually asymptomatic
β Thalassemia major
  β chain is absent, leading to a severe anemia that requires blood transfusions
Target Cells: In a normal RBC, there are concentrations of hemoglobin on the edges giving it a biconcave shape. A target cell has a bleb of membrane in the center of the central pallor where some of the hemoglobin builds up. There is reduced hemoglobin in the cytoplasm, so the cytoplasm can bulge out in the center.

Heme Synthesis: Heme Synthesis begins with glycine and succinyl CoA combining to form alpha-aminolevulinic acid (ALA) in the mitochondria by ALA synthase and Vitamin B6. ALA is transported into the cytoplasm and then converted to porphobilinogen by ALA Dehydrogenase. Then there is a series of reactions to form which get coproporphyrinogen III. That gets transported back into the mitochondria to make protoporphyrin, which combines with iron to make heme by ferrochelatase. There are different diseases that occur at each step, but we are just going to address two that present with an anemia. If protoporphorin is deficient, iron will come into the cells

Sideroblastic Anemia: Defect in heme synthesis
Causes:
  • Hereditary: defect in δ- aminolevulinic acid synthase gene
  • Lead Poisoning: lead inhibits ferrochelatase and ALA dehydrogenase, leading to ↓ heme synthesis
• This can be an X-linked disorder or caused by:
  • Alcohol
  • Isoniazid Therapy: causes a Vitamin B6 deficiency

Labs:
• ↑ iron
• ↑ transferrin but ↓TIBC because there is not iron in the blood
• ↑ ferritin: Ferritin is going to store all of the iron because it is not being used to make heme

Histological Finding:
• Ringed Sideroblast: iron is accumulating in a ring around the nucleus of the cell

Macrocytic Anemias have an MCV >100, indicating there are less divisions that are occurring from the RBC precursors.

**Macrocytic Megaloblastic Anemia:** Macrocytic Anemias are most commonly due to folate or Vitamin B12 deficiency. The cells are megaloblastic because there is one less division because there are less DNA synthesis precursor molecules. You will see hyper-segmented neutrophils (>5 lobes).

**Folate Deficiency:** folate is converted to tetrahydrofolate (THF), assisting in the conversion of homocysteine to methionine.
Causes:
• Malnutrition (alcoholics)
• Impaired metabolism (TMP/SMX)
• Pregnancy

Labs:
• ↑ homocysteine
• Normal methylmalonic acid

**Vitamin B12 Deficiency:** Vitamin B12 is found in fatty foods, and is absorbed in the small intestine when it is bound to intrinsic factor (produced in the stomach). It helps in the conversion of homocysteine to methionine and methylmalonyl CoA to Succinyl CoA
Causes:
• Insufficient intake (vegan diet)
• Malabsorption (Crohn’s)
• Pernicious Anemia: autoimmune destruction of parietal cells in the body of the stomach, leading to a deficiency in intrinsic factor
• Diphyllobothrium latum: competes for Vitamin B12

Labs:
• ↑ homocysteine
• ↑ methylmalonic acid
• Neurologic Symptoms: peripheral neuropathy, change in sensation, spasticity, dementia
**Nonmegaloblastic Macrocytic Anemia**
DNA synthesis is not impaired
Causes include alcoholism and other liver diseases, drugs (5-FU, AZT)

**Normocytic Anemia**
MCV = 80-100
Divided into:
Hemolytic
  - Extravascular
    - Hereditary Spherocytosis
    - Sickle Cell Anemia
  - Intravascular
    - Paroxysmal Nocturnal Hemoglobinuria (PNH)
    - G6PD Deficiency
    - Immune Hemolytic Anemia
    - Microangiopathic Hemolytic Anemia
    - Malaria
Non-Hemolytic
  - Aplastic Anemia
  - Anemia of Chronic Disease***

**Hereditary Spherocytosis**: The RBC usually have a biconcave shape, that is maintained by these tethering proteins, including Ankyrin. In HS, these are not there, and small blebs come off the membrane and are removed from the spleen and slowly becomes spherical. These Spherocytes are less able to maneuver through the spleen and will get removed from circulation, causing the anemia. This also leads to the splenomegaly. It is diagnosed by putting the blood into a hypotonic solution. There is little membrane to take up the solution, making them fragile.

Findings:
  - Splenomegaly
  - Jaundice
  - Spherocytes on peripheral smear
Dx: + osmotic fragility test
Tx: Splenectomy
Spherocytes will still be present but the anemia will resolve

**Sickle Cell Anemia**: Gene is carried by 10% of people of African Descent, probably because of its protection against malaria. Caused by a HbS mutation, but there must be two abnormal beta genes present. During acidosis, dehydration, hypoxemia, the cells will polymerize, resulting in sickle cells. Most patients don’t present until around 6 months of age because before that, they are protected by hemoglobin F.
Homozygotic Complications:
- Some get autosplenectomies, which can cause an increased risk of encapsulated organism infections
- Salmonella Osteomyelitis
- Renal Papillary Necrosis
- Aplastic Crisis due to Parvo Infection
- Heterozygotes have resistance to malaria

**Other Extravascular Hemolytic Anemias**

**Pyruvate Kinase Deficiency**: autosomal recessive
\[ \downarrow \text{ATP} \rightarrow \text{rigid RBCs} \]

**HbC Defect**:

**G6PD Deficiency**
- X-linked
- African Variant: mildly reduced half-life of G6PD leading to mild hemolysis
- Mediterranean Variant: markedly reduced half life of G6PD: more severe hemolysis
- Defect in G6PD: decreased glutathione \(\rightarrow\) RBC susceptibility to oxidant stress
- Triggered by: infection, sulfa drugs, fava beans
- Labs: The Hemoglobin precipitates to form these Heinz bodies within the RBCs, and then they are ripped out as they pass through the spleen, forming these bite cells

**Paroxysmal Nocturnal Hemoglobinuria**
- Acquired mutation that causes impaired synthesis of GPI, the factor that protects the RBC membrane from complement
- Intravascular, complement-mediated RBC lysis that occurs periodically, especially during sleep when there is a mild respiratory acidosis
- Triad of Findings:
  - Hemolytic Anemia
  - Pancytopenia
  - Venous Thrombosis
- Dx: CD55/59 of RBCs is absent

**Autoimmune Hemolytic Anemia**
- IgG: chronic anemia due to SLE, CLL
  - IgG binds to RBCs in the warm temperature of the central body
- IgM: seen in CLL, Mycoplasma pneumonia infections, infectious Mononucleosis
  - Painful blue fingers and toes*
- Erythroblastosis fetalis: Rh antigen incompatibility, seen in newborns
- Coomb’s Test positive
**Microangiopathic Hemolytic Anemia**
- RBCs are damage when passing through an obstructed or narrowed vessel.
- Seen in DIC, TTP, HUS, SLE, malignant hypertension
- Shistocytes (helmet cells) are seen on smear due to mechanical destruction

**Malaria**
- Infection of RBCs and liver with Plasmodium, transmitted by the female Anopheles mosquito
- During the plasmodium life cycle, RBCs are rupture, resulting in intravascular hemolysis and a cyclic fever
- There can be mild extravascular hemolysis and splenomegaly as the spleen consumes some infected RBCs

**Aplastic Anemia**
Caused by destruction of myeloid stem cells:
- Radiation or drugs: benzene, chloramphenicol, animetabolites, alkylating agents
- Viruses: Parvovirus B19, EBV, HIV, HCV
- Fanconi’s Anemia: DNA repair defect; short stature, increased incidence of tumors/leukemia
- Idiopathic

Characteristics:
- Pancytopenia
- Cell morphology will be normal but hypocellular bone marrow
- Fatigue, malaise, pallor, Purpura, mucosal bleeding, infection

**Chronic Kidney Disease:**
↓erythropoietin -> ↓hematopoiesis
Practice Questions:

1. A 3-year-old boy from Sicily has a poor appetite and is underweight for his age and height. Physical examination shows hepatosplenomegaly. The hemoglobin concentration is 6 g/dL, and the peripheral blood smear shows severely hypochromic and microcytic RBCs. The total serum iron level is normal, and the reticulocyte count is 10%. A radiograph of the skull shows maxillofacial deformities and expanded marrow spaces. Which of the following is the most likely cause of this child’s illness?
   a. Imbalance in α-globin and β-globin chain production
   b. Increased fragility of erythrocyte membranes
   c. Reduced synthesis of hemoglobin F
   d. Relative deficiency of vitamin B₁₂
   e. Sequestration of iron in reticuloendothelial cells

2. A 23-year-old African-American man passes dark reddish brown urine 3 days after taking an anti-inflammatory medication that includes phenacetin. He is surprised, because he has been healthy all his life and has had no major illnesses. On physical examination, he is afebrile, and there are no remarkable findings. CBC shows a mild normocytic anemia, but the peripheral blood smear shows precipitates of denatured globin (Heinz bodies) with supravital staining and scattered “bite cells” in the population of RBCs. Which of the following is the most likely diagnosis?
   a. α-Thalassemia minor
   b. β-Thalassemia minor
   c. Glucose-6-phosphate dehydrogenase deficiency
   d. Sickle cell trait
   e. Abnormal ankyrin in RBC cytoskeletal membrane
   f. Warm antibody autoimmune hemolytic anemia

3. A 37-year-old woman has experienced abdominal pain and intermittent low-volume diarrhea for the past 3 months. On physical examination, she is afebrile. A stool sample is positive for occult blood. A colonoscopy is performed, and biopsy specimens from the terminal ileum and colon show microscopic findings consistent with Crohn disease. She does not respond to medical therapy, and part of the colon and terminal ileum are removed. She is transfused with 2 U of packed RBCs during surgery. Three weeks later, she appears healthy, but complains of easy fatigability. On investigation, CBC findings show hemoglobin of 10.6 g/dL, hematocrit of 31.6%, RBC count of 2.69 million/μL, MCV of 118 μm³, platelet count of 378,000/mm³, and WBC count of 9800/mm³. The reticulocyte count is 0.3%. Which of the following is most likely to produce these hematologic findings?
   a. Anemia of chronic disease
   b. Chronic blood loss
   c. Hemolytic anemia
   d. Myelophthlsic anemia
   e. Vitamin B₁₂ deficiency
4. A 42-year-old woman has had nosebleeds, easy bruising, and increased bleeding with her menstrual periods for the past 4 months. On physical examination, her temperature is 37°C, pulse is 88/min, and blood pressure is 90/60 mm Hg. She has scattered petechiae over the distal extremities. There is no organomegaly. Laboratory studies show hemoglobin of 12.3 g/dL, hematocrit of 37%, platelet count of 21,500/mm³, and WBC count of 7370/mm³. A bone marrow biopsy specimen shows a marked increase in megakaryocytes. The prothrombin and partial thromboplastin times are within the reference range. What is the most likely diagnosis?
   a. Disseminated intravascular coagulation
   b. Hemophilia B
   c. Immune thrombocytopenic purpura
   d. Metastatic breast carcinoma
   e. Thrombotic thrombocytopenic purpura
   f. Vitamin K deficiency
   g. Von Willebrand disease

5. A clinical study is performed involving adult patients diagnosed with microangiopathic hemolytic anemia. A subgroup of patients who had fever or diarrhea preceding the initial diagnosis of anemia were excluded. The patients had schistocytes present on peripheral blood smears. Some of these patients were found to have a deficiency of a metalloproteinase known as ADAMTS13. Which of the following conditions were the patients with this deficiency most likely to have?
   a. Disseminated intravascular coagulation (DIC)
   b. Hemolytic-uremic syndrome (HUS)
   c. Heparin-induced thrombocytopenia (HIT)
   d. Idiopathic thrombocytopenic purpura (ITP)
   e. Thrombotic thrombocytopenic purpura (TTP)
Marrow examination in this case shows numerous megakaryocytes, which excludes decreased Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder that affects about 10% of African-American males. The lack of this enzyme subjects hemoglobin to damage by oxidants, including drugs such as primaquine, sulfonamides, nitrofurantoin, phenacetin, and aspirin (in large doses). Infection can also cause oxidative damage to hemoglobin. Heinz bodies are denatured hemoglobin, and they damage the RBC membrane, giving rise to intravascular hemolysis. The “bite cells” result from the attempts of overeager splenic macrophages to pluck out the Heinz bodies, adding an element of extravascular hemolysis. Heterozygotes with α-thalassemia (1 or 2 abnormal genes out of 4 total α-globin genes) have no major problems, but in cases of α-thalassemia major, perinatal death is the rule. Likewise, β-thalassemia minor and sickle cell trait are conditions usually with no major problems and no relation to drug usage. RBC membrane abnormalities, such as hereditary spherocytosis (caused by abnormal spectrin), typically produce a mild anemia without significant hemolysis, and there is no drug sensitivity. Some autoimmune hemolytic anemias can be drug related, but the hemolysis is predominantly extravascular.
production. Accelerated destruction can be caused by hypersplenism, but there is no splenomegaly in this case. Peripheral platelet destruction is often immunologically mediated and can result from well-known autoimmune diseases such as systemic lupus erythematosus, or it can be idiopathic. When all known causes of thrombocytopenia are excluded, a diagnosis of idiopathic (immune) thrombocytopenic purpura (ITP) can be made. This patient seems to have no other symptoms or signs and has no history of drug intake or infections that can cause thrombocytopenia. ITP is most likely. Thrombotic thrombocytopenic purpura (TTP) is another entity to be considered, but TTP produces a microangiopathic hemolytic anemia (MAHA) that typically is associated with fever, neurologic symptoms, and renal failure. Disseminated intravascular coagulation (DIC) is another form of MAHA. Hemophilia B, similar to hemophilia A, leads to soft tissue bleeding, and the partial thromboplastin time is prolonged, but the platelet count is normal. Metastases can act as a space-occupying lesion in the marrow to reduce hematopoiesis, but this is unlikely to be selective with megakaryocytes, and in this case, there is a megakaryocytic hyperplasia. Vitamin K deficiency prolongs the prothrombin time initially and the partial thromboplastin time if severe, but does not affect platelets. In von Willebrand disease, bleeding is due to abnormal platelet adhesion, but platelet numbers are normal.

5. E A deficiency of ADAMTS13, from an acquired antibody to this metalloproteinase or a genetic mutation in the encoding gene, can lead to accumulation of large von Willebrand multimers that promote platelet microaggregate formation, resulting in TTP that is marked by a pentad of microangiopathic hemolytic anemia, fever, neurologic changes, thrombocytopenia, and renal failure. DIC results from acquired conditions that promote consumption of coagulation factors, not a metalloproteinase deficiency. HUS is very similar to TTP, but is more likely related to a preceding infectious gastroenteritis with diarrhea. HIT occurs in about 5% of individuals receiving heparin, and the most serious complication is widespread arterial and venous thrombosis. ITP is mainly complicated by bleeding from thrombocytopenia.