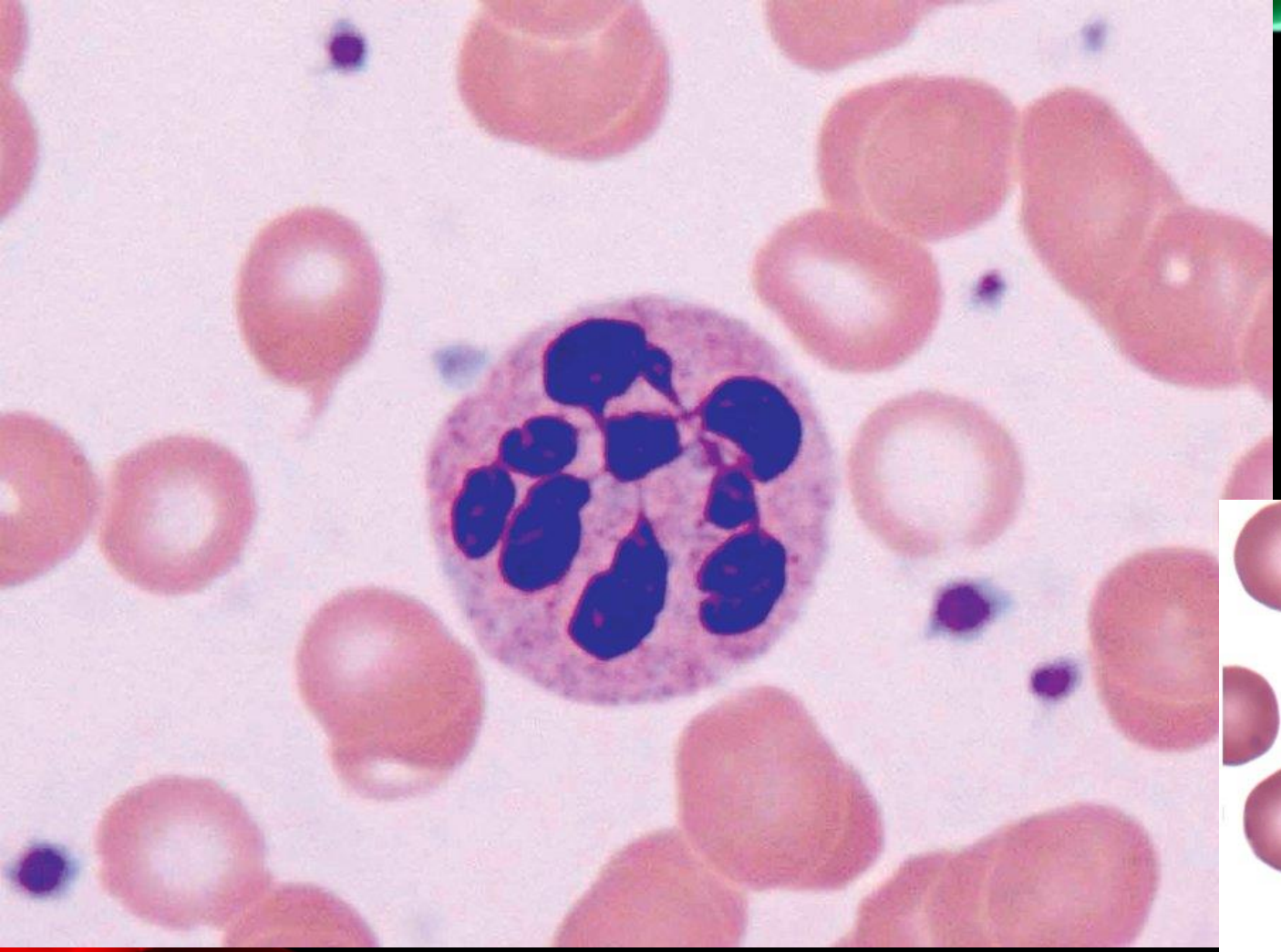
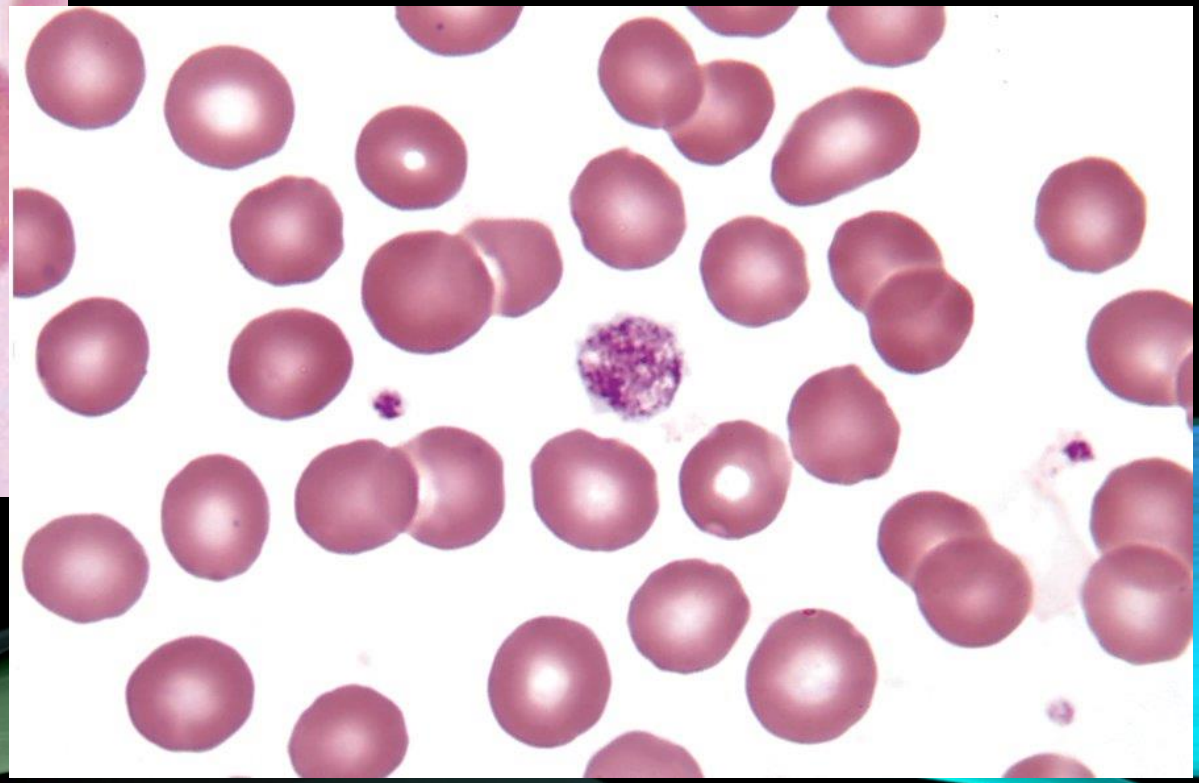


Question Number 1.

Number 7.



HEMATOLOGY REVIEW

Greg Dodaro

September 25th, 2018

QUESTION 1

- A 30-year-old woman is evaluated for progressive difficulty walking and numbness in both feet of 1 to 2 months' duration. She is otherwise healthy. She has followed a vegan diet for the past several years. Her only medication is an oral contraceptive pill.
- On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/66 mm Hg, pulse rate is 76/min, and respiration rate is 12/min; BMI is 25. She has decreased sensation and vibratory sense in both legs below the knees. No other neurologic deficits are observed.

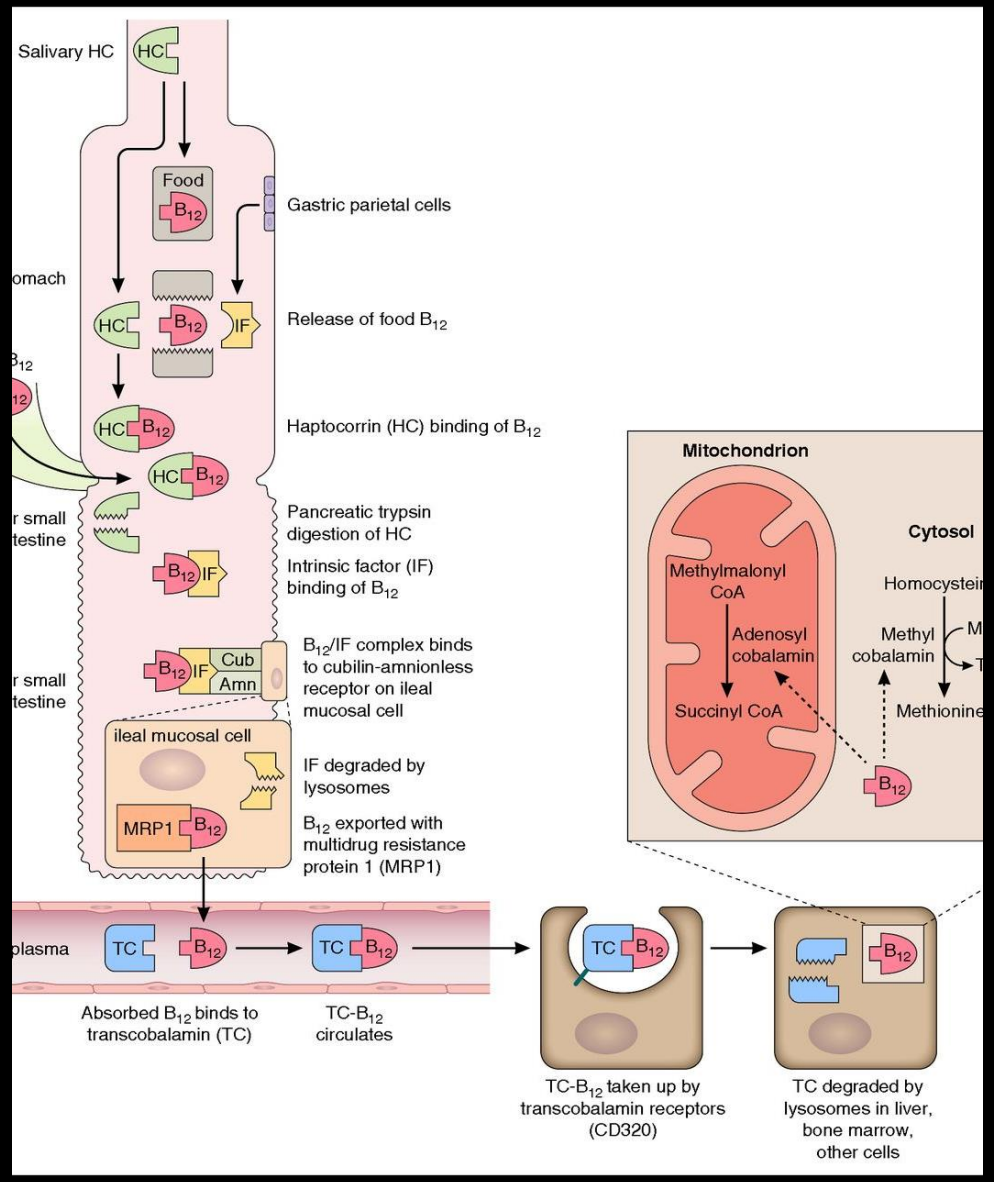
Hemoglobin	10.4 g/dL (104 g/L)
Leukocyte count	2800/µL (2.8×10^9/L)
Mean corpuscular volume	105 fL
Vitamin B_{12}	210 pg/mL (155 pmol/L)

Smear shown on slide 1. What is your next diagnostic test?

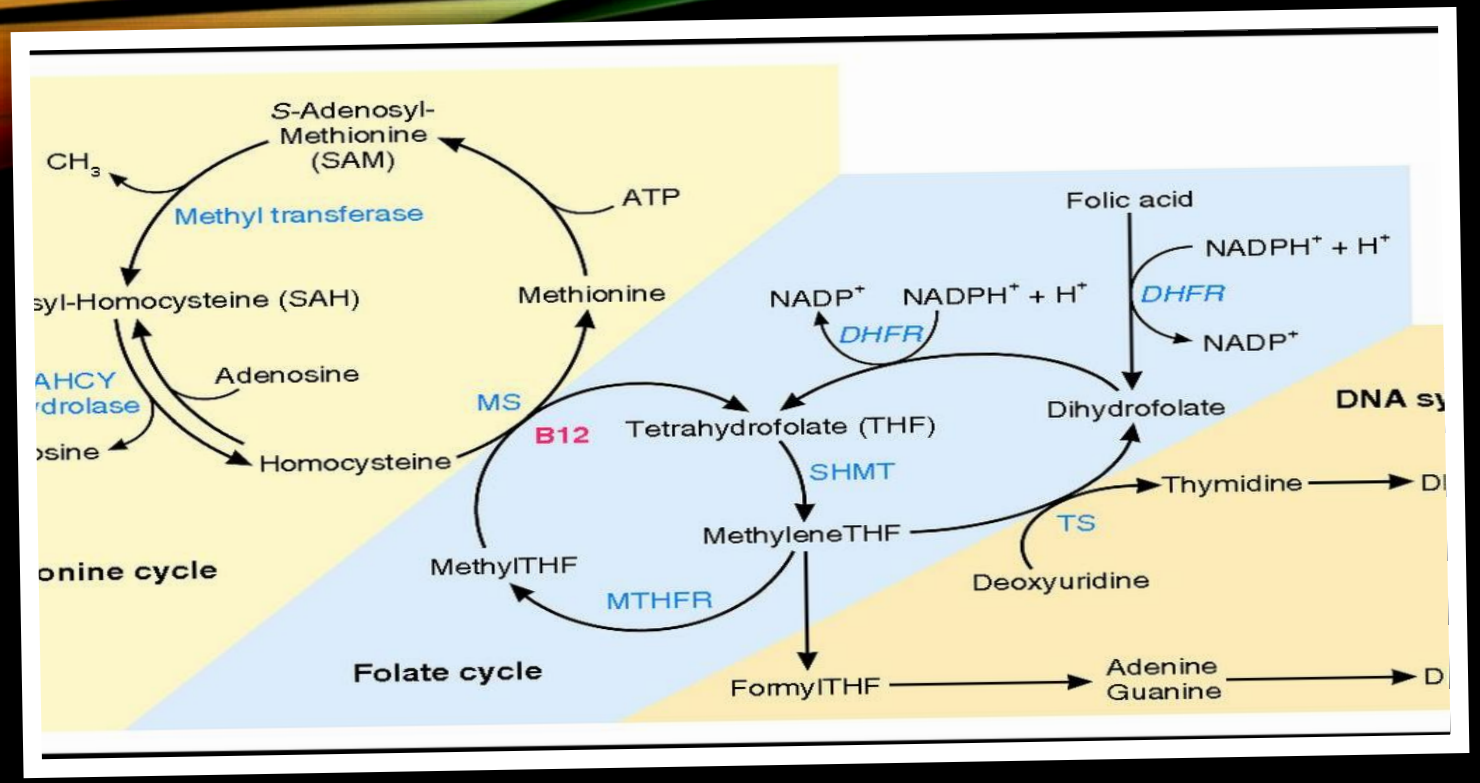
ANSWER 1: METHYLMALONIC ACID LEVEL

WAIT, DO I HAVE ENOUGH B12?

Stomach: B12 releases from food, binds HC.
Small intestine, B12 from food AND bile is released from HC by pancreatic enzymes, and then binds intrinsic factor.
Terminal ileum: B12-IF binds a special cubam (Cubilin [Cub]–amnionless [Amn]) receptor ifor internalization and release to plasma.
Plasma: It is bound by TC (Transcobalamin) and delivered to the TC receptor (CD320) on cells.
In cells: B12 is reduced and converted to adenosylcobalamin in the mitochondria and methylcobalamin in the cytosol, where they serve as cofactors for the 2 B12-dependent reactions. CoA, coenzyme A; THF, tetrahydrofolate.



So, what do I do with it?



MEMORIZE THIS FOR YOUR TEST.

Just kidding.

Essentially, you need it to make DNA, which matters in the world of rapid blood cell production. If the newly generated cells are all defective, they will be destroyed by your own body's defense mechanisms.

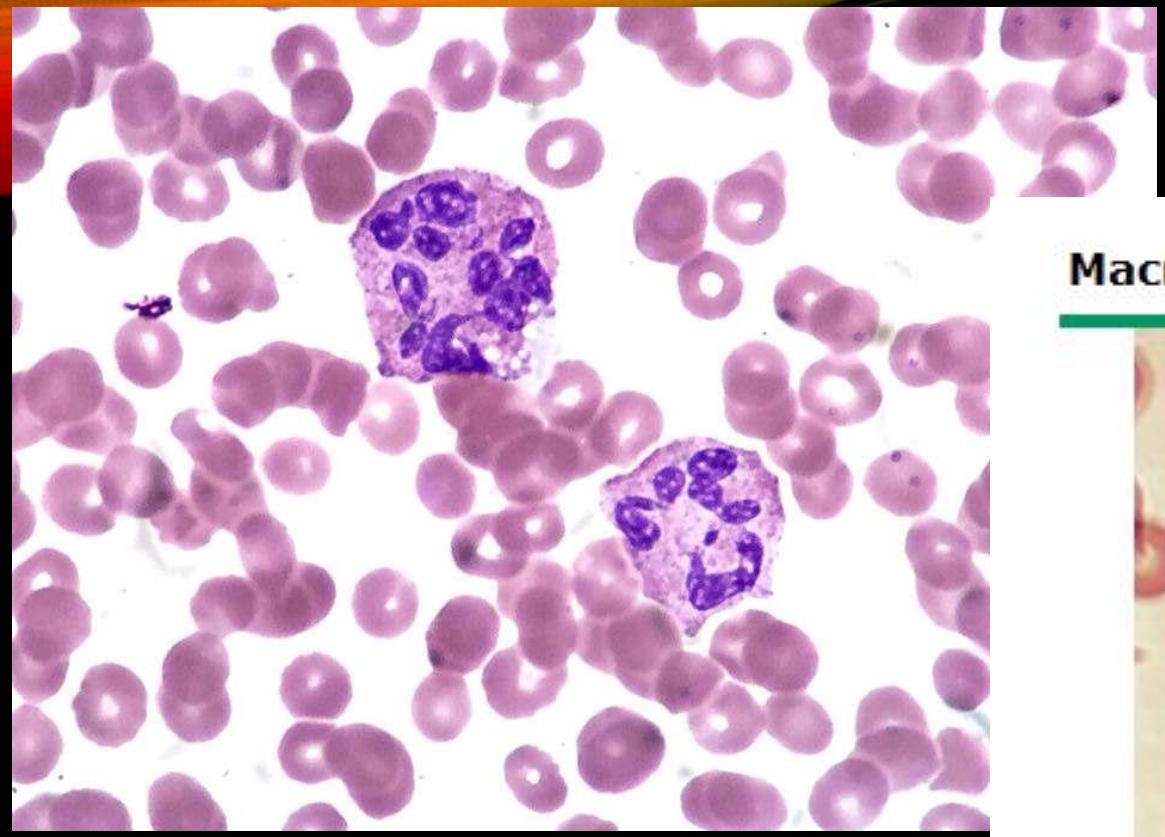
WHAT COULD GO WRONG?

- Decreased intake (eg, reduced intake of animal products, strict vegan diet, breastfeeding by a vitamin B12-deficient mother).
- Decreased absorption (eg, gastrectomy, bariatric surgery, Crohn disease, celiac disease, pancreatic insufficiency, bacterial overgrowth, fish tapeworm infection).
- Other autoimmune conditions, such as thyroid disease or vitiligo, in individuals with pernicious anemia.
- Medications and drugs that interfere with absorption or stability (eg, metformin, histamine receptor antagonists, proton pump inhibitors, nitrous oxide).
- Rare genetic disorders

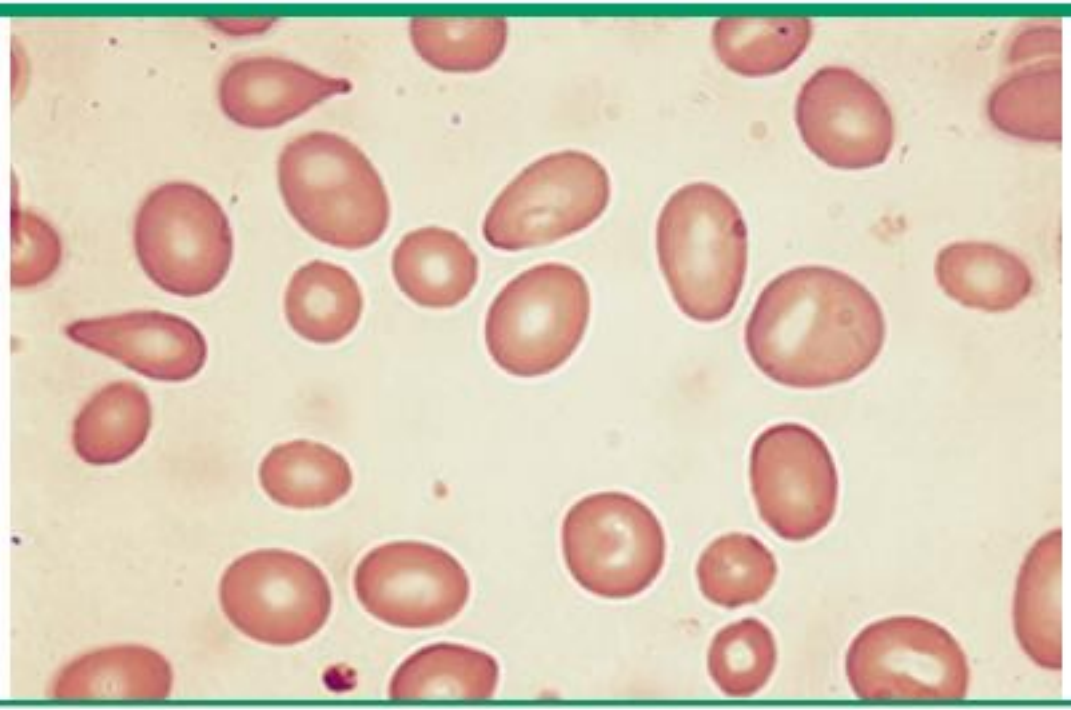
A. Severe deficiency
1. Severe malabsorption (affecting the physiological intrinsic factor cubam receptor axis)
a. Pernicious anemia (autoimmune gastritis)
b. Total or partial gastrectomy
c. Gastric bypass or other bariatric surgery
d. Ileal resection or organ reconstructive surgery (ileal conduit diversion & ileocystoplasty)
e. Inherited disorders affecting B_{12} absorption (affecting either intrinsic factor or the cubam receptor)
2. Abuse of nitrous oxide
3. Inherited metabolic
a. Impaired ability to transport B_{12} (TC deficiency)
b. Impaired ability to process B_{12} (8 distinct inborn errors of cobalamin metabolism resulting in homocystinuria and/or methylmalonic acidemia) with varying clinical spectra involving the nervous system and blood
B. Mild to moderate deficiency
1. Mild to moderate malabsorption (impaired ability to render food B_{12} bioavailable)
a. Protein-bound vitamin B_{12} malabsorption
b. Mild, nonimmune, chronic atrophic gastritis
c. Use of metformin
d. Use of drugs that block stomach acid
e. Chronic pancreatic disease
2. Dietary deficiency
a. Adults: vegans/vegetarian diet, or diet low in meat and dairy products
b. Infants: breastfeeding in infants with vitamin B_{12}–deficient mothers

BUZZWORDS:

- Unexplained anemia
- Macrocytosis (mean corpuscular volume [MCV] >100 fL) ESPECIALLY if >120
- Pancytopenia
- Hypersegmented neutrophils
- Unexplained neurologic or psychiatric symptoms.



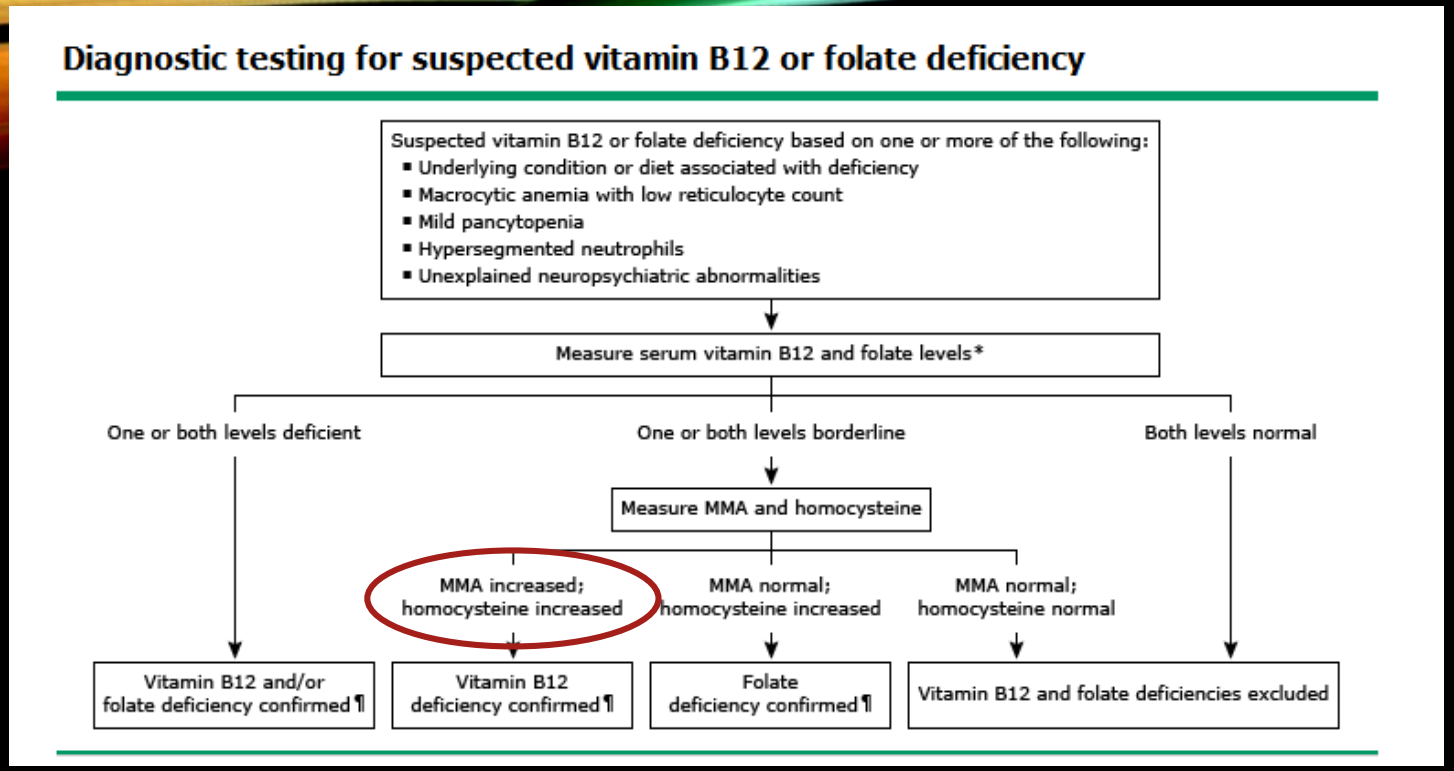
Macro-ovalocytes in vitamin B12 deficiency



Peripheral smear shows marked macro-ovalocytosis in a patient with vitamin B12 deficiency. In this case, teardrop cells are an advanced form of macro-ovalocytes.

Courtesy of Stanley L Schrier, MD.

UpToDate®



Remember, serum B12 in the low-normal range (~200) can be falsely reassuring, and an elevated MMA is more sensitive. (Don't order JUST MMA, because it can fluctuate, and be affected by renal function. Two tests >1 in this case.)

Remember, B12 deficiency makes MMA AND homocysteine high. Folate deficiency makes homocysteine high, and MMA normal.

Remember, folate supplementation will improve the anemia in B12 deficiency, but not the neuropsychiatric complications!

QUESTION 2

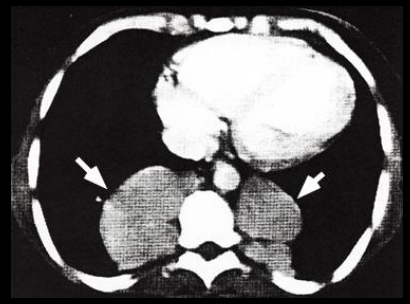
- A 30-year-old woman is evaluated in follow-up for anemia diagnosed during a recent evaluation for symptoms of fatigue. She reports no shortness of breath, dizziness, or chest pain. Medical history is notable only for heavy menses. Family history is remarkable for anemia in her mother. Her only medication is an iron supplement. She is white.
- On physical examination, the patient appears well. Temperature is 36.9 °C (98.4 °F), blood pressure is 100/60 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 25. No lymphadenopathy or organomegaly is identified, and the remainder of her physical examination is unremarkable.
- Labs: Hgb 8.5, MCV 68, Plts 400K, Retic Count 6%, Bili 2.0, LDH 300, Ferritin 450, Irone 60, TIBC 300.
- Electropharesis: Hgb A: 94% (Slightly low) Hgb A1: 4% (increased)
- Hgb F: 2% (increased) Hgb S: 0% (normal)

Numerous target cells are seen on peripheral smear.
What is the most likely diagnosis?

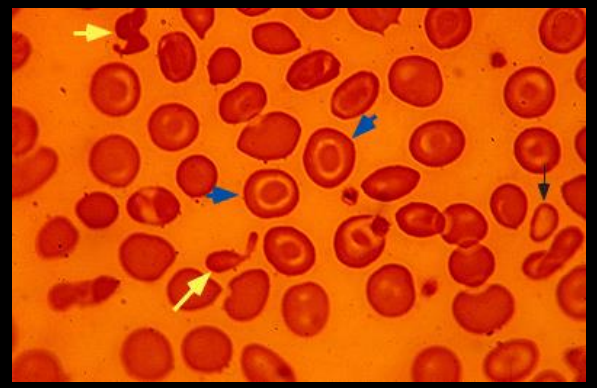
ANSWER 2: BETA-THALASSEMIA

THALASSEMIA

Normal RBC count, normal iron studies
Hemoglobin A_2 ($a_2\delta_2$) and hemoglobin F ($a_2\gamma_2$) increased



- Alpha
  - Chromosome 16
  - Normal Hgb Electrophoresis
    - DNA PCR, High-performance liquid chromatography, or gene sequencing will diagnose
- Beta
  - Chromosome 11
  - Hgb Electrophoresis: globin A_2 ($a_2\delta_2$) and hemoglobin F ($a_2\gamma_2$) increased
  - Beta thal cannot be diagnosed in neonates. Big Bonus Question: Why?
    - No beta-globin (still Hgb F)



Folic acid supplementation – just as in hemolytic anemias

- Beta- thal major
  - Transfusion dependent
  - Will present early in life, but not too early.
    - Pallor, failure to thrive, hemolytic anemia, erythroid hyperplasia in bone marrow, bone deformities, massive hepatosplenomegaly and extramedullary hematopoiesis
  - Deadly if untreated

- Alpha thal HbH disease
  - Not transfusion dependent
  - Periods of increased hemolysis
    - Infection
    - Pregnancy
    - Aplastic crisis
  - Extramedullary hematopoiesis

Classical thalassemia syndromes (genotypes and laboratory findings)

Syndrome	Genotype	Typical findings on CBC	Hemoglobin analysis (HPLC or electrophoresis)
Alpha thalassemias (reduction in alpha globin chains)			
Hydrops fetalis with Hb Barts	(– – / – –)	Severe microcytic anemia with hydrops fetalis; usually fatal in utero	Hb Barts (γ globin tetramers); Hb Portland (embryonic hemoglobin); no HbF, HbA, or HbA_2
HbH disease	(α – / – –) or (α^t – / – –)*	Moderate microcytic anemia	HbH (up to 30%); HbA_2 (up to 4%)
Minor	(α – /α –) or (α α /– –)	Mild microcytic anemia	Hb Barts (3 to 8%)
Silent carrier	(α α /α –)	Normal hemoglobin, normal MCV	Normal
Beta thalassemias (reduction in beta globin chains)¶			
Major (transfusion-dependent)	β^0 / β^0 or β^0 / β^+	Severe microcytic anemia with target cells (typical Hb 3 to 4 g/dL)	HbA_2 (5% or more); HbF (up to 95%); no HbA
Intermedia (non-transfusion-dependent)	β^+ / β^+	Moderate microcytic anemia	HbA_2 (4% or more); HbF (up to 50%)
Minor (also called trait or carrier)	β / β^0 or β / β^+	Mild microcytic anemia	HbA_2 (4% or more); HbF (up to 5%)

QUESTION 3

- A 48-year-old woman is evaluated for fatigue and intermittent abdominal discomfort of 2 months' duration and occasional dark urine. Medical and family histories are unremarkable. Her only medication is an oral contraceptive pill.
- On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 125/74 mm Hg, pulse rate is 68/min, and respiration rate is 13/min. Pallor is observed, and abdominal tenderness is present on palpation. No icterus, bruising, or splenomegaly is noted.
- Labs: Hgb 7.2, Leukocytes 3000, Plts 125k, Retic Count 8%, Bilirubin normal, Direct antiglobulin (Coombs) test negative.
- A bone marrow biopsy shows 20% cellularity. Flow cytometry reveals erythrocytes lacking CD55 and CD59. Abdominal ultrasonography shows portal vein thrombosis.

What is the most likely diagnosis?

ANSWER 3: PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

SO MANY HEMOLYTIC ANEMIAS… HOW DO WE CATEGORIZE THESE?

- CONGENITAL:
  1. Hereditary Spherocytosis
  2. G6PD Deficiency
  3. Sickle Cell
  4. Other hemaglobinopathies (there are 1000+ mutations identified to the alpha or beta globulin genes!)
- ACQUIRED:
  1. Chemicals and physical agents = Arsenic, high copper, brown recluse spiders, skin burns
  2. Hemolysis from infections
     - Malaria, babesiosis, clostridia, bartonella
  3. Immune-mediated:
     - Warm-autoantibody
     - Cold agglutinin disease

4. Non-Immune:
   1. **PNH (Paroxysmal Nocturnal Hemaglobinuria**
   2. MACROangiopathic = artificial valves or LVADs
   3. MICROangiopathic (MAHA) aka **SCHISTOCYTES!**
      - TTP
      - DIC
      - HUS
      - Complement-mediated (Diarrhea negative HUS)
      - Drug-Induced (DITMA) like cyclosporine or gemcitabine
      - Rare genetic B12 metabolism disorders
      - Malignancy
      - Eclampsia
      - Hypertensive crisis

PNH FACTOIDS:

- Actually one of the first clinically recognized hematologic disorders because the nocturnal hematuria was so characteristic
- Genetic defect in a STEM cell that leads to erythrocytes, leukocytes, and platelets that are missing important surface proteins – CD55 (intravascular) and CD59 (extravascular hemolysis)
- The gene that is defective is called PIGA (phosphatidylinositol glycan anchor biosynthesis, class A)
- Clinical signs: hemolysis, abdominal pain, and thromboses in odd locations (abdominal and cerebral veins)

Complement mediated
Not antibodies

Some patients have more unusual presentations in which nonspecific symptoms predominate. Intravascular hemolysis releases free hemoglobin into the circulation, and the resulting depletion of nitric oxide (NO) may cause symptoms of increased smooth muscle tone including dysphagia, abdominal pain, or erectile dysfunction. Over time, hemoglobinemia may also cause renal insufficiency and pulmonary hypertension.

THERE IS TREATMENT NOW!

- Folate supplementation, glucocorticoids
- Bone marrow transplant
- Eculizumab… a novel monoclonal antibody to C5 which inhibits activation of the terminal complement cascade, decreases hemolysis, reduces thrombotic complications, and improves quality of life
- Eculizumab is associated with Neisseria infections, so pts should get meningococcal vaccination

QUESTION 4

- A 35-year-old woman is evaluated in the emergency department for a 3-day history of worsening dyspnea on exertion. She reports no chest pain. Medical history is notable for systemic lupus erythematosus, which is well controlled with hydroxychloroquine. She takes no other medications.
- On physical examination, the patient appears pale and fatigued. Temperature is 37.0 °C (98.6 °F), blood pressure is 110/72 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Oxygen saturation is 97% breathing ambient air. Neurologic examination is normal. Scleral icterus is noted. She has no lymphadenopathy. A grade 2/6 crescendo-decrescendo systolic murmur is auscultated at the upper right sternal border, and the lung fields are clear bilaterally. Abdominal examination reveals no hepatosplenomegaly or tenderness. Rectal examination shows no masses, and a stool sample is guaiac negative.
- Labs: Hgb 6.2, Leukocytes 15k, MCV 101, Plts 280k, Retic count 18%, Bili 2.3, Creatinine WNL, LDH 980, Direct antiglobulin test POSITIVE for C3 and IgG
- Peripheral blood smear shows spherocytes and polychromatophilic erythrocytes, but is otherwise normal.

What is the next step in management?

ANSWER 4: PREDNISONE

BACK TO THOSE HEMOLYTIC ANEMIAS! HOW DO WE CATEGORIZE THESE?

- CONGENITAL:
  1. Hereditary Spherocytosis
  2. G6PD Deficiency
  3. Sickle Cell
  4. Other hemaglobinopathies (there are 1000+ mutations identified to the alpha or beta globulin genes!)
- ACQUIRED:
  1. Chemicals and physical agents = Arsenic, high copper, brown recluse spiders, skin burns
  2. Hemolysis from infections
     - Malaria, babesiosis, clostridia, bartonella (Visible on smear)
  3. Immune-mediated: (Spherocytes!)
     - Warm-autoantibody
     - Cold agglutinin disease

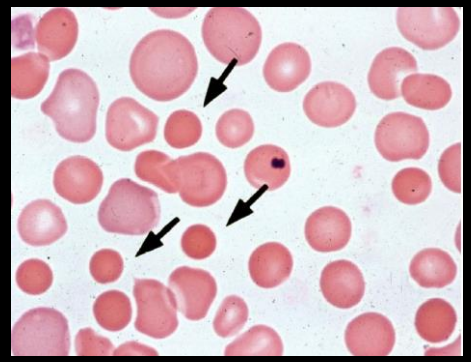
4. Non-Immune:
   1. PNH
   2. MACROangiopathic = artificial valves or LVADs
   3. MICROangiopathic = MAHA aka **SCHISTOCYTES!**
      - TTP
      - DIC
      - HUS
      - Complement-mediated (Diarrhea negative HUS)
      - Drug-Induced (DITMA) like cyclosporine or gemcitabine
      - Rare genetic B12 metabolism disorders
      - Malignancy
      - Eclampsia
      - Hypertensive crisis

AUTO IMMUNE HEMOLYTIC ANEMIAS

A diagnosis you may make accidentally… when you order a transfusion, the Coombs it automatically run, since these patients will not tolerate (aka waste) unmatched blood products!

Clinical manifestations:

- Hemolysis, AKA high reticulocyte count + high bili + high LDH + low hapto
- Positive direct antiglobulin (Coombs) test
- Spherocytes



Spherocytes because…
Antibodies are directed against erythrocyte surface membrane molecules, which leads to phagocytosis by macrophages that cause erythrocytes to become progressively more spherocytic. These abnormal erythrocytes are then destroyed in the spleen.

When it's WARM you need an IgGLASS of something…

When it's COLD you need an IgMUG of something! C3+

ASSOCIATIONS WITH AIHA:

WARM AIHA:

- SLE, CLL, Lymphoma

(Think 3 Ls!)

- Drugs: Methyldopa, PCN, Procainamide

- TREATMENT:
- Steroids, danazol, IVIG, Rituximab, splenectomy, immunosuppression

- COLD AIHA:
- Quinidine
- Lymphoma
- Mono, Mycoplasma, and Influenza

- TREATMENT:
- No steroids or IVIG!
- Keep patient and their IV fluids warm
- Cyclophosphamide, chlorambucil, Rituximab

QUESTION 5

- A 45-year-old woman is evaluated in the emergency department for a 1-day history of abdominal pain and fever. She also reports unexpected, heavy menstrual bleeding of 1 day's duration and easy bruising of 2 days' duration. Medical and family histories are unremarkable, and she takes no medications.
- On physical examination, the patient is oriented to person and place, but not time. Temperature is 38.1 °C (100.6 °F), blood pressure is 170/98 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Other than confusion, neurologic examination is normal. Subconjunctival hemorrhages are present. Cardiopulmonary examination is normal. Abdominal examination reveals tenderness to palpation without guarding or rebound. Pelvic examination shows blood in the vaginal vault with no cervical motion tenderness or adnexal masses.
- Labs: Hematocrit 26%, Leukocytes 10.3K, Platelets 24,000, Reticulocyte Count 8.3%, Bilirubin 2.3, Creatinine 3.2, and LDH 1500

What is your next test?

ANSWER 5: PERIPHERAL SMEAR

YET ANOTHER HEMOLYTIC ANEMIA! HOW DO WE CATEGORIZE THESE?

- CONGENITAL:
  1. Hereditary Spherocytosis
  2. G6PD Deficiency
  3. Sickle Cell
  4. Other hemaglobinopathies (there are 1000+ mutations identified to the alpha or beta globulin genes!)
- ACQUIRED:
  1. Chemicals and physical agents = Arsenic, high copper, brown recluse spiders, skin burns
  2. Hemolysis from infections
     - Malaria, babesiosis, clostridia, bartonella
  3. Immune-mediated:
     - Warm-autoantibody
     - Cold agglutinin disease

4. Non-Immune:
   1. PNH
   2. MACROangiopathic = artificial valves or LVADs
   3. MICROangiopathic (MAHA) aka **SCHISTOCYTES!**
      - TTP
      - DIC
      - HUS
      - Complement-mediated (Diarrhea negative HUS)
      - Drug-Induced (DITMA) like cyclosporine or gemcitabine
      - Rare genetic B12 metabolism disorders
      - Malignancy
      - Eclampsia
      - Hypertensive crisis

A FEW MORE DEFINITIONS:

- MAHA = Microangiopathic Hemolytic anemia = A clinical state of NON IMMUNE hemolysis (AKA negative Coombs) with intravascular hemolysis (AKA schistocytes). They don't have low platelets right away, but eventually they will. There are usually microscopic abnormalities in the tiniest vasculature, like arterioles and capillaries.
- TMA = thrombotic microangiopathy = A specific pathologic lesion in which abnormalities in the vessel walls lead to thrombosis. This is a PATHOLOGY diagnosis, not the name of a syndrome or clinical pattern we would recognize in patients. Not all MAHA is caused by a TMA, but nearly all TMAs will eventually start to cause MAHA and thrombocytopenia.
- The primary TMA syndromes include TTP (hereditary or acquired), Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), drug-induced TMA (DITMA) syndromes, complement-mediated TMA (hereditary or acquired), and rare hereditary disorders of vitamin B12 metabolism or factors involved in hemostasis.
- The secondary TMA syndromes = preeclampsia/HELLP syndrome, severe hypertension, systemic infections and malignancies, and sometimes even complications of hematopoietic stem cell or solid organ transplantation – these are different because you treat the underlying disorder rather than specific therapy for the TMA.

THROMBOTIC THROMBOYCYTOPENIC PURPURA (TTP)

- MAHA + thrombocytopenia (SHISTOCYTES)
- Deficiency in the metalloprotease ADAMTS13 <10% (usually because of an antibody against it)
- ADAMTS13 is supposed to clear high-molecular-weight vWF multimers. Without it, the multimers accumulate, and make platelet-rich thrombi in small vessels. These shear erythrocytes, and cause schistocytes.
- The thrombi wreak havoc and cause severe and non-specific clinical features: pallor and fever, bruising and petechiae, kidney injury with blood and protein, neuro findings like confusion and numbness, abdominal pain and nausea from bowel ischemia, and even chest pain and arrhythmias.

TTP

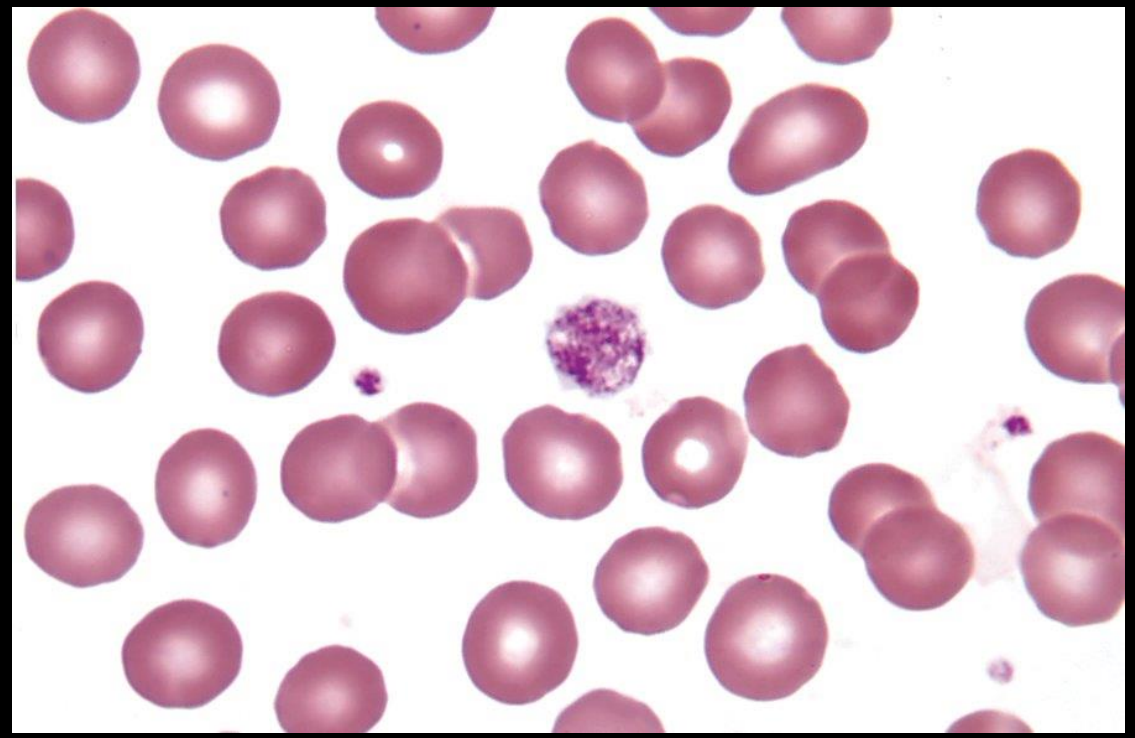
- Diagnosis can be difficult and can look like severe sepsis, lupus, or other non-specific states!
- ADAMST13 levels take several days to come back, so if you suspect it, you must treat it BEFORE you get a confirmatory test
- Mortality is ~90% without treatment. Survival is 85% with plasma exchange.
- Treatment for TTP is plasma exchange therapy (PEX - also called therapeutic plasma exchange [TPE]) (Not just "plasmapheresis") Needs an HD Cath!
- PEX = removal of patient's plasma by apheresis and replacement with donor plasma, which presumably replaces the ADAMTS13 and removes the antibodies and residual ultralarge VWF multimers.
- Correcting ADAMTS13 deficiency in turn restores proper cleavage of ultralarge von Willebrand factor (VWF) multimers, prevents microvascular thrombosis, and reverses symptoms of organ damage
- Continue until platelets are normal

- Bonus question: Does everybody know what you have to type into Cerner to order a peripheral blood smear?

PATH REVIEW!

QUESTION 6

- A 35-year-old woman is evaluated for the recent onset of a rash on her legs. She has no other symptoms. She does not drink alcohol. Medications are an oral contraceptive and a multivitamin.
- On physical examination, vital signs are normal. Nonpruritic, nonblanching red macules are noted on the lower extremities. Abdominal examination reveals no splenomegaly.
- Laboratory study results show a hematocrit of 38%, leukocyte count of 7000/μL (7×10^9/L), and platelet count of 78,000/μL (78×10^9/L).
- The peripheral blood smear is shown.



What is your next step?

ANSWER 6:
REPEAT CBC IN 1 WEEK

LOW PLATELETS?

- Decreased Production
  - Bone marrow infiltration like meylofibrosis, tumors, or granulomatous disease
  - Nutritional deficiencies like B12 or folate
  - Abnormalities in stem cell maturation like aplastic anemia and myelodysplasia
- Increased Destruction
  - Non-Immune Mediated
    - TTP
    - HUS
  - Immune Mediated
    - ITP (also sometimes with decreased production)
    - HIT

IMMUNE THROMBOCYTOPENIC PURPURA (ITP) AKA PRIMARY IMMUNE THROMBOCYTOPENIA

- Low platelets – usually asymptomatic until <10,000 and start to develop petechiae and ecchymoses without lymphadenopathy or splenomegaly
- Cased by autoantibodies against glycoproteins on the platelet surface membrane, but testing is poor so not done
- Red and white cells should be NORMAL, and coags should be normal! DDX is drug-related, liver disease, MAHA, inherited, myelodysplastic syndromes – usually can garner from history
- Can occur alone, be trigged by meds, or be associated with diseases like lupus, HIV, Hep C, CLL, or H pylori – **so we DO test for HIV and Hep C**
- No bone marrow biopsy unless you're worried it's something else…

Platelet transfusion:

- Asymptomatic: <10K (associated with spontaneous intracranial hemorrhage)
- Central line: <20K
- Surgery: <50K
- Neurosurgery, epidural: <100K

ITP CONTINUED

- When plts < 30,000, start with prednisone
- If symptomatic or you need results sooner for a surgery etc, start with IVIG
- If refractory, second line treatments are splenectomy or rituximab
- If resistant to these, there are other options including thrombopoietin receptor agonists like eltrobopag or romiplostim

QUESTION 7

- A 45-year-old man is evaluated following a recent diagnosis of hereditary hemochromatosis. He was screened after a relative was diagnosed with hereditary hemochromatosis. He is asymptomatic and has no clinical or laboratory evidence of liver disease, diabetes mellitus, or cardiomyopathy. Medical history is otherwise negative, and he takes no medications.
- On physical examination, vital signs are normal. The examination is unremarkable.
- Weekly phlebotomy is planned.

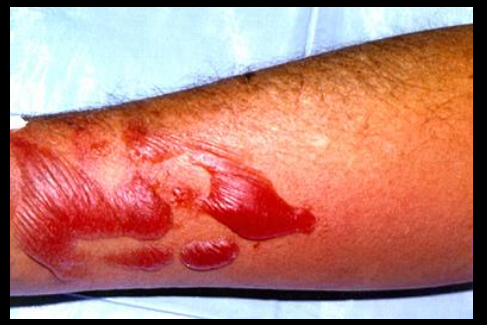
What dietary constituent should be avoided?

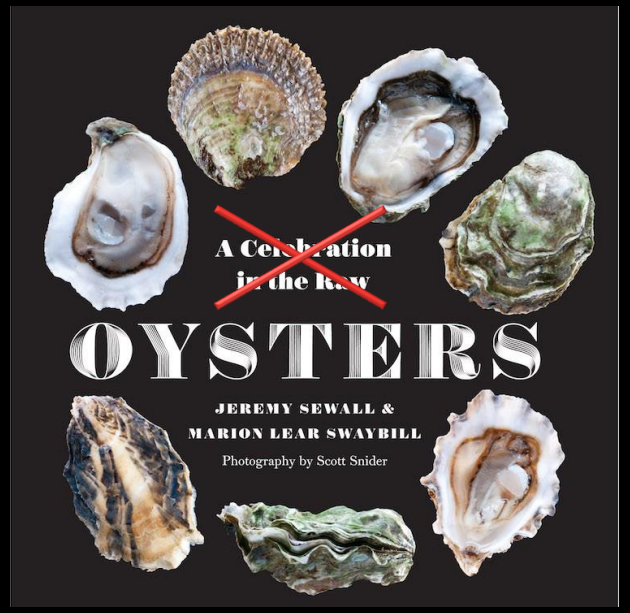
ANSWER 7:
RAW OR UNDERCOOKED SEAFOOD

IRON OVERLOAD SYNDROMES

- Primary:
  - Hemochromatosis
  - Syndromes of ineffective erythropoiesis leading to suppression of hepcidin (e.g. thalassemia, sideroblastic anemia).
    - Hepcidin suppression = increased iron absorption and circulation
    - Increased hepcidin = decreased available iron (e.g. anemia of inflammation)
- Secondary
  - Transfusions
    - Sickle cell, MDS, hemolytic anemias
  - Hemin infusions
    - Used to treat acute porphyria
    - Reduced production of porphyrins

- Infectious complications:
  - Vibrio vulnificus ← raw seafood/oysters
  - E. coli
  - Yersinia enterocolitica
  - Listeria monocytogenes
  - CMV
  - Hep B and C
  - HIV
  - Aspergillus
  - Mucormycoses





QUESTION 8

- A 23-year-old woman is evaluated in the emergency department for profound shortness of breath, which developed earlier in the day. She reports no chest pain but feels very weak. Medical history is significant for homozygous sickle cell anemia (Hb SS). She was evaluated in the emergency department 1 week ago for symptomatic anemia; she received a transfusion of 2 units of packed red blood cells, her hemoglobin level increased to 8.5 g/dL (85 g/L), and she was sent home. Her only medication is folic acid.
- On physical examination, she appears pale and weak. Temperature is 37.1 °C (98.8 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 32/min. Oxygen saturation is 96% breathing ambient air. Scleral icterus is noted. Cardiac examination reveals a grade 3/6 early systolic murmur at the base of the heart. Lungs are clear. Abdominal palpation reveals no hepatosplenomegaly.
- Labs: Hgb 3.5, Plts 415k, Retic count 8%, Bilirubin 7.7, LDH 650

What is the most likely diagnosis?

ANSWER 8:
DELAYED HYPERHEMOLYTIC TRANSFUSION REACTION

DELAYED HYPERHEMOLYTIC TRANSFUSION REACTION

- Caused by re-exposure to RBC alloantibodies preformed from prior transfusions.
- Typically 2-19 days post transfusion
- Supportive care
- Prevention: Match pRBC transfusions for C, E, K antigens in SCD patients
  - Do not transfuse above Hgb of 10 in SCD patient due to risk for hyperviscosity
  - Bonus points: At what hemoglobin does the risk for stroke increase in CKD patients treated with ESA? 11.5g/dL

- Think of these in patients with acute anemia and SCD:
  - DHTR
  - Splenic sequestration
  - Aplastic episode

QUESTION 9

- A 28-year-old woman is evaluated for a 1-week history of progressive dyspnea and fatigue. She was diagnosed with Hodgkin lymphoma 2 months ago and is receiving chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). She takes no other medications.
- On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 134/82 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Conjunctival pallor is noted but no scleral icterus. The lungs are clear to auscultation, and the cardiac examination is normal. The remainder of the examination is unremarkable.
- Labs: Hgb 6.8, Leuk 1300, Plts 83k, CMV IgG antibody Positive.
- A peripheral blood smear shows pancytopenia.

What is the most appropriate erythrocyte transfusion product for this patient?

ANSWER 9: LEUKOREDUCED, IRRADIATED

- Irradiated – to prevent GVHD
  - 1. Severe combined immunodeficiency (SCID)
  - 2. Hodgkins lymphoma
  - 3. Receiving or received purine or purine-like antagonist treatment such as fludarabine or bendamustine (CLL therapy)
  - 4. Receiving or having received a potent T-cell inhibitor therapy such as alemtuzumab (anti CD-52) and anti-thymocyte globulin (ATG) for cellular rejection of a kidney transplant
  - 5. Allogenic hematogenous bone marrow transplant recipients
- Leukoreduced – prevents febrile nonhemolytic transfusion reaction
- Washed – clears plasma to remove antibodies
  - IgA deficiency
  - What happens if you give unwashed blood to IgA deficiency ?

Anaphylaxis

QUESTION 10

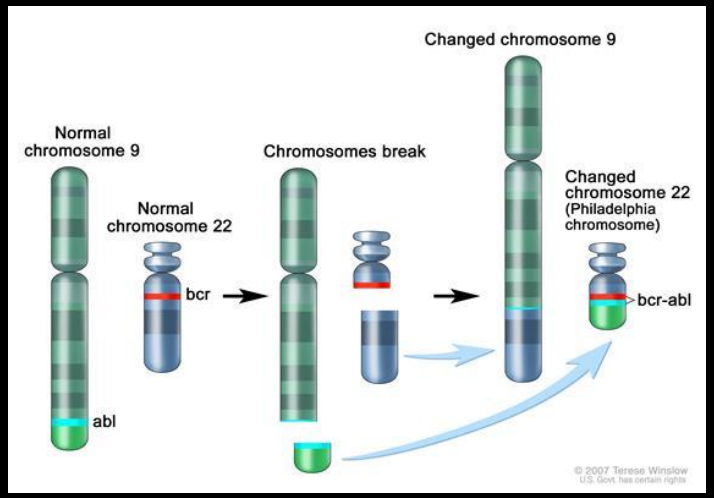
- A 70-year-old man is admitted to the hospital for fatigue and malaise of 3 weeks' duration and easy bruising and fever of 1 week's duration. Medical and family histories are unremarkable. He takes no medications.
- On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 128/83 mm Hg, pulse rate is 115/min, and respiration rate is 13/min; BMI is 28. Conjunctivae are pale. Splenomegaly is noted and lower extremity petechiae are observed.
- Laboratory studies show a hemoglobin level of 7.3 g/dL (73 g/L), a leukocyte count of 20,000/µL (20 × 10^9/L), and a platelet count of 14,000/µL (14 × 10^9/L). Bone marrow examination reveals 35% lymphoblasts. A peripheral blood smear demonstrates immature cells identified as lymphoid blasts by flow cytometry. Cytogenetic testing using fluorescence in situ hybridization is positive for t(9;22).

In addition to dexamethasone, what is the most appropriate treatment?

ANSWER 10: DASATINIB

CML

- Translocation of the long arm of chromosomes 9 and 22 [t(9;22), Philadelphia chromosome] leading to a *BCR-ABL* fusion gene
- This codes for an abnormal activated tyrosine kinase that promotes dysregulated cell proliferation
- Presentation: can be symptomatic with high neutrophil count, OR can have fatigue, weight loss, splenomegaly, and bleeding. It can just look like a leukemoid reaction from sepsis!
- Three phases of progression: the chronic phase, the accelerated phase, and blast crisis. The chronic phase is an indolent phase and responds well to therapy. Most patients with CML present in the chronic phase. Accelerated and blast crisis phases denote more aggressive disease that is less responsive to treatment. Blast crisis is considered to be secondary AML.
- Chronic phase, fewer than 10% of blasts are present in circulation.

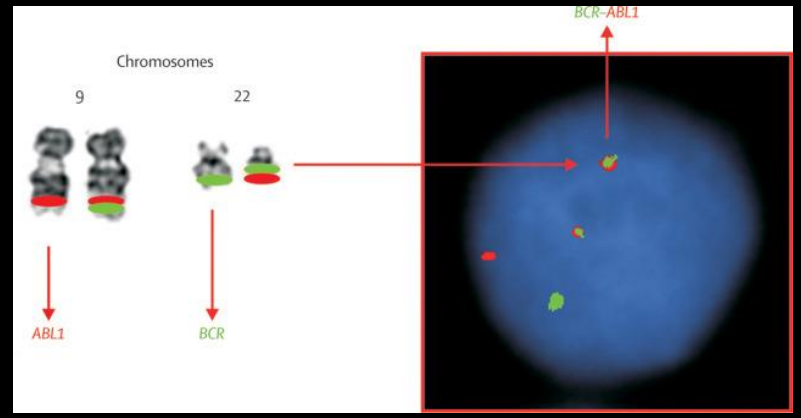


CML

- Median WBC approx 100,000 – almost all neutrophils, including myeloblasts to matures, including myelocytes and segmented neutrophils – few but some blasts
- The neutrophils LOOK normal, but they are cytochemically abnormal, so you can ask the lab to do a Leukocyte Alkaline Phosphatase (LAP) score to help differentiate them from a regular leukemoid reaction
- Elevated basophils always, and almost always eosinophilia
- The platelet count can be normal or elevated, even >600,000. Low platelets make us think more of myelodysplastic syndromes.

CML

- Diagnosis: Fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction.
- Therapy is required at diagnosis in all patients to treat symptoms and to prevent progression to blast phase and subsequent AML.
- Tyrosine kinase inhibitors (TKIs) are highly effective imatinib, dasatinib, and nilotinib
  - TKIs bind to the BCR-ABL oncoprotein and prevent downstream signaling.
  - Fluid retention and prolonged QTc. Contraindicated in pregnancy.
  - For patients with accelerated or blast phase CML, allogeneic hematopoietic stem cell transplantation is considered.



QUESTION 11

A 43-year-old woman is admitted to the hospital for fatigue of 4 weeks' duration, easy bruising and bleeding gums of 1 week's duration, and a 1-day fever of 38.9 °C (102.0 °F).

On physical examination, the patient appears ill. Temperature is 39.4 °C (103.0 °F), blood pressure is 105/62 mm Hg, pulse rate is 115/min, and respiration rate is 22/min. She has gingival bleeding, bleeding around her intravenous insertion site, and multiple ecchymoses and petechiae. Hepatomegaly is also noted.

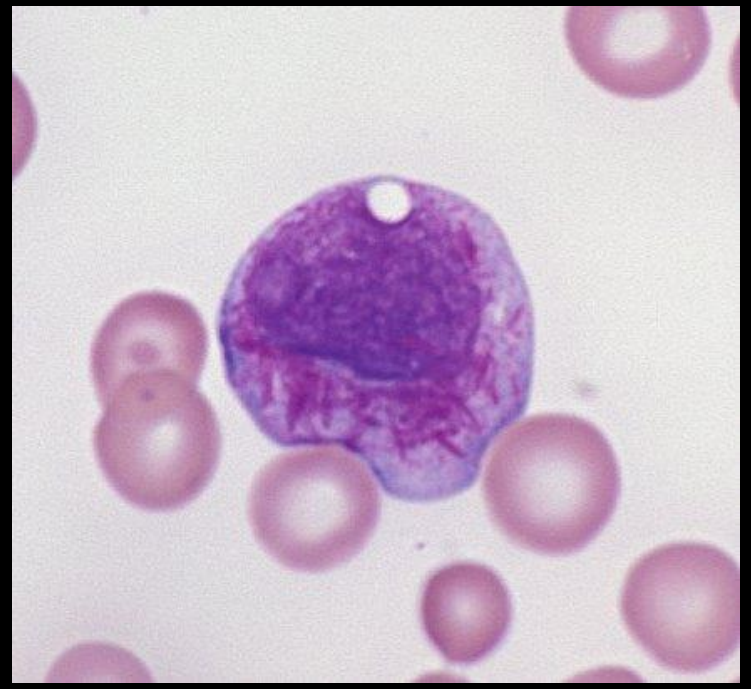
Laboratory studies: Activated partial thromboplastin time 65 s, Hemoglobin 7.6 g/dL (76 g/L), Leukocyte count 32,000/µL (32 × 109/L), Platelet count 25,000/µL (25 × 109/L), Prothrombin time 24 s, Fibrinogen 97 mg/dL (0.97 g/L),

A peripheral blood smear shows 80% immature blasts with prominent Auer rods phenotypically consistent with promyelocytes.

ANSWER 11:
ALL TRANS-RETINOIC ACID

ACUTE PROMYELOCYTIC LEUKEMIA

- AML + t(15;17) = APL (PML-RARa)
- Auer rods are pathognomonic
- DIC
- ATRA + Arsenic trioxide (ATO)
  - Start as soon as APL suspected
  - Differentiation syndrome
    - Hypoxia, pulmonary infiltrate, fever, edema, hypotension, renal failure
    - Cytokine release syndrome: inflammatory cytokines released from promyelocytes
    - Treat with steroids and holding ATRA/ATO



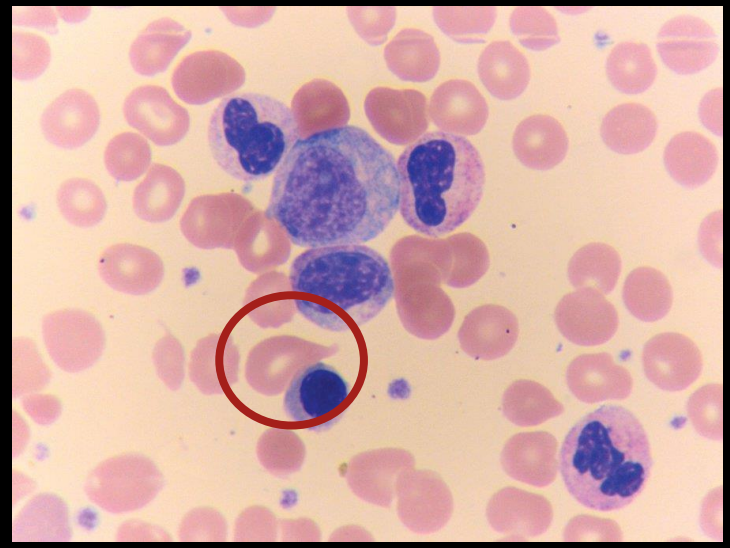
QUESTION 12

- A 65-year-old man is evaluated in the emergency department for a 3-day history of abdominal pain. The pain began acutely and is constant. Medical history is remarkable only for a 4-month history of generalized progressive pruritus without a skin rash. He does not drink alcohol or smoke cigarettes and has no risk factors for chronic hepatitis. He takes no medications.
- On physical examination, vital signs are normal. He has a plethoric complexion. Cardiopulmonary examination is normal. Tender hepatomegaly and splenomegaly are present.
- Laboratory evaluation discloses erythrocytosis, leukocytosis, thrombocytosis, and markedly elevated serum aminotransferase levels.
- Abdominal ultrasonography reveals hepatomegaly, splenomegaly, ascites, and a lack of blood flow in two of the hepatic veins, compatible with Budd-Chiari syndrome.

ANSWER 12:
JAK2 V617F MUTATION ANALYSIS

POLYCYTHEMIA VERA

- **Pruritis, worse with bathing**
- **Erythromelalgia** – burning palms/soles
- Plethora
- Hepatosplenomegaly – associated with Budd-Chiari syndrome
- Hgb >18.5 (male), >16.5 (female)
  - Basophilia, elevated B12, hyperuricemia due to cell turnover
- 20% of patients present with thrombosis
- 95% of patients have JAK2 mutation
- Can check EPO to rule out secondary causes (hypoxia, RCC)
- Treat with low dose ASA, phlebotomy, hydroxyurea
  - Goal Hct <45%
- Can progress to AML or secondary bone marrow fibrosis (leading to extramedullary hematopoiesis)



QUESTION 13

- A 61-year-old man is evaluated for worsening symptoms of edema and dizziness with standing over the past 6 months. His only medication is as-needed acetaminophen.
- On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 105/60 mm Hg sitting and 80/50 mm Hg standing, pulse rate is 105/min, and respiration rate is 18/min. Indentations are noted on the sides of the tongue, which appears enlarged. Jugular venous distention is noted. Cardiopulmonary examination reveals decreased breath sounds at the lung bases and an S_3 gallop. Dependent edema is present.
- On laboratory evaluation, the serum creatinine level is 1.5 mg/dL (132.6 µmol/L); 24-hour urine collection shows 3.5 g of albumin. Serum protein electrophoresis shows an IgG λ spike of 1.2 g/dL (0.012 g/L).
- Echocardiography shows increased thickening of the left ventricular wall and significant diastolic dysfunction. Left ventricular ejection fraction is 51%.

ANSWER 13:
ABDOMINAL FAT PAD BIOPSY

AMYLOIDOSIS

- Group of disorders of deposition of low molecular weight proteins into tissue, causing dysfunction.
- Clinical presentation depends on organ involved.
- Diagnosed with tissue biopsy – abdominal fat pad or bone marrow first, affected tissue second
  - Apple green birefringence with polarized light microscopy with Congo Red Staining

Kidney: nephrotic proteinuria, nephromegaly
Heart: low voltage EKG, ventricular hypertrophy, starry-night echo
Heme: bleeding diathesis, periorbital purpura form vascular deposition and blood vessel fragility
Neuro: Distal sensorimotor polyneuropathy
Liver: Portal hypertension, hepatosplenomegaly

AL Amyloid

- Monoclonal free λ or κ light chains
- Plasma cell dyscrasias (MGUS, MM, Waldenstrom)

AA Amyloid

- Amyloid A protein
- RA, IBD, familial Mediterranean fever, chronic infections
- SPEP and IFE negative for monoclonal proteins

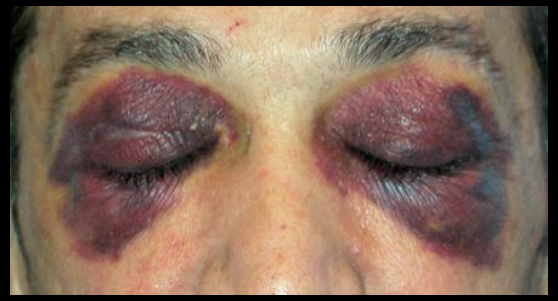
Hereditary Amyloid

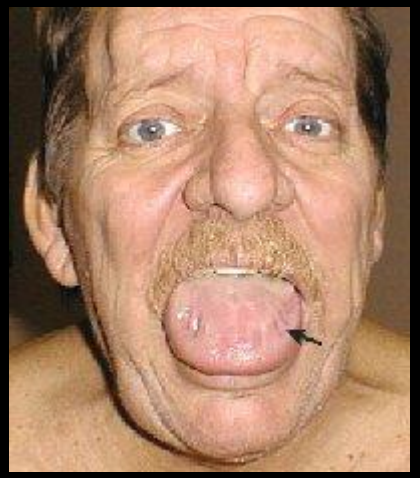
- Mutated transthyretin (TTR) fibrinogen a chain
- Family history
- Cardiac and neuro involvement
- SPEP and IFE negative for monoclonal proteins

Treatment is autologous HSCT if :

- <70 years old
- Good performance status
- Depending on extent of organ injury

Melphalan- or bortezomib-based chemotherapy



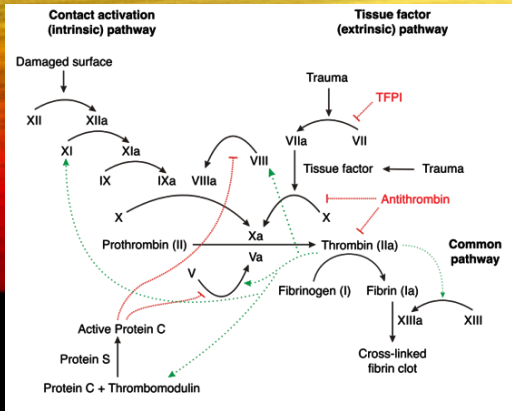


QUESTION 14

- A 24-year-old man is evaluated in the emergency department for prolonged and severe bleeding 3 days after undergoing hemorrhoidectomy. He reports continually bleeding and soaking through four bath towels. Medical history is significant for prolonged bleeding following wisdom tooth removal. Family history is notable for a brother who experienced heavy bleeding with tooth extraction and a maternal grandfather who died of an intracerebral hemorrhage at age 32 years. He takes no medications.
- On physical examination, the patient appears pale. Temperature is 36.7 °C (98.1 °F), blood pressure is 90/55 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Continued rectal bleeding is observed, with no clear source on anoscopy.

Laboratory studies:	
Hematocrit	17%
Leukocyte count	12,000/μL (12×10^9/L)
Platelet count	380,000/μL (380×10^9/L)
Activated partial thromboplastin time (aPTT)	45 s
Prothrombin time	12.2 s
aPTT following 1:1 mixing study with normal plasma	32 s

ANSWER 14:
FACTOR VIII LEVEL



HEMOPHILIA

Hemophilia A

- Increased aPTT
- Corrects with mixing study
- X-linked recessive
- Factor VIII deficient
- DDAVP test:
  - Promotes release of factor VIII and vWF
  - Check baseline factor activity level, give DDAVP, repeat factor level in 60-90 minutes
  - Increase in factor VIII activity by 2-4x is positive.
  - DDAVP can be useful in mild hemophilia A with minor bleeding.

Hemophilia B

- Increased aPTT
- Corrects with mixing study
- X-linked recessive
- Factor IX deficient

Treatment:

- Severe/life threatening bleed: Factor activity level >50% at all times
- Elective surgery:
  - Inhibitor screen prior to surgery
  - Dental procedure: 50%
  - Major surgery: 80-100% A; 60-80% B

QUESTION 15

- A 73-year-old woman is evaluated for increasing dyspnea on exertion and left buttock pain of 1 week's duration. She reports pain with standing straight or sitting down. She has no history of trauma. Family history is unremarkable, and she takes no medications.
- On physical examination, the patient is pale and displays significant distress by bending over and grasping the back of the chair. Temperature is 36.6 °C (98.1 °F), blood pressure is 140/80 mm Hg, pulse rate is 108/min, and respiration rate is 19/min. A 10-cm hematoma is noted on the left buttock with tracking down the back of the thigh, with smaller ecchymoses scattered over her arms and shins. She has no bleeding of the gums or nose. A stool sample is guaiac negative.

Laboratory studies:	
Hematocrit	35%
Leukocyte count	9100/µL (9.1×10^9/L)
Mean corpuscular volume	89 fL
Platelet count	310,000/µL (310×10^9/L)
Activated partial thromboplastin time (aPTT)	90 seconds
Prothrombin time	10.3 seconds
aPTT following 1:1 mixing study with normal plasma	45 seconds
Factor VIII activity	3% (normal, 50%-150%)
Factor VIII inhibitor	Markedly elevated

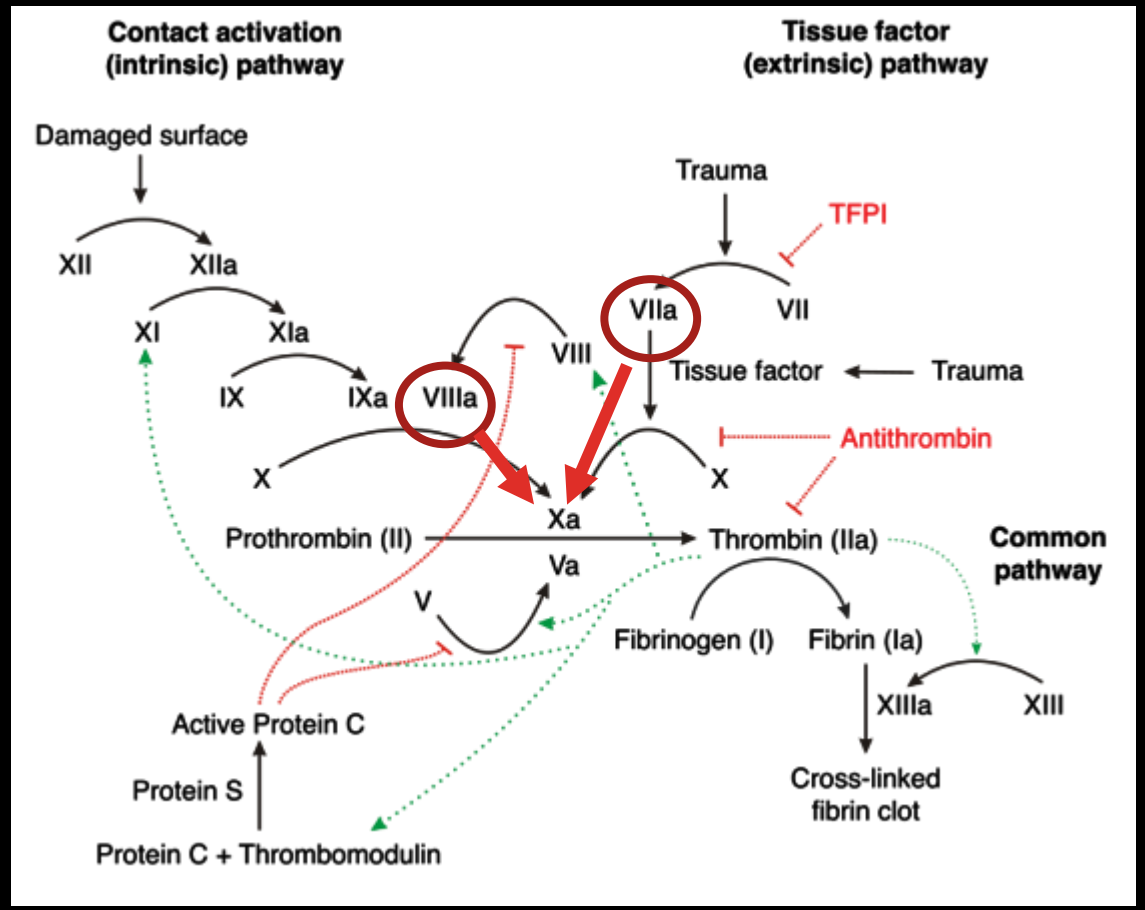
ANSWER 15: ADMINISTER RECOMBINANT ACTIVATED FACTOR VII

ACQUIRED HEMOPHILIA

- Antibodies to factor VIII
- Elderly, SLE, malignancy, postpartum associated
- Mucocutaneous and intramuscular bleeding
- Will not correct with mixing study
  - Corrects = deficient factor
  - No correction = inhibitor OR lupus anticoagulants
  - Correction with addition of phospholipids or no correction in dilute Russell's viper venom test = APLA→ clots.
    - Test for anti-cardiolipin, beta-2-glycoprotein, lupus anticoagulant antibodies
  - Bethesda assay: serial dilutions with normal plasma. More dilutions required = higher inhibitor titer.

- Treatment:
  - Low inhibitor titers (<5 Bethesda units): desmopressin, factor VIII concentrates
  - High inhibitor titers (>5): recombinant activated factor VII or prothorombin complex concentrates
  - Immune suppression to decrease inhibitor levels.

Bonus points: What is the ristocetin assay used to test for?



QUESTION 16:

- A 38-year-old man is evaluated in the hospital for increasing right leg pain and swelling. He experienced a right femur fracture 2 days ago and underwent surgical repair. Medical history is unremarkable, but family history reveals his mother experienced a pulmonary embolism at age 66 years while receiving breast cancer treatment, and a maternal uncle had a "leg clot" at age 82 years. Medications are as-needed oxycodone and prophylactic-dose enoxaparin.
- On physical examination, vital signs are normal. The right leg shows increased circumference of 2 cm at the midcalf compared with the left. The surgical site is clean and dry.
- Laboratory studies show normal activated partial thromboplastin and prothrombin times.
- Doppler ultrasonography shows a right proximal leg deep venous thrombosis.

ANSWER 16:
NO TESTING

THROMBOPHILIAS:

- Inherited:
  - Factor V Leiden/Protein C resistance (Most common! Mostly in whites.)
  - Prothrombin G20210A Gene Mutation
  - Antithrombin deficiency (Rare but highest risk. Acquired is more common than congenital. Think of this if you're having a hard time keeping heparin drip therapeutic!)
  - Protein C Deficiency (associated with warfarin necrosis because it depletes first)
  - Protein S Deficiency (rare)
- Acquired:
  - Surgery, trauma, hospitalization, and immobilization
  - Cancer – Diagnosed within 1 year in 10% of unprovoked DVTs.
  - Medications – estrogen, tamoxifen, thalidomide, and steroids
  - Antiphospholipid antibody syndrome – autoimmune anticardiolipid antibodies and lupus anticoagulant
  - Others – myeloproliferative neoplasms, PNH, etc


What do we want?!
Thrombophilia Eval!
When are we supposd to get it?
Later!
What are we gonna do?
Order it anyway!

Indications for thrombophilia eval:

- Thromboses at unusual sites (hepatic, portal, cerebral – these should be checked for PNH and JAK2 mutations as well!)
- Recurrent idiopathic thromboses
- Patients with more than 1 first-degree relative with thrombosis and a thrombus
- Patients younger than 45 with unprovoked thrombosis IF it's symptomatic (not an incidental finding)
- Warfarin-induced skin necrosis – think factor C deficiency!
- Planning to use OCP

Do not test someone with family history and no clot!

Choosing Wisely®
An initiative of the ABIM Foundation

TIMING

Preferably not during an acute thrombosis because:

-Acute thrombosis can reduce plasma concentrations of protein C, protein S, and antithrombin.

-Heparin can reduce plasma concentration of antithrombin and falsely lead to detection of lupus anticoagulant.

-Warfarin reduced functional activity of protein C and S, and decreases detection of LA

-Dabigatran can OVER estimate antithrombin, protein C and S levels in some labs

-Rivaroxiban and apixaban can overestimate antithrombin levels in some labs

Clinical settings that may interfere with testing for thrombophilia

Hypercoagulable disorder for testing	Confounding factors		
	Acute thrombosis	Heparin therapy	Warfarin therapy
Antithrombin (deficiency)	Can be lowered*	Lowered	NC; rarely increased
Antiphospholipid antibodies	NC	NC	NC
Factor V Leiden	NC	NC	NC
Factor VIII level	Acute phase reactant. Do not test while inflammation is still present.		
Lupus anticoagulant	NC	Cannot measure¶	False positives possible
Protein C (deficiency)	Can be lowered*	NC	Cannot measure△
Protein S (deficiency)	Can be lowered*	NC	Cannot measure△
Prothrombin gene mutation	NC	NC	NC
Acquired AT deficiency:			
Neonatal period, pregnancy, liver disease, DIC, nephrotic syndrome, major surgery, acute thrombosis, treatment with L-asparaginase, heparin, or estrogens			
Acquired protein C deficiency:			
Neonatal period, liver disease, DIC, chemotherapy (CMF), inflammation, acute thrombosis, treatment with warfarin or L-asparaginase			
Acquired protein S deficiency:			
Neonatal period, pregnancy, liver disease, DIC, acute thrombosis, treatment with warfarin, L-asparaginase, or estrogens			

- If it must be done, do it on heparin or LMWH, 2 weeks after stopping warfarin, and at least several weeks after acute thrombosis.

QUESTION 17

- A 76-year-old woman arrives for follow-up consultation regarding a recent diagnosis of essential thrombocythemia. She was hospitalized 5 days ago for a cerebrovascular accident. Evaluation at the time showed a platelet count of 660,000/µL (660 × 10^9/L). Results of iron studies, *JAK2 V617F*mutation testing, and polymerase chain reaction for *BCR-ABL* were normal. No secondary cause of thrombocythemia was found. Medical history is also notable for type 2 diabetes mellitus and dyslipidemia. Medications are low-dose aspirin, metformin, and atorvastatin.
- On physical examination, vital signs are normal. She displays slight left hemiparesis. The spleen tip is palpable.
- A bone marrow biopsy specimen showed hypercellularity with increased numbers of enlarged megakaryocytes.

ANSWER 17:
ADD HYDROXYUREA

ESSENTIAL THROMBOCYTOSIS

- Most are asymptomatic
  - Platelets >450,000
  - Headache
  - Visual disturbances
  - Dysesthesia of palms and soles
  - Syncope
  - Livedo reticularis
  - Thrombosis
  - Hemorrhage (Plt >1.5M)
- Gene mutations: JAK2, calreticulin, MPL
- Rule out:
  - CML
  - PV
  - MDS
  - Iron deficiency anemia
  - Reactive thrombocytosis
- Treatment
  - Symptoms:
    - Aspirin 81mg
  - >60 y/o or history of thrombosis
    - Hydroxyurea
  - Plateletpheresis
    - Severe organ dysfunction or bleeding due to acquired vWd
- Acquired von Willebrand disease
  - Suspected due to proteolysis of vWF multimers

Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count ≥2,000/uL; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/uL.
- Maintain platelet count ≥80,000/uL
- If neutropenia or thrombocytopenia occurs:
  - Hold hydroxyurea dosing
  - Monitor CBC with WBC differential weekly
  - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
  - Increase by 5 mg/kg/day increments every 8 weeks
  - Give until mild myelosuppression (absolute neutrophil count 2,000/uL to 4,000/uL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
  - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6- month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
  - Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

HYDROXYUREA

Clinical properties of hydroxyurea

Characteristic	Hydroxyurea
Drug class	Antimetabolite
Mechanism of action	Not genotoxic, impairs DNA repair by inhibiting ribonucleotide reductase, increases HbF production
Specificity	Affects all cell lines
Pharmacology	Half-life 4 hours; 40% renally excreted, 60% metabolized
Starting dose	15 to 20 mg/kg per day orally for routine treatment of MPNs or sickle cell disease; 50 to 100 mg/kg per day orally for treatment of hyperleukocytosis
Onset of action	3 to 5 days for routine treatment of MPNs; weeks, up to 6 months, for treatment of sickle cell disease; 1 to 2 days for hyperleukocytosis
Side effects observed in >10% of patients	Neutropenia, anemia, oral ulcers, mild gastrointestinal upset, hyperpigmentation, rash, nail changes
Side effects observed in ≤10% of patients	Ankle ulcers, lichen planus-like lesions of the mouth and skin, nausea, diarrhea
Rare side effects	Fever, liver function test abnormalities
Contraindications	Severe bone marrow suppression (eg, neutropenia, thrombocytopenia); pregnancy, attempted conception, breast feeding

QUESTION 18

- A 24-year-old man is admitted to the hospital for fever, chest pain, shortness of breath, and cough of 3 days' duration. He is homozygous for hemoglobin S (Hb SS). Medications are folate and hydroxyurea.
- On physical examination, temperature is 38.9 °C (102 °F), blood pressure is 100/70 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. Oxygen saturation is 90% breathing 40% oxygen. He appears ill. Cardiopulmonary examination reveals a grade 2/6 systolic flow murmur and crackles in the lower lung fields bilaterally. The remainder of the examination is unremarkable.
- Laboratory studies show a hemoglobin level of 7.8 g/dL (78 g/L) and a leukocyte count of 22,000/µL (22×10^9/L).
- Bilateral lower lobe infiltrates are seen on a chest radiograph. The patient receives intravenous saline, prophylactic doses of low-molecular-weight heparin, and ceftriaxone and levofloxacin. Incentive spirometry is begun. Six hours later, he has worsening hypoxia and respiratory distress requiring intubation and mechanical ventilation. A repeat chest radiograph shows worsening infiltrates.

ANSWER 18:
EXCHANGE TRANSFUSION

ACUTE CHEST SYNDROME

- Fever, respiratory signs (tachypnea, hypoxia, chest infiltrate). Clinical diagnosis.
- Most common cause of death in sickle cell disease.

- Oxygen, analgesia, incentive spirometry, antibiotics.
- Simple or exchange transfusion (goal Hgb 10)
  - Drop in hemoglobin by more than 1 g/dL below baseline
  - Respiratory distress, progressing infiltrates, worsening anemia despite simple transfusion.

Simple or exchange transfusion?

• Splenic sequestration plus severe anemia.	Simple
• Planned surgery and Hgb <10	Simple
• Aplastic crisis	Simple
• Pain crisis	No!
• Priapism	No!
• Stroke	Simple or exchange

HYDROXYUREA

- Indications in SCD:
  - >2 sickle cell pain crises in one year
  - Pain interfering with daily activities
  - History of severe or recurrent acute chest syndrome
  - Severe symptomatic chronic anemia that interferes with quality of life
  - Offer to infants >9 months, children, and adolescents to reduce SCD complications.

  - Teratogenic, not safe for breastfeeding

QUESTION 19

- An 80-year-old woman is evaluated for fatigue and exertional dyspnea developing over several months. Medical history is significant for longstanding hypertension, but she has not been adherent with her medications.
- On physical examination, vital signs are normal except for blood pressure of 180/110 mm Hg. She is frail, with pallor of mucous membranes and nail beds. The remainder of the examination is normal.
- Laboratory studies: Hemoglobin 9 g/dL (90 g/L) Leukocyte count 8700/µL (8.7 × 109/L), with a normal differential Mean corpuscular volume 85 fL Platelet count 380,000 (380 × 109/L) Reticulocyte count 1% of erythrocytes Creatinine 1.8 mg/dL (159 µmol/L) Folate 8 ng/mL (18.1 nmol/L) Iron studies Ferritin 120 ng/mL (120 µg/L) Iron 70 µg/dL (13 µmol/L) Total iron-binding capacity 250 µg/dL (44.8 µmol/L) Vitamin B12 540 pg/mL (399 pmol/L)
- Peripheral blood smear shows normal erythrocyte morphology.
- On kidney ultrasonography, kidneys are small bilaterally, with echographic features suggesting chronic kidney disease.

ANSWER19:
ERYTHROPOIETIN DEFICIENCY

ANEMIA OF CKD

- Monitoring:
  - CKD III: yearly
  - CKD IV-V: Every 6 months
  - Dialysis: Every 3 months
  - Iron studies every 3 months while on ESA
- ESAs for Hgb <10
  - Avoid Hgb >11.5 (HTN, stroke)
- Iron therapy
  - Transferrin sat <30%, ferritin < 500

QUESTION 20

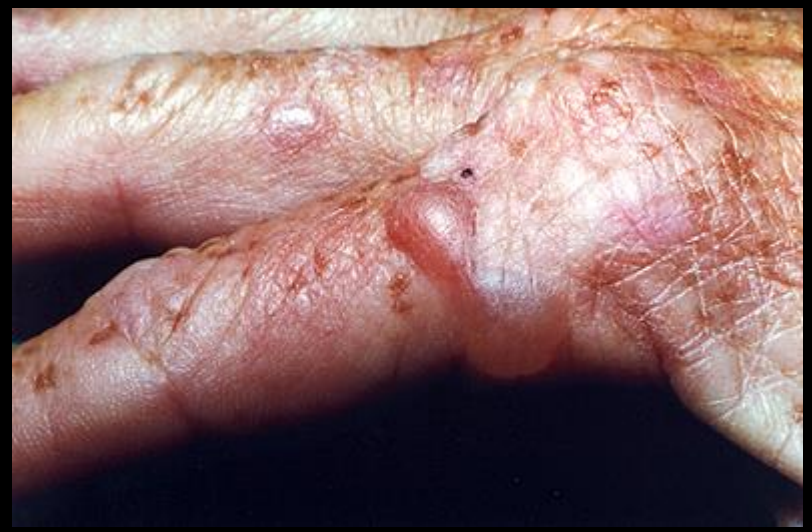
- A 76-year-old woman is evaluated for worsening fatigue. She reports no additional symptoms. Medical history is significant for myelodysplastic syndrome diagnosed 3 years ago, which has required the transfusion of 1 to 2 units of blood every 5 to 6 weeks to maintain a hemoglobin level of approximately 8 g/dL (80 g/L); she has exertional dyspnea when the hemoglobin level drops below 7 g/dL (70 g/L).
- On physical examination, vital signs are normal. The abdomen is soft. Conjunctival pallor is noted. The examination is otherwise noncontributory.
- Laboratory studies show a hemoglobin level of 7.5 g/dL (75 g/L) and a serum ferritin level of 1638 ng/mL (1638 µg/L).
- Which of the following is the most appropriate management?

ANSWER 20:
BEGIN DEFERASIROX

SECONDARY IRON OVERLOAD

- No regulated mechanism for iron excretion
  - Endocrinopathy, cardiac effects, hepatic deposition, arthropathy
- Threshold for treatment ferritin >1000 ng/mL
  - Deferoxamine (IV)
  - Deferasirox (PO)
  - Deferiprone (PO)
  - Kidney, liver, agranulocytosis, ophthalmic disease

- Phlebotomy for primary iron overload
  - Hereditary hemochromatosis (Transferrin sat, HFE gene incomplete penetration)
  - Porphyria cutanea tarda
  - 200mg iron per pint



IRON OVERLOAD IN SCD

- In patients who receive chronic transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, or MRI R2 or MRI T2* and R2* techniques. The optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics
- Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload.