HEMATOLOGY REVIEW

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September 24th, 2019

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.

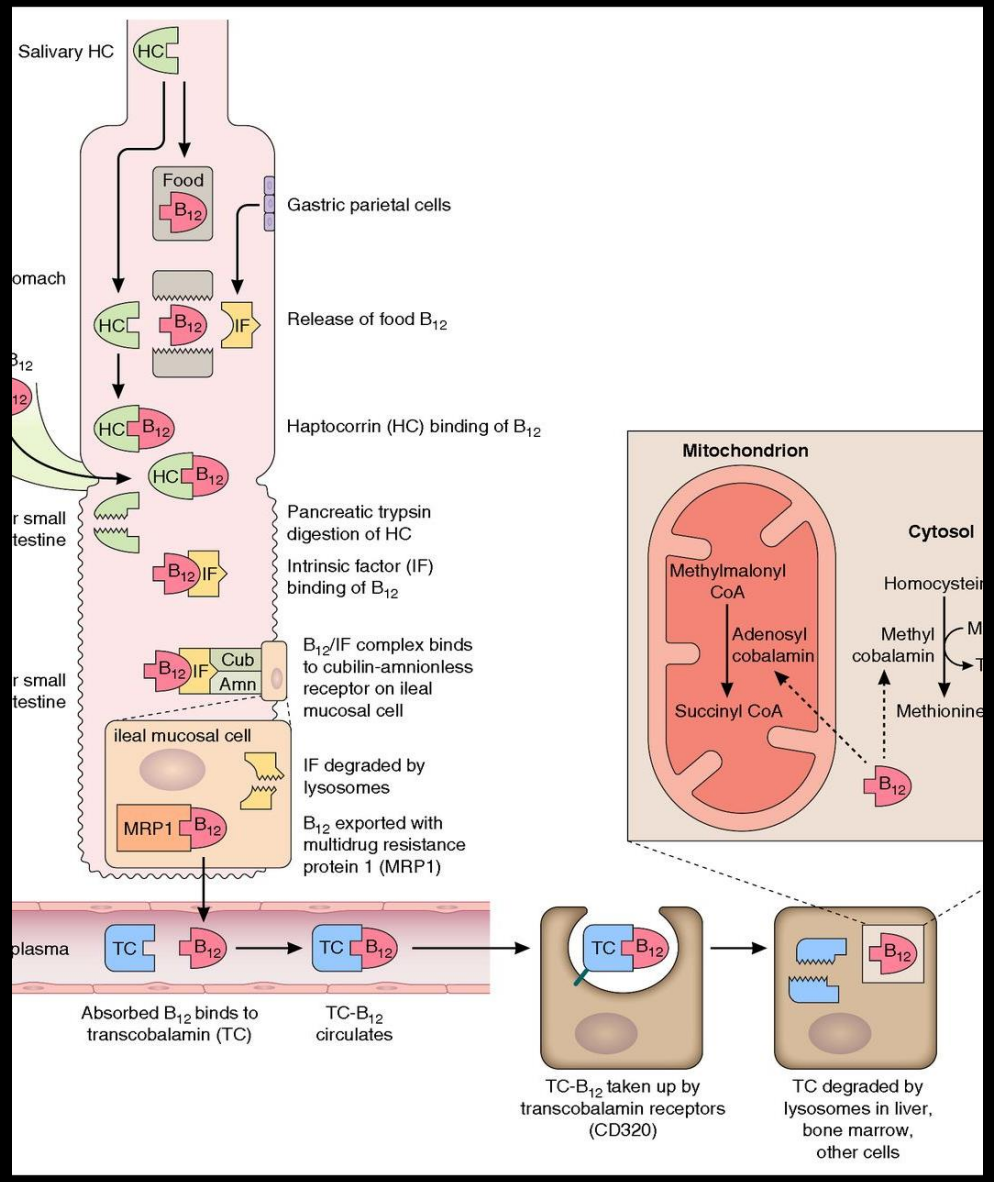
Hemoglobin	10.4 g/dL (104 g/L)
Leukocyte count	2800/µL (2.8×10^9/L)
Mean corpuscular volume	105 fL
Vitamin B_{12}	210 pg/mL (155 pmol/L)

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

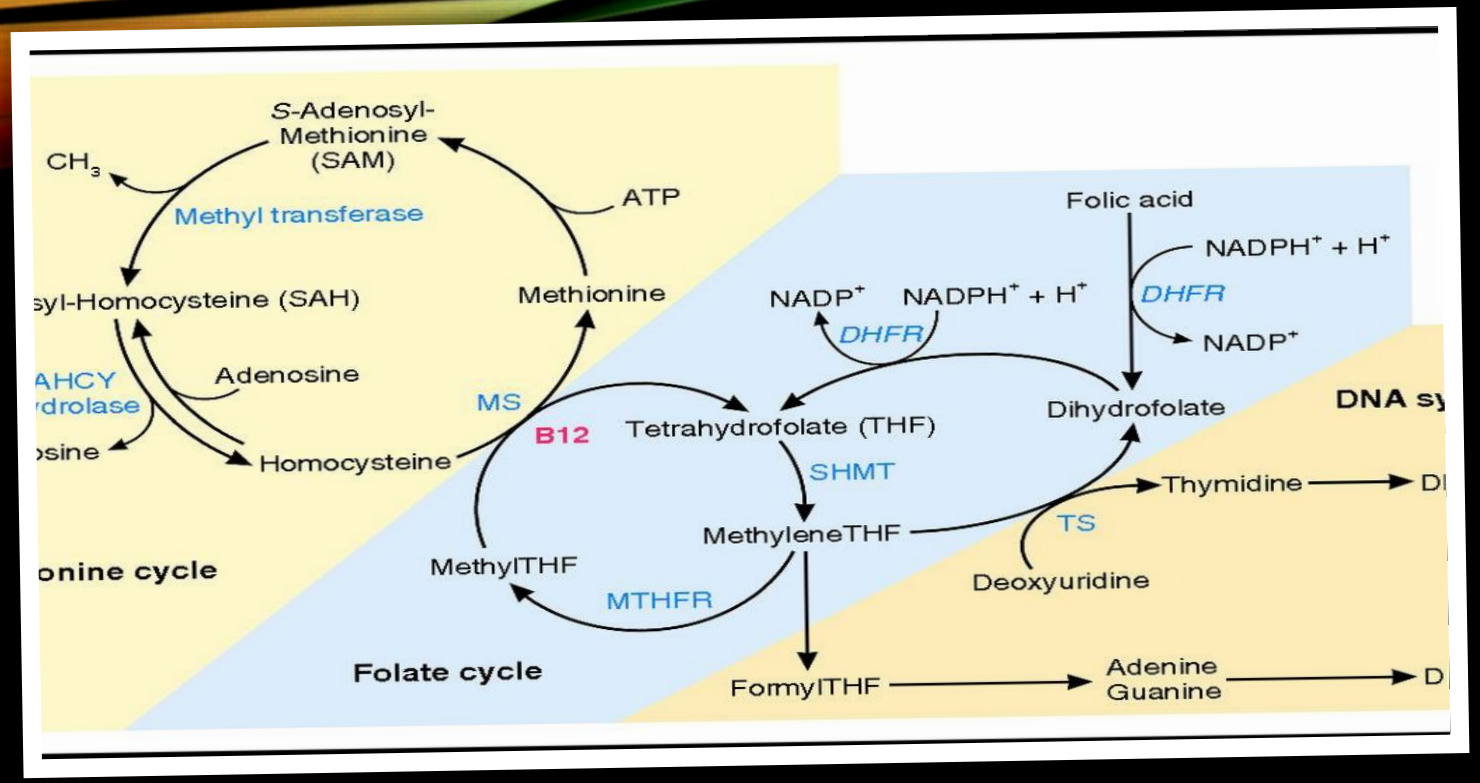
ANSWER 1: METHYLMALONIC ACID LEVEL

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.

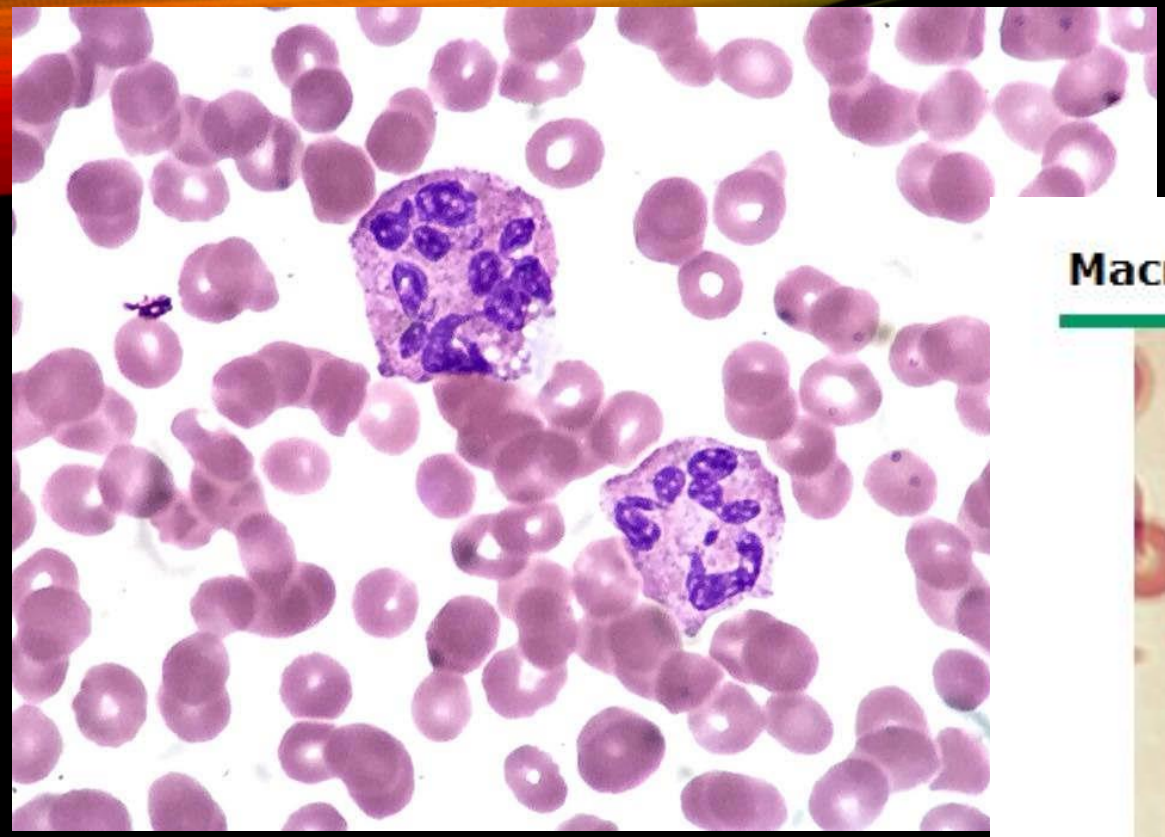
Just kidding.

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.

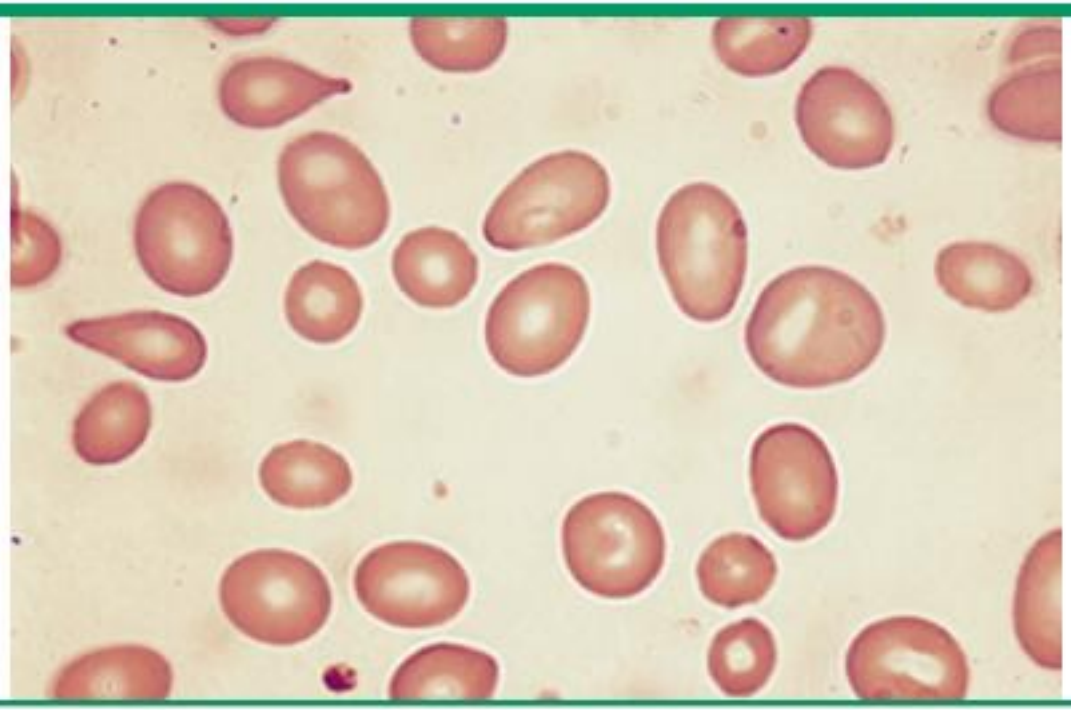
WHAT COULD GO WRONG?

- 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



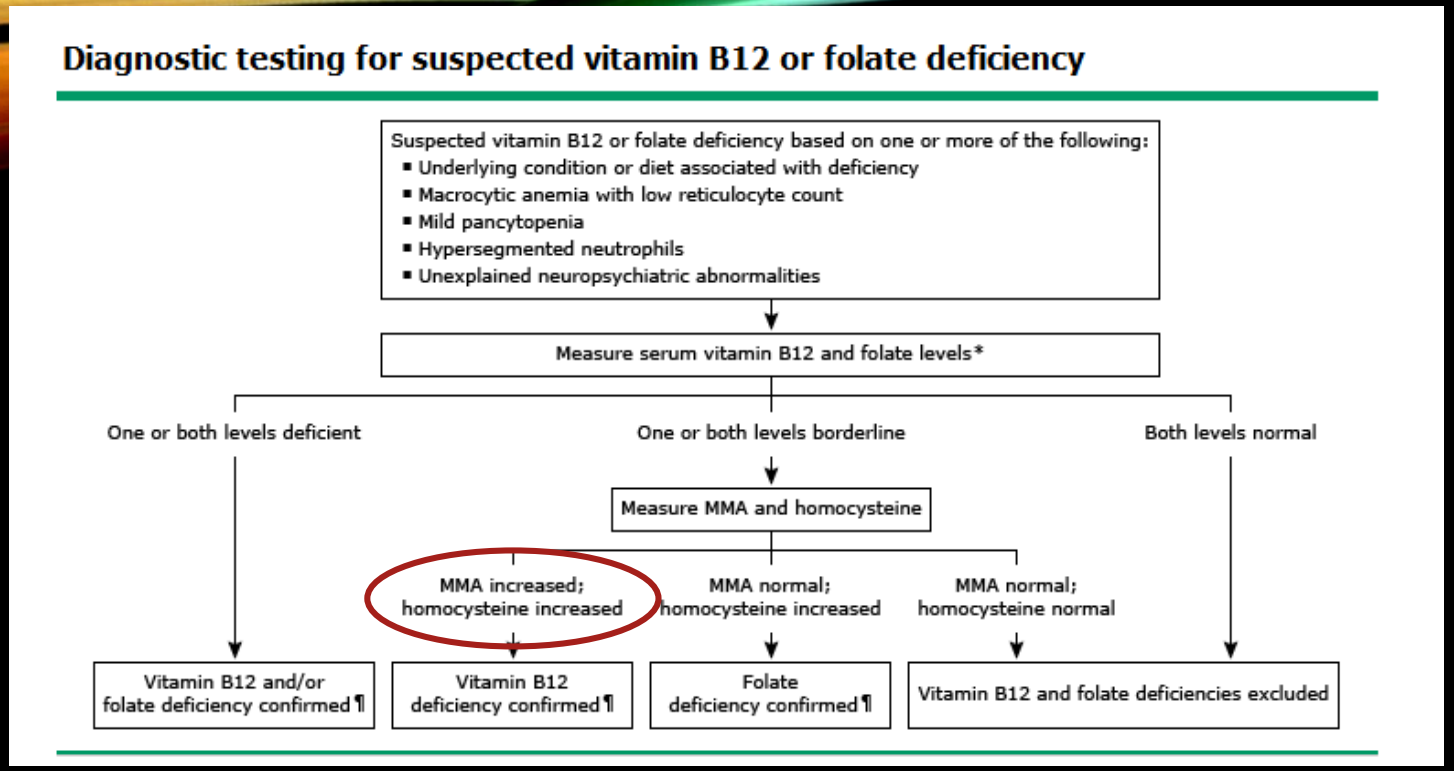
Macro-ovalocytes in vitamin B12 deficiency



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.)

	B12 deficient	Folate deficient
MMA level	High	Normal
Homocysteine level	High	high

QUESTION 2

- A 24-year-old man with progressive fatigue and intermittent dark urine over several months is evaluated in the emergency department for exertional dyspnea, abdominal pain, and red urine.
- On physical examination, he is pale. Temperature is 37.0 °C (98.6 °F), blood pressure is 110/70 mm Hg, pulse rate is 112/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Scattered petechiae are visible on the skin. The abdomen is not distended and is diffusely tender to palpation without guarding. Bowel sounds are normal. The remainder of the examination is normal.

Laboratory studies:	
Haptoglobin	Undetectable
Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	1200/μL (1.2 × 10^9/L) with 70% neutrophils and 30% lymphocytes
Mean corpuscular volume	84 fL
Platelet count	23,000/μL (23 × 10^9/L)
Reticulocyte count	8% of erythrocytes
Lactate dehydrogenase	500 U/L
Urinalysis	4+ blood; 0-1 erythrocytes/hpf; 0 leukocytes/hpf

- The peripheral blood smear shows normal-appearing erythrocytes without spherocytes, schistocytes, agglutinated erythrocytes, or immature-appearing leukocytes.
- Which of the following is the most appropriate next test?

ANSWER 2:
FLOW CYTOMETRY

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

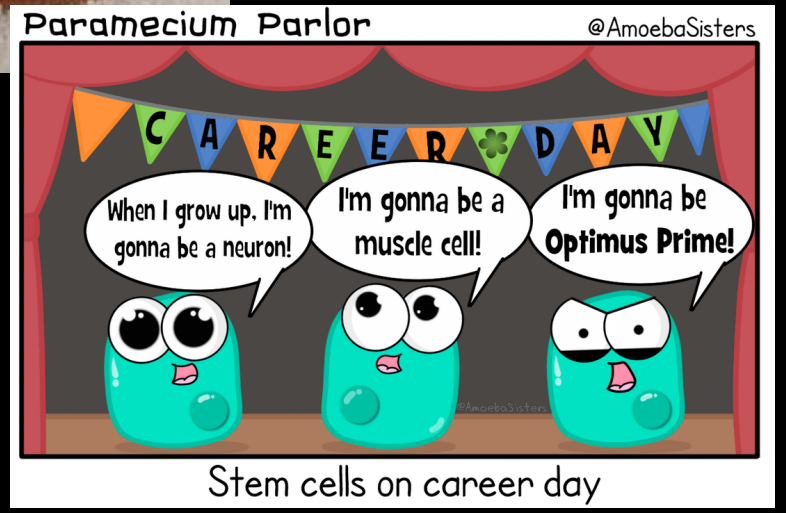
4. Non-Immune:
   1. **PNH (Paroxysmal Nocturnal Hemaglobinuria**
   2. MACROangiopathic = artificial valves or LVADs
   3. MICROangiopathic (MAHA) aka **SCHISTOCYTES!**
      - TTP
      - DIC
      - HUS
      - Complement-mediated (Diarrhea negative HUS)
      - Drug-Induced (DITMA) like cyclosporine 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) – seen on flow cytometry
- 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



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 3

- A 53-year-old woman undergoes follow-up evaluation for anemia found incidentally on routine laboratory testing. She reports no specific symptoms. Medical history is remarkable for stable autoimmune hepatitis. Her only medication is azathioprine.
- On physical examination, vital signs are normal. Hepatomegaly is palpated on abdominal examination.
- Serum protein electrophoresis and immunofixation show a polyclonal pattern with elevated IgG levels.
- Which of the following is the most appropriate next step in evaluating the elevated protein?

Laboratory studies:	
Hemoglobin	11.5 g/dL (115 g/L)
Leukocyte count	7000/µL (7×10^9/L)
Platelet count	300,000/µL (300×10^9/L)
Albumin	4 g/dL (40 g/L)
Ferritin	300 ng/mL (300 µg/L)
Total iron-binding capacity	189 µg/dL (33.8 µmmol/L)
Protein, total	10 g/dL (100 g/L)

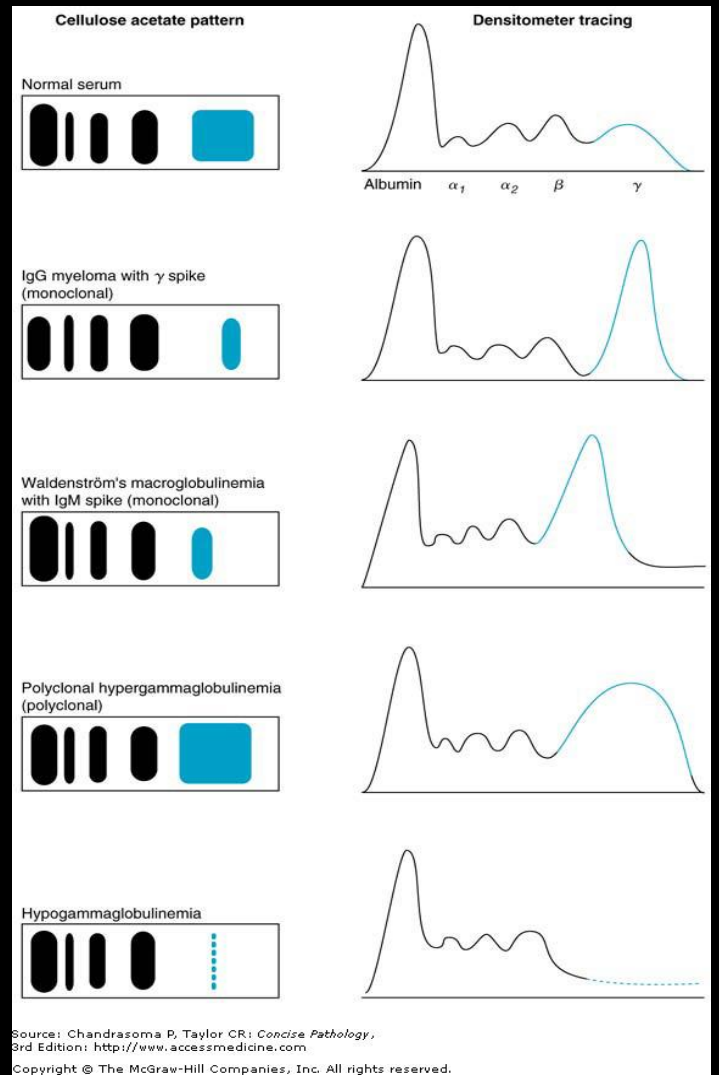
ANSWER 3:
NO FURTHER TESTING

POLYCLONAL SPIKE?

- Inflammatory disorders, infections, reactive processes.
- If unexplained, can check CBC, liver chemistries, hepatitis C, HIV.
- Exclude infection.

- 148 patients with polyclonal spike
  - 61% had liver disease, 22% had connective tissue disease
  - 3% had hematologic malignancies
  - None developed myeloma or clonal plasmaproliferative disorder.

Mayo Clin Proc. 2001 May;76(5):476-87



MONOCLONAL SPIKE!

- Polyclonal spike

- Monoclonal M-spike >3g/dL
- Kappa:lambda free light chain ratio <0.26 or >1.65

Diagnostic:

- >10% clonal plasma cells on bone marrow AND
  - CRAB criteria

  OR ANY OF:
  - ≥60% clonal plasma cells on bone marrow
  - >1 focal lesion on MRI
  - Involved:uninvolved serum free light chain ratio ≥100

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.

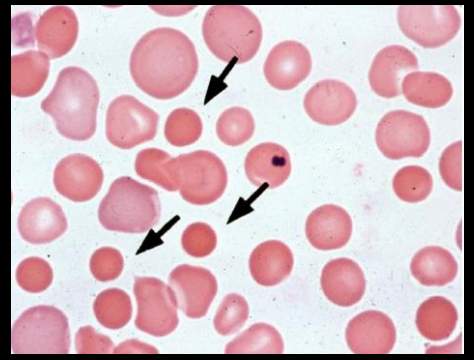
When you order transfusion, crossmatch of compatible blood will be incompatible due to the auto-antibodies attacking donor cells.

>Tranfuse least incompatible blood!

Clinical manifestations:

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

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



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 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
- RITUXIMAB, Cyclophosphamide, chlorambucil

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
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  3. Immune-mediated:
     - Warm-autoantibody
     - Cold agglutinin disease

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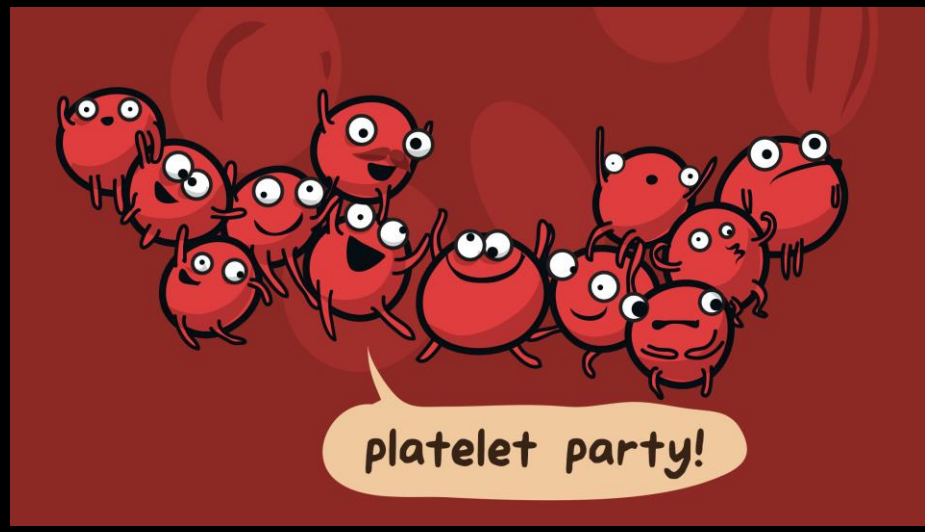
      - TTP
      - DIC
      - HUS
      - Complement-mediated (Diarrhea negative HUS)
      - Drug-Induced (DITMA) like cyclosporine or gemcitabine
      - Rare genetic B12 metabolism disorders
      - Malignancy
      - Eclampsia
      - Hypertensive crisis

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.

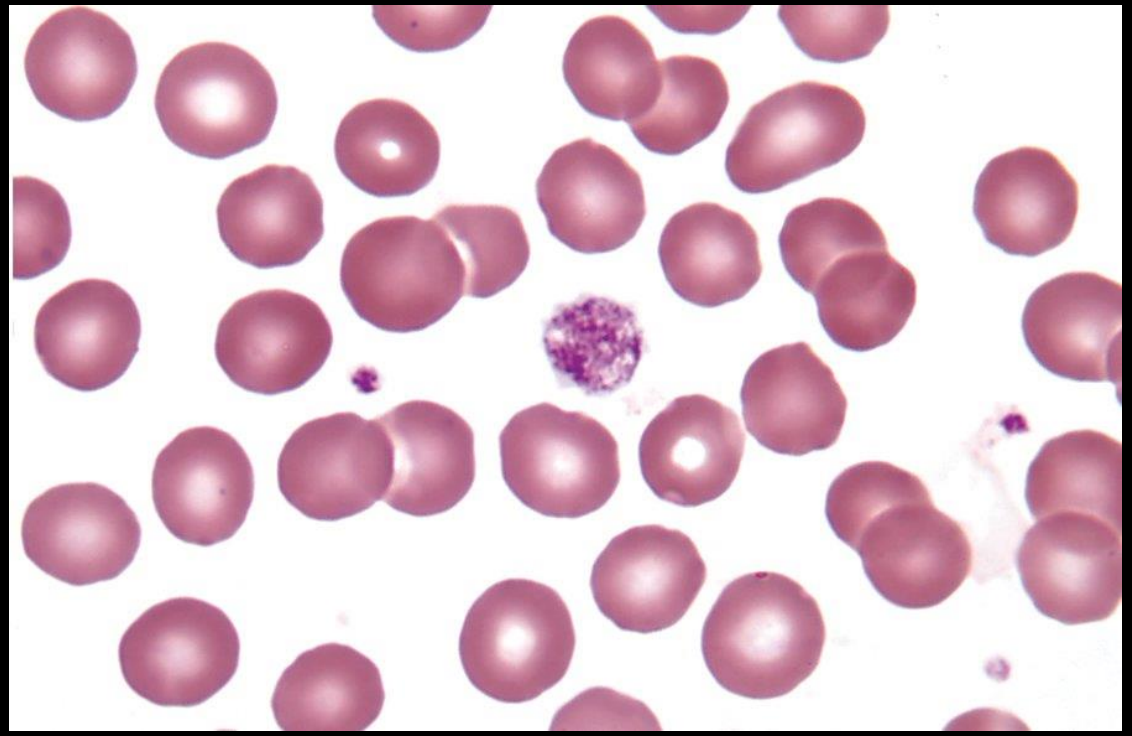


TTP

- 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!
- Plasma exchange = 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

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
    - 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 (Grade 1B)**
- No bone marrow biopsy (Grade 2C) 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

"I'm concerned about his platelets."

Blood. 2011 Apr 21;117(16):4190-207

QUESTION 7

- A 68-year-old man notes 3 days of melena and the recent onset of epistaxis and easy bruising. He had no bleeding problems until the past week. He has advanced ischemic cardiomyopathy and had a left ventricular assist device (LVAD) placed 3 months ago. He had no bleeding history before LVAD implantation surgery, and his preoperative coagulation studies were normal. Medications are atorvastatin, carvedilol, lisinopril, spironolactone, and warfarin initiated after LVAD placement.
- On physical examination, other than a pulse rate of 112/min, vital signs are normal. Oxygen saturation is 94% breathing ambient air. He has crusted blood in the left nares, scattered ecchymoses, and multiple petechiae. The surgical scar on the anterior chest appears well healed. Stool for fecal occult blood is strongly positive. The remainder of the examination is normal.
- Which of the following is the most likely cause of this patient's new bleeding symptoms?

Laboratory studies:	
Activated partial thromboplastin time	40 s
Hemoglobin	8.0 mg/dL (80 g/L)
Platelet count	130,000/µL (130 × 10^9/L)
Prothrombin time	19 s
INR	2.0
Platelet Function Analyzer-100	Prolonged
Aminotransferases	Normal
Fibrinogen	350 mg/dL (3.5 g/L)

ANSWER 7: ACQUIRED VON WILLEBRAND DISEASE

ACQUIRED VON WILLEBRAND DISEASE

- Associated with shear stress
  - Mechanical valves, LVADs, ECMO, HCM
  - Excessive degradation of high-molecular-weight von Willebrand multimers by ADAMTS-13.
  - This decreases the von Willebrand factor size and adhesive activity, essentially deactivating it.
- Von Willebrand/platelet activity returns to normal after LVAD explant.

Hematologic complications of LVADs

- Pump thrombosis- 2-4% incidence in HeartMate2 devices
- Stroke – poor prognosis
- LVAD associated bleeding in 19-40% of HeartMate2 patients
  - GI bleeding – commonly due to AVMs (Heyde syndrome) – tx: octreotide
  - Epistaxis

Blood. 2016 Jun 23;127(25):3133-41

QUESTION 8

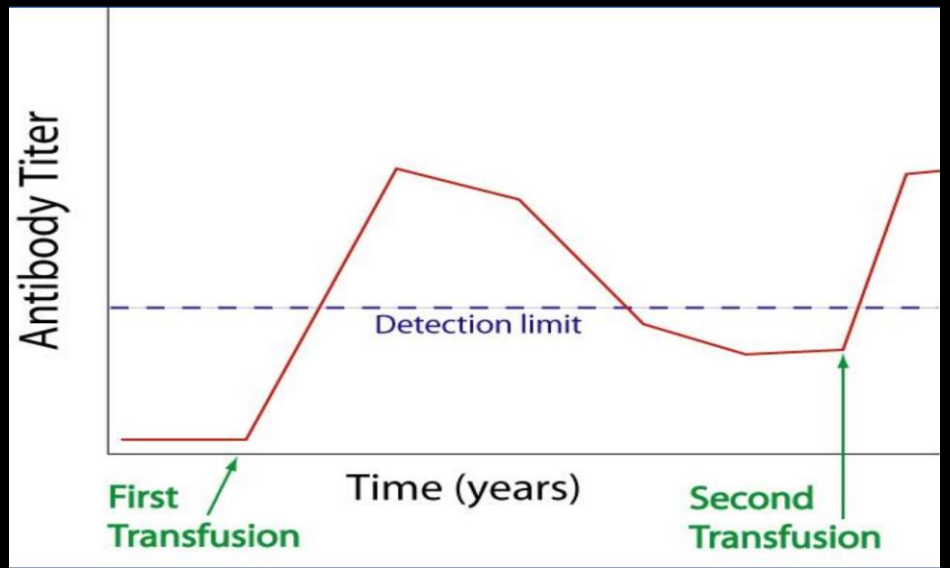
- A 53-year-old man is evaluated for tea-colored urine. He reports no other symptoms. He was hospitalized 2 weeks ago with melena. Upper gastrointestinal endoscopy and colonoscopy at the time did not show a bleeding source, but he stabilized after the transfusion of one unit of blood. He was discharged 10 days ago and has returned to work. Medical history is otherwise significant for trauma sustained in a motor vehicle accident 5 years ago, requiring multiple surgeries. He takes no medications.
- On physical examination, temperature is 37.8 °C (100.1 °F), and other vital signs are normal, with no postural blood pressure or pulse changes. Scleral icterus is noted. The stool guaiac test result is negative. The remainder of the examination is unremarkable.
- Which of the following is the most appropriate next step in the management of this patient?

Laboratory studies:		
	Current	10 Days Ago
Hemoglobin	6.9 g/dL (69 g/L)	8 g/dL (80 g/L)
Bilirubin	---	----
Total	5 mg/dL (34.2 µmol/L)	1.1 mg/dL (18.8 µmol/L)
Direct	0.7 mg/dL (12 µmol/L)	—
Urinalysis	4+ blood, 2-3 erythrocytes/hpf, 1 leukocyte/hpf	—

ANSWER 8: DIRECT ANTIGLOBULIN (COOMBS) TEST

DELAYED HYPERHEMOLYTIC TRANSFUSION REACTION

- Caused by re-exposure to RBC alloantibodies preformed from prior transfusions or pregnancy.
- Typically 2-19 days post transfusion
- Supportive care
- Prevention: Match pRBC transfusions for C, E, K antigens.



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
  - Decreases CMV transmission
- Washed – clears plasma to remove antibodies
  - IgA deficiency or history of severe allergic reactions
  - 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?

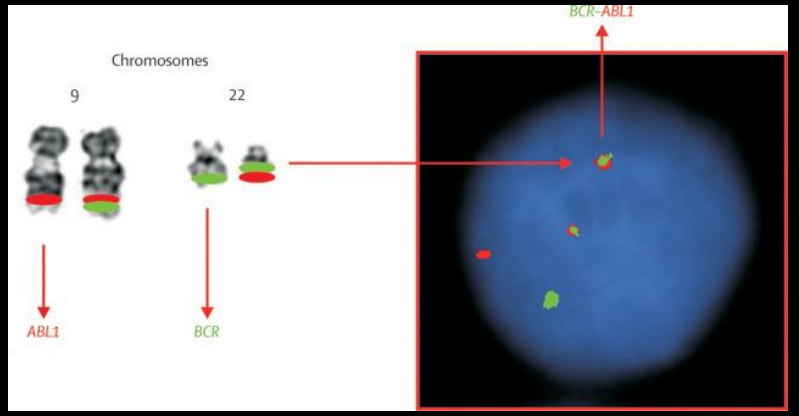
ANSWER 10: DASATINIB

MYELOPROLIFERATIVE NEOPLASMS

- CML
- Polycythemia Vera
- Essential Thrombocytosis
- Primary myelofibrosis

Philadelphia chromosome

JAK2 +



CML Diagnosis – FISH for t(9:22), bone marrow biopsy for blast assessment.
Three phases

- Chronic phase
- Accelerated phase: 10-19% blasts
- Blast phase: >20% blasts (myeloid or lymphoid 40%)

Treatment: Tyrosine kinase inhibitors
Treat blast phase like AML or ALL

BUT WHAT ABOUT ALL

- ALL is a pediatric cancer. Worse prognosis in adults.
- Similar clinical presentation to AML.
- Diagnosis: >25% lymphoblasts in blood or bone marrow
- Can be Philadelphia chromosome positive – poor prognosis prior to TKIs
  - Treat with TKI
- Treatment:
  - same chemotherapy as pediatric disease
    - Asparaginase containing regimens
    - Allogenic stem cell transplant
  - Intrathecal chemotherapy for CNS disease (diagnosed with CSF testing)
    - 50% have CNS relapse without intrathecal chemotherapy
  - PH+ disease:
    - Induction with TKI + steroids
    - Intrathecal chemotherapy
    - In one study 53/53 patients achieved complete hematologic remission. 43% remained free of relapse at 20 month

Blood. 2011 Dec 15;118(25):6521-8

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),

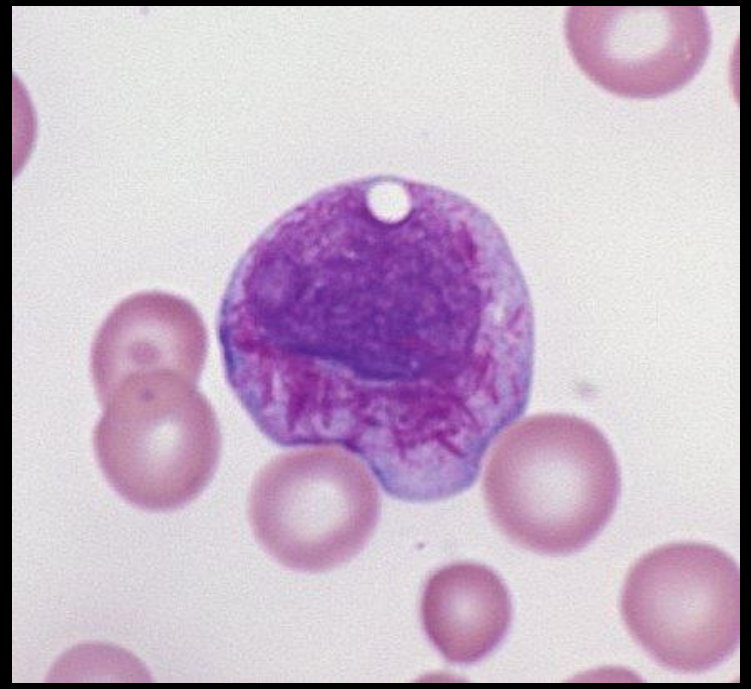
A peripheral blood smear shows 80% immature blasts with prominent Auer rods phenotypically consistent with promyelocytes.

What do you do next?

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

MYELOPROLIFERATIVE NEOPLASMS

- CML
- Polycythemia Vera
- Essential Thrombocytosis
- Primary myelofibrosis

Philadelphia chromosome

JAK2 +

PV Diagnosis: 3 major criteria or first 2 major and 1 minor

Major Criteria:

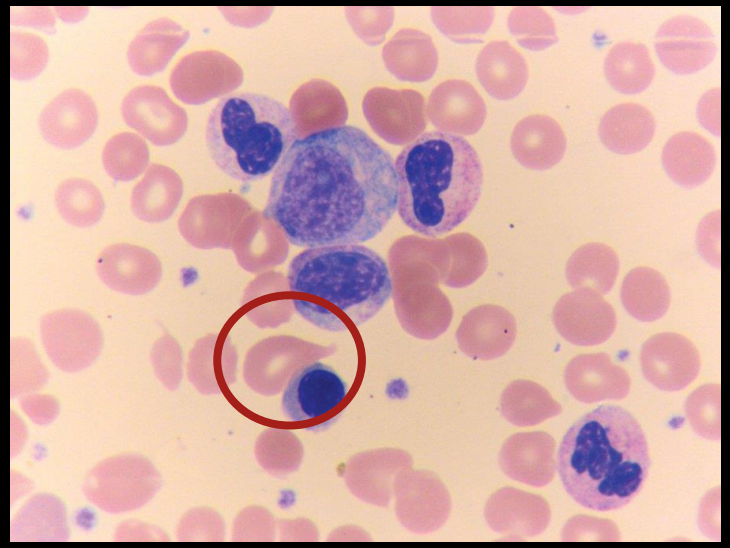
- Hgb>16.5 men, >16 women
- Bone marrow showing hypercellularity with trilineage hyperproliferation
- JAK2 +

Minor Criterion:

- Low EPO

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
- Check EPO to rule out secondary causes (hypoxia, RCC)
- Treat with low dose ASA, phlebotomy, hydroxyurea, JAK2 inhibitors
  - 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%.
- What do you do next?

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

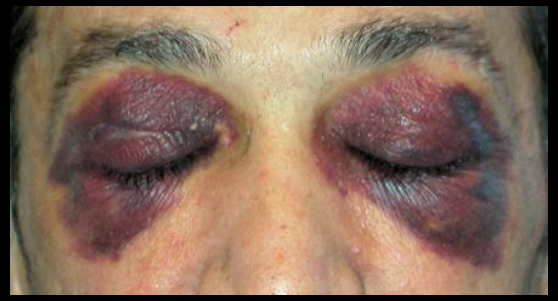
Hereditary Amyloid

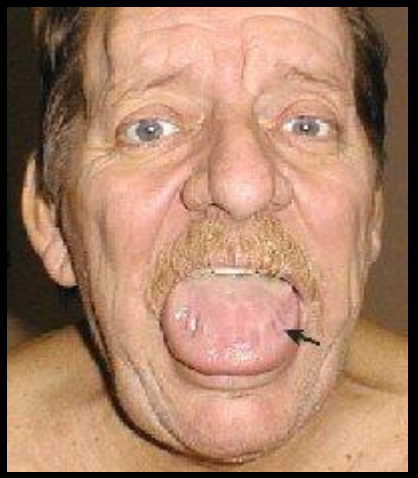
- Mutated transthyretin (TTR) fibrinogen a chain
- Family history
- Cardiac and neuro involvement
- SPEP and IFE negative for monoclonal proteins

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

What if FVIII levels and vWF levels are low?

von Willebrand disease type 3 – unmeasurable vWF levels
So always check vWF levels in hemophilia A

QUESTION 15

- A 64-year-old woman is evaluated in the emergency department for large ecchymoses, bleeding gums, and a hematoma extending from her upper thigh to her knee. Medical history is significant for chronic lymphocytic leukemia, which has been asymptomatic and managed expectantly. She has experienced no previous bleeding symptoms and has no family history of bleeding disorders. She takes no medications.
- On physical examination, other than a pulse rate of 104/min, vital signs are normal. Ecchymoses are present on her arms and legs. Small cervical and axillary lymph nodes are palpable. Other examination findings are normal.
- Administration of which of the following is the most appropriate management?

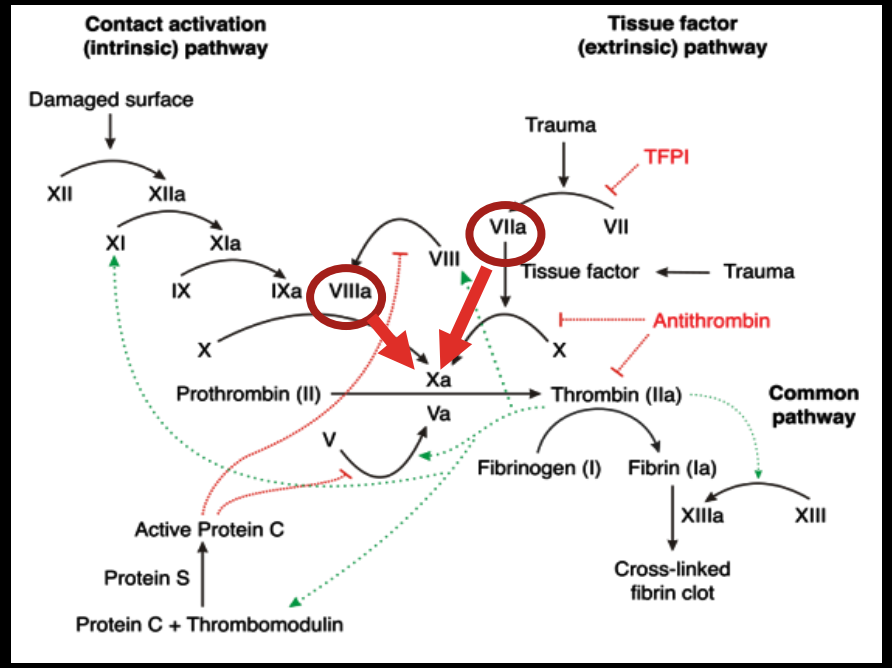
Laboratory studies:	
Activated partial thromboplastin time (aPTT)	88 s
aPTT with mixing study	64 s
Hemoglobin	10.8 g/dL (108 g/L)
Leukocyte count	65,000/μL (65 × 10^9/L)
Platelet count	215,000/μL (215 × 10^9/L)
Prothrombin time	11.5 s
Factor VIII	1%

ANSWER 15:
ACTIVATED FACTOR VII

ACQUIRED HEMOPHILIA

- Antibodies to factor VIII
- 50% idiopathic, 10% occur post-partum, 10% have malignancy
- 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 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.
  - Plasmapheresis



Am J Hematol. 2005 Sep;80(1):55-63.

LUPUS ANTICOAGULANT

- Antiphospholipid antibodies:
  - Anticardiolipin
  - Anti-beta2 glycoprotein
  - Lupus anticoagulant

Antibody tests (ELISA)

Three step test

Presentation will be prolonged aPTT and clots (…wait, what?)

- aPTT will not correct with mixing study.
- Will not correct with addition of dilute Russell viper venom, a phospholipid dependent clotting assay, indicating an antibody to phospholipids.
- Will correct with the addition of phospholipids.

Antiphospholipid syndrome is the presence of one or more antiphosphlipid antibody PLUS either vascular thrombosis OR pregnancy loss

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 and family history

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.
- What do you o next?

ANSWER 17:
ADD HYDROXYUREA

MYELOPROLIFERATIVE NEOPLASMS

- CML
- Polycythemia Vera
- Essential Thrombocytosis
- Primary myelofibrosis

Philadelphia chromosome

JAK2 +

Diagnosis of ET: 4 major or first 3 major and minor

Major Criteria

- Platelets> 450
- BM morphology showing megakaryocyte hyperproliferation without erythroid or granulocytic proliferation
- Not meeting criteria for CML, PV, MF, or MDS
- Jak2, CALR, or MPL mutation

Minor criterion

- No evidence of reactive thrombocytosis

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

QUESTION 18

- A 21-year-old woman is seen for follow-up evaluation after a hospitalization 1 week ago for an acute ischemic stroke in the right middle cerebral artery distribution. In the hospital, she was treated with blood transfusion and aspirin. She is homozygous for hemoglobin S (Hb SS) and experiences frequent pain crises; she has had two episodes of acute chest syndrome within the past 3 years. Medications are folic acid, hydroxyurea, and low-dose aspirin.
- On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 120/70 mm Hg, pulse rate is 90/min, and respiration rate is normal. She has left-sided weakness of the upper and lower extremities. No hepatosplenomegaly is noted.
- Laboratory studies at hospital discharge showed a posttransfusion hemoglobin level of 10 g/dL (100 g/L) and LDL cholesterol level of 92 mg/dL (2.38 mmol/L).
- Which of the following is the most appropriate management to prevent subsequent stroke in this patient?

ANSWER 18: MONTHLY ERYTHROCYTE TRANSFUSION

SICKLE CELL DISEASE

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	Exchange
• Acute chest syndrome	Exchange transfusion

STROKE IN SCD

- 39% have silent cerebral infarcts by age 18
  - Commonly manifest as cognitive impairment.
- 70% risk of subsequent stroke without treatment

- Monthly transfusion can decrease risk of subsequent stroke by 50%
- Target Hgb S <30-50%
- Risk of iron overload, need to use iron chelator.

- Blood. 2016 Feb 18;127(7):829-38

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

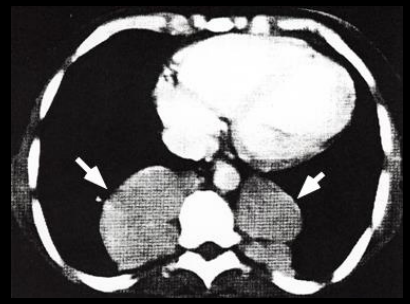
- A 22-year-old woman undergoes routine evaluation for chronic anemia, which was diagnosed 6 years ago. Medical history is otherwise unremarkable, but a maternal aunt also has anemia. Her only medication is a combination oral contraceptive pill. On physical examination, vital signs are normal. No hepatosplenomegaly is noted.
- Hemoglobin electrophoresis reveals a normal pattern of migration of hemoglobin A and normal levels of hemoglobin A_2 and hemoglobin F.
- Which of the following is the most likely diagnosis?

Laboratory studies:	
Hemoglobin	10 g/dL (100 g/L)
Mean corpuscular volume	67 fL
Iron studies	
Ferritin	200 ng/mL (200 µg/L)
Iron	150 µg/dL (27 µmol/L)
Total iron-binding capacity	340 µg/dL (61 µmol/L)

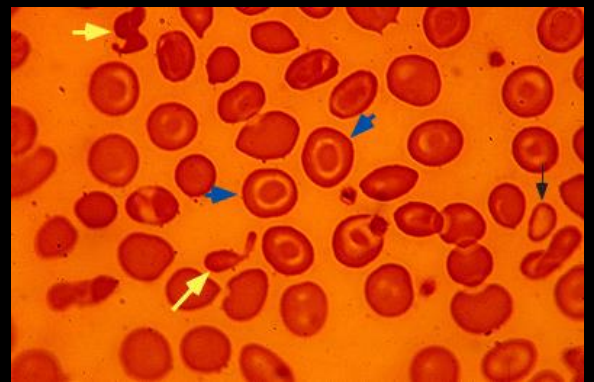
ANSWER19:
ALPHA-THALASSEMIA TRAIT

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
    - High performance liquid chromatography (HPLC) can show Hgb Barts (beta tetramers)
    - DNA PCR or gene sequencing will confirm
- 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
No iron!

Int J Lab Hematol. 2016 May;38 Suppl 1:32-40

- 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 20

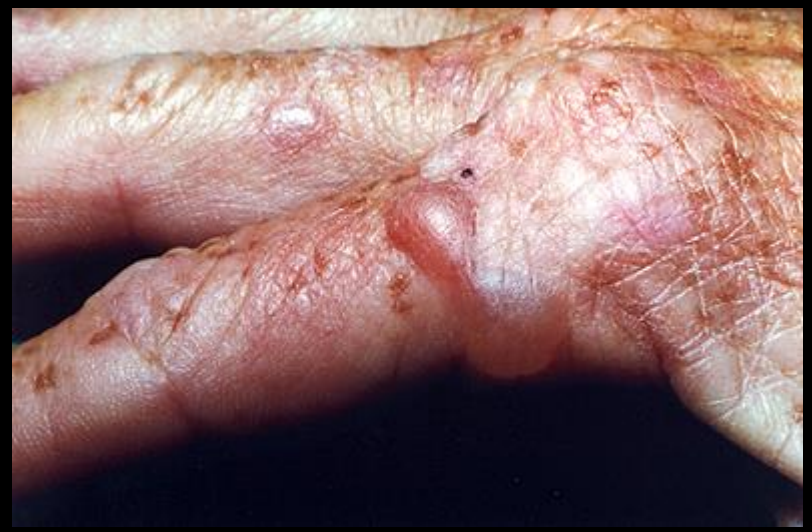
- A 76-year-old woman is evaluated for worsening fatigue. She reports no additional symptoms. Medical history is significant for myelodysplastic syndrome diagnosed 3 years ago, which has required the transfusion of 1 to 2 units of blood every 5 to 6 weeks to maintain a hemoglobin level of approximately 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.