Academic Half Day: Anemia

Facilitator Guide

Case #1: A 26 y/o African American female presents to clinic for a new patient visit, and reports she has been feeling fatigued for the past several months. She informs you that she had gestational diabetes that resolved after delivery two years ago. However, she was told around the time of her delivery that her blood counts were low, but never followed up about this.

1. What additional elements of her history will you ask the patient?

Discuss in terms of "kinetic approach" to anemia: Hgb production, destruction, or loss:

Production: Does the factory have enough supplies? Think about lack of nutrients, bone marrow suppression, hormonal deficiency.

Questions to ask our pt:

- Dietary History: sufficient iron, folate, B12 intake; use of pre-natal or multivitamins
- Increased risk for poor nutrient absorption: celiac disease, Crohn's/UC, gastric bypass, PPI use
- Hx of chronic disease/inflammatory conditions

- Jaundice, dark urine
- Family hx of sickle cell anemia, auto-immune diseases (inherited hemolytic conditions)
- Medications, recent infections (acquired hemolytic conditions)

- Melena, hematochezia, hematemesis
- Blood donation
- Menstrual hx: ***You will tell your team that the pt reports that her cycles have always been heavy but regular, uses 6-7 tampons/day***

2. What are characteristic symptoms of anemia?

Frequently asymptomatic; however, it depends on time of onset as well as severity. Symptoms are mostly due to impaired oxygen delivery or hypovolemia.

- Mild anemia: Easy fatigability, muscle cramps, headache, tinnitus, change in taste, restless leg syndrome
- Moderate: Dyspnea on exertion, symptoms of hyper-dynamic state (i.e. bounding pulses, palpitations, roaring in the ears), orthostatic hypotension, angina
- Severe: Congestive heart failure symptoms, arrhythmia, syncope, MI symptoms, unresponsiveness

Trivia: Dysphagia, glossitis, angular stomatitis, and esophageal webs (also known as Plummer-Vinson syndrome) associated with IDA. Pica (unusual cravings for non-food items like clay, ice, dirt, starch) is also characteristic of IDA

3. What pertinent findings are you looking for on her physical exam? Vitals: Orthostatic hypotension, tachycardia

Skin: Pallor (best seen on the palms of the hands and in conjunctiva, capillary refill), nail changes - Koilonychia (spoon-shaped)
HEENT: angular stomatitis, glossitis, scleral icterus
CV: systolic flow murmur, arrhythmia
Resp: shortness of breath, crackles if severe enough to cause HF
Abdomen: splenomegaly, pelvic fullness (fibroids)
Extremities: LE edema, perfusion

You tell your team that you are relieved to hear that your patient is not having any associated symptoms, denies any family history of bleeding or sickle cell disease, and her physical exam is unremarkable. You decide to order a CBC.

WBC 6.4 \ Hgb 9.4 \ Hct 28 \ PLT 456

MCV 75 \ RBC 3.1 \ MCH 25.4 \ MCHC 29 \ RDW 17

4. How do you describe this anemia? What is your differential diagnosis? What workup do you pursue?

Discuss "morphologic approach" to anemia based on RBC characteristics: micro-, normo-, macrocytic

- MCV – mean corpuscular volume = average size of RBC
  - **Microcytic anemia – MCV <80**
  - Normocytic anemia – MCV 80-100
  - Macrocytic anemia – MCV >100
- MCH and MCHC – mean corpuscular Hgb = amount of Hgb (and Hgb concentration) per RBC
  - Normal range MCH 27-31 pcg/cell; MCHC 32-36 g/dL
- RDW – red cell distribution width = variation in RBC size (aka anisocytosis)
  - Normal range 11.5-14.5%

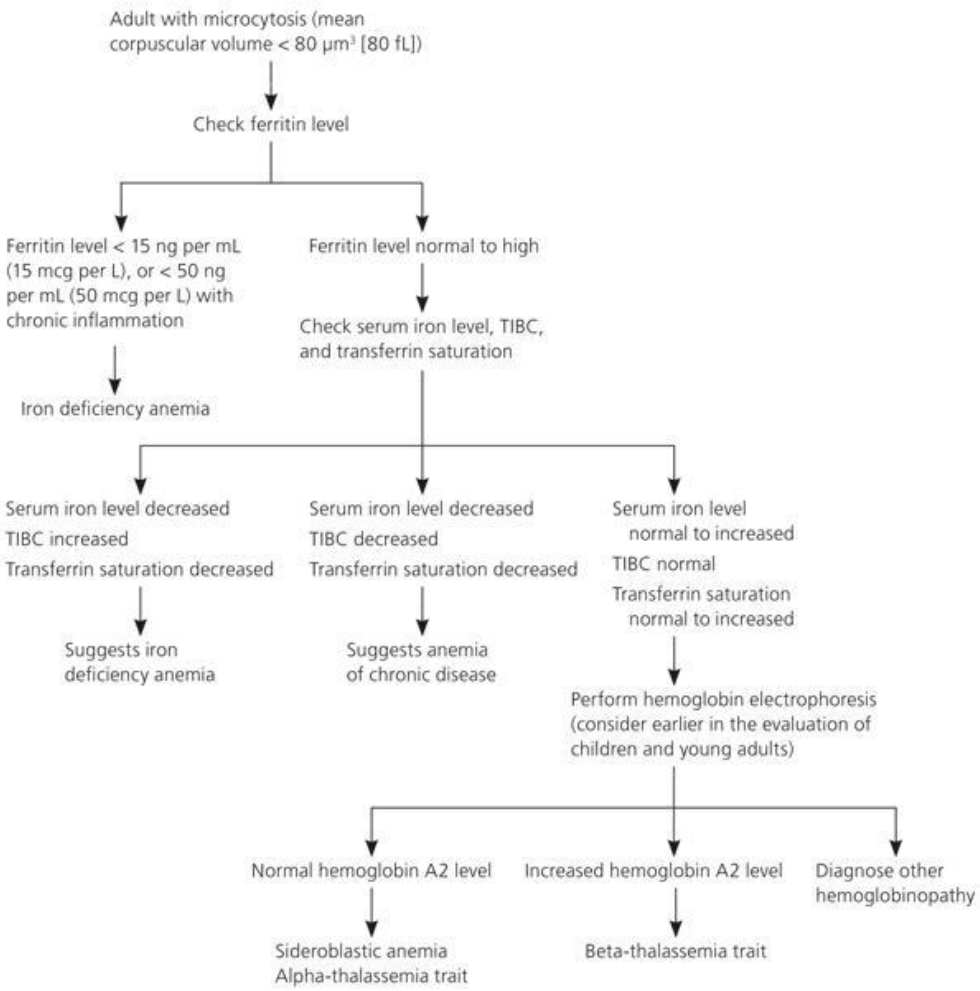
Differential Dx of microcytic anemia:

Table 2. Differential Diagnosis of Microcytosis

Children and adolescents	Menstruating women	Men and nonmenstruating women
Iron deficiency anemia	Iron deficiency anemia	Iron deficiency anemia
Thalassemia trait	Thalassemia trait	Anemia of chronic disease
Other hemoglobinopathies	Pregnancy	Unexplained anemia
Lead toxicity	Anemia of chronic disease	Thalassemia trait
Chronic inflammation	Sideroblastic anemia	
Sideroblastic anemia		

- Iron deficiency anemia (IDA) most common cause across all populations
- Anemia of chronic disease may be micro- vs normocytic; second most common cause of anemias worldwide
- Thalassemias are related to genetic aberrations resulting in defective quantitative globin chain production
  - Thalassemia trait indicative of heterozygote condition resulting in fewer correct globin chains
- Sideroblastic anemia results from defective incorporation of iron into heme molecule, characterized by abnormal cytoplasmic iron deposits in RBC precursor cells (seen on Prussian blue staining). Can be inherited or acquired.

Work-up of microcytic anemia:



- Iron studies: ***If some one asks for iron studies, then ask what all is in included in iron studies and what is the sifinificance of each one.***
    - Serum iron
        - Will usually be < 50 with IDA
    - Ferritin = complex of iron and the binding protein apoferritin
        - Acute phase reactant so will be elevated with inflammation/chronic disease
        - Ferritin < 15 has a **LR+ 52** $\rightarrow$ diagnostic of IDA, may be sufficient to test alone before pursuing further workup
        - Ferritin > 100 has LR+ 0.08 $\rightarrow$ unlikely to have IDA, though confounding factors of inflammation may mask true iron deficiency
    - Total Iron Binding capacity = ability of unsaturated transport protein transferrin to bind iron
        - Will be increased with IDA; normal/decreased with chronic disease; and normal with thalassemia
    - Transferrin saturation = number of free binding sites on transferrin molecule
        - Transferrin %sat < 16 = IDA
    - Iron saturation = serum iron/TIBC
        - <5% = IDA whereas >12% unlikely to be IDA
- Other labs to consider in anemia workup: Thyroid function, renal panel (CKD), LFTs (hyperbilirubinemia)

- Important to discuss the distinction between IDA and other microcytic anemias
    - TIBC is key in differentiating between types of microcytosis → only elevated in IDA ○ RDW is also elevated in IDA
    - RBC count will be low in IDA, but normal in thalassemias
    - Reticulocyte index – indicative of hypoproliferative (IDA) vs hyperproliferative etiologies (hemolysis, blood loss)
- ***Your team has a blank copy of the table listed below, discuss what lab results they would suspect for each of the listed conditions.***

Table 4. Laboratory Tests in the Differential Diagnosis of Microcytosis

	Suggested diagnosis			
Test	*Iron deficiency anemia*	*Thalassemia*	*Anemia of chronic disease*	*Sideroblastic anemia*
Serum ferritin level	Decreased	Increased	Normal to increased	Normal to increased
Red blood cell distribution width	Increased	Normal to increased	Normal	Increased
Serum iron level	Decreased	Normal to increased	Normal to decreased	Normal to increased
Total iron-binding capacity	Increased	Normal	Slightly decreased	Normal
Transferrin saturation	Decreased	Normal to increased	Normal to slightly decreased	Normal to increased

Your patient's labs: Ferritin 14 \ TIBC 455 \ Serum Iron 27 \ %Fe 5

5. Now that you've confirmed the diagnosis, what are the next steps in management?

Diagnosis of IDA always warrants further evaluation for underlying cause

- Nutritional deficiency, GI losses/malabsorption (concomitant PPI use, bariatric surgery)
- In our patient, heavy menses is the most likely culprit, though frequently comorbidities can contribute Treatment:
- Oral iron supplementation: 65-100 mg *elemental* iron every other day or three times weekly
    - Ferrous sulfate 325mg = 65mg elemental iron (FYI: improved absorption if taken with Vit C!)
    - Discuss that previously recommended 100-200 mg mg elemental iron divided into BID or TID
    - Newer evidence shows that this old dosing causes up regulation in hepcidin which prevents further GI absorption of iron, may alter gut microbiome, and may cause damage due to reactive oxygen species (ROS)
    - Expect 1g/dL rise in 4-6 weeks (If not meeting this, may need to look for source of bleeding or mal-absorptive conditions)
    - Treat for 3-6months to help replete iron stores, do not stop just because normalization of Hb
- Side effects: GI upset, metallic taste, constipation, dark stools
    - Frequently limit adherence to regimen

6. When is it appropriate to refer a patient for iron infusion therapy?

Table 3. Indications for Parenteral Iron Therapy.

Established indication
Failure of oral therapy
Iron intolerance or with low iron levels that are refractory to treatment (e.g., after gastrectomy or duodenal bypass, with *Helicobacter pylori* infection, or with celiac disease, atrophic gastritis, inflammatory bowel disease, or genetically induced IRIDA*)
Need for quick recovery (e.g., with severe iron deficiency in the second or third trimester of pregnancy or with chronic bleeding that is not manageable with oral iron, as may occur in patients with congenital coagulation disorders)
Substitution for blood transfusions when not accepted by patient for religious reasons
Use of erythropoiesis-stimulating agents in chronic kidney disease
Potential indication
Anemia of chronic kidney disease (without treatment of erythropoiesis-stimulating agents)
Persistent anemia after use of erythropoiesis-stimulating agents in patients with cancer who are receiving chemotherapy
Anemia of chronic disease unresponsive to treatment with erythropoiesis-stimulating agents alone
Potential indication with insufficient supporting data
Iron deficiency in heart failure
Transfusion-sparing strategy in surgical patients

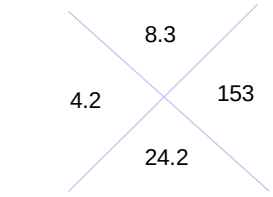
- The elderly often intolerant of PO supplementation, and have reduced absorption (PPIs, decreased acid production)
- IBD: taking PO iron can worsen disease activity; inflammation may interfere with Fe absorption

Potential questions for the expert:

- *Is it appropriate to just check a ferritin level as part of initial workup, if being mindful of cost-effective approach to diagnosis?*
- *Is a peripheral smear helpful in the evaluation microcytic anemia?*
- *What threshold to transfuse Hgb in the setting of CAD? Hgb< 8?*
- *Is ferrous gluconate better tolerated by patients?*
- *Can you comment on emerging evidence to dose Ferrous sulfate 325 mg PO once three times weekly?*

Case 2: A 67 y/o Caucasian male schedules an urgent visit because has been feeling increasingly lethargic and has been told he looks pale. He has a history of HTN, T2DM, and GERD. You order basic lab work: CBC, renal, TFTs, LFTs.

Labs



Renal: normal
TFTs: normal
LFTs: normal

B12: 253
Folate: normal

MCV- 106.4
MCH- 31
MCHC- 35
RDW-16

Diff: normal
Retic: 0.4%
Retic Index: 0.35

1. **What are some of the causes of macrocytic anemia?**
    - Decreased Production: (Low Reticulocyte Index) Megaloblastic changes
        - B12 deficiency – occurs in the setting of other autoimmune conditions
        - Folate deficiency – occurs in the setting of inadequate dietary intake, alcoholism, liver disease, certain meds (methotrexate, anti-epileptics)
    - Increased Production: (High Retic Index) – any high production state can have elevated MCV from the retics themselves
        - Hemolysis, blood loss, splenectomy
    - Large dyspmorphic cells: seen with HAART Therapy, hemoglobinopathies, myelodysplastic syndrome
    - Metabolic disorders: hypothyroidism

2. **What else do you want to know about his history?**

    Constitutional: fevers, chills, weight loss, night sweats (think MDS, infiltrative process) – ***pt denies***

    Neuro: any paresthesias – ***pt denies***

    Psych: mild depression, increased forgetfulness, decreased concentration – ***pt denies***

    GI: mild abdominal discomfort, occasional nausea and heartburn, diarrhea, glossitis – ***pt denies***

    Skin: rash, nail changes, hair changes - ***you tell the team that the patient reports vitiligo, sking change, and hair loss***

    Fam Hx: hypothyroidism and other autoimmune conditions ***you tell the team that the patients mother has hypothyroidism***

    Soc Hx: alcohol and IVDU ***you tell the team that he endorses rare EtOH only 2 drinks/ year; no h/o IVDU (think Hep C and other liver dx)***

3. **What other labs do you want?**
   Work up of macrocytic anemia

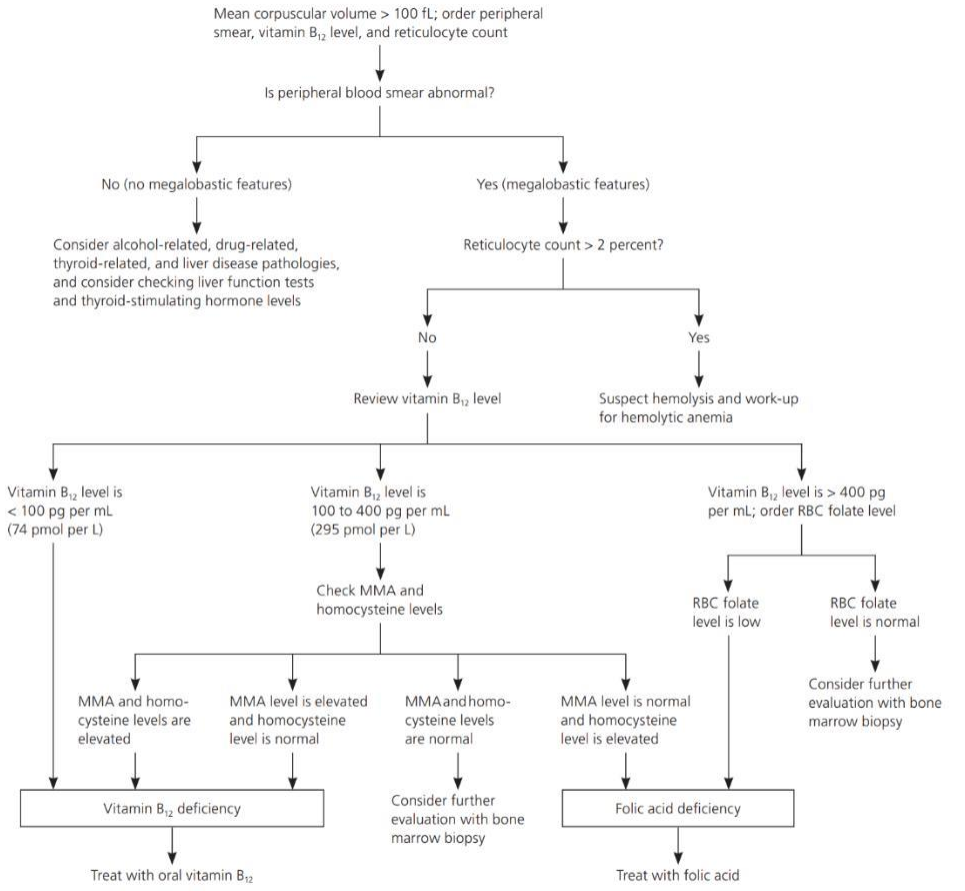
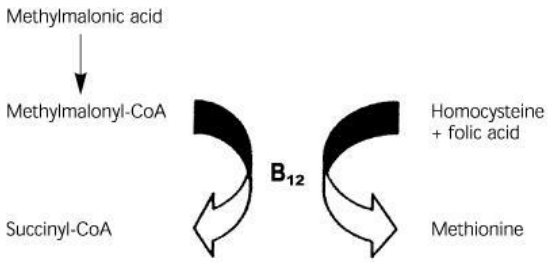


Figure 3. Algorithm for the evaluation of macrocytic anemia. (RBC = red blood cell; MMA = methylmalonic acid.)

- **Peripheral smear:** helpful for identifying megaloblastic features (ie. Hypersegmented neutrophils)
- MMA: elevated only in B12 deficiency
  - Studies have shown that up to 50% of B12 deficient people have serum B12 in the normal range



MMA much more sensitive.

Lab	"+LR"	"-LR"
B12<123	6.6	0.71
B12<280	1.8	0.6
MMA>0.36	2.19	0.3

- Homocysteine: can be high in B12 deficiency **and** folate deficiency

• Parietal cell antibodies: sensitive for pernicious anemia, not specific (seen in other autoimmune dx)
• Intrinsic factor antibodies: only 50% sensitive, but very specific for pernicious anemia • Schilling test, now seldom preformed

3. What are some common causes of B12 deficiency?

- Pernicious anemia
- Gastric surgery resulting in loss of parietal cells
- Bariatric surgeries causing malabsorption, resection of terminal ileum and IBD
- Achlorhydria - PPI use, most common cause in elderly
- Vegan diets/Tea and Toast diets - takes at least 6 months to deplete B12 stores, folate deficiency can occur much faster
- Chronic parasitic infections (giardia, Diphyllobothrium latum-Fish Tapeworm)
- Bacterial overgrowth and Pancreatic insufficiency
- Metformin

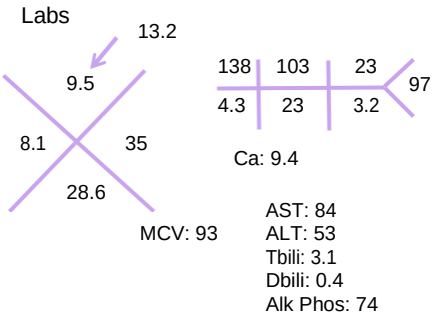
4. How should you treat a patient with B12 deficiency?

Oral supplementation is just as effective as IM based on a Cochrane review: high dose 1000-2000 mcg daily with expected improvement over weeks

- Oral also works for pernicious anemia
- Supplement gastric bypass pts with 1000 mcg daily (could consider IM if not responsive)

Break

Case #3: 44 y/o Caucasian female with no significant PMHx is brought to the ER by her husband for 2 days of fevers to 101F, lethargy, and confusion. Vitals T 101F BP 110/75, HR 96, RR 24, SpO2 94% on RA. She can't give you much of a history. You get basic labs.



1. What is alarming about the presentation and labs?

- Mental status changes + RR >/= 22 = +qSOFA (2 of following: SBP </= 100, RR >/= 22, AMS)
- Significant drop in Hgb
- Profound thrombocytopenia
- Renal dysfunction
- Transaminitis and indirect hyperbilirubinemia $\longrightarrow$ indicative of destruction

2. **What additional labs do you want now?**
   - Lactate dehydrogenase: ***2300*** (released from RBC, as well as areas of ischemia/necrosis in setting of thrombosis)
   - Retic count: ***12.5%*** -- increased production in setting of hemolysis and loss
   - Haptoglobin ***<10*** -- DECREASES in INTRAVASCULAR hemolysis by binding to hemoglobin then cleared by spleen
     - In extravascular hemolytic anemia, the splenic phagocytes remove erythrocytes from the circulation (i.e. no FREE hemoglobin). Therefore, haptoglobin is normal
   - Peripheral smear 1-18% ***schistocytes*** usually seen in TTP
   - PT/PTT: usually ***normal*** in TTP (elevated in DIC)
   - Fibrinogen: ***normal*** in TTP (low in DIC)
   - Direct coombs: ***negative*** (Postive in autoimmune hemolytic anemia)
   - ADAMTS13: will take several days to come back. It is a metalloprotease which cleaves very large von Willebrand factor multimers. If not cleaved reacts, then these long multimers react with platelets to cause thrombocytopenia, micro-thrombi, and the classic changes of TTP. Usually < 10% to give you TTP picture. In acquired TTP, autoantibodies are formed to ADAMTS13.

3. **What is your differential for hemolytic anemia?**
   - *Intravascular hemolytic anemia*: - microangiopathic**,** you see schistocytes.
     - TTP, DIC (much lower amount), malignant HTN, hemolytic uremic syndrome, mechanical valves, calcified aortic valves, eclampsia, HELLP syndrome
   - *Extravascular hemolytic anemia -* most also have some component of intravascular hemolysis
     - Immune-mediated: autoimmune hemolytic anemia (positive direct antiglobulin or coomb's test)
     - Drugs, malignancy, infections, transfusion related
   - *Intra- and Extra- Vascular: unstable cells*
     - G6PDH (fava beans/infections), Spherocytes, Thalassemia, Sickle Cell, PNH, Pyruvate Kinase Deficiency (Glycolysis problems)
   - *Infections:* malaria, bartonellosis, babesiosis, clostridium perfringens septicemia

4. **What is the diagnosis and how do you manage this patient?**

   Thrombotic thrombocytopenic purpura, characterized by pentad of signs and symptoms:
   - Thrombocytopenia
   - Microangiopathic hemolytic anemia
   - Neurologic abnormalities
   - Renal failure
   - Fever

   - Clinically, would be concerned when patient had thrombocytopenia, schistocytes and elevated LDH -
   More commonly acquired than inherited; often presents as single acute episode

   Treatment = Plasma exchange! Have to use plasma rather than albumin for plasmapheresis to replace ADAMTS13. If overnight or somewhere that doesn't have plasma exchange capabilities, then give FFP to replace ADAMTS13.

5. **Do you give platelet transfusions for that low PLT 35?**

   NO! It "adds fuel to the fire" and increases thrombosis. Only give platelets if patient is having serious bleeding (oozing doesn't count!) This is true of ALL thrombocytopenias. It as a general rule is not preferred but if your patient is bleeding (especially into a closed area i.e head) you must give platelets. Also gives back functioning ADAMTS13 in this case.

6. **How is TTP different from HUS?**
   - Acquired TTP is due to auto-antibody to ADAMTS13. Has increased neurologic symptoms.
   - HUS is due to shiga toxin producing bacterial infection, usually entero-hemorrhagic E.coli O157:H7.
     - Toxin binds to endothelial cells and inactivates ADAMTS13.
     - HUS usually preceded by bloody diarrhea, but not always.
     - Has increased renal symptoms.
   - Very hard to distinguish clinically. Likely treat patient as if it were TTP with plasma exchange

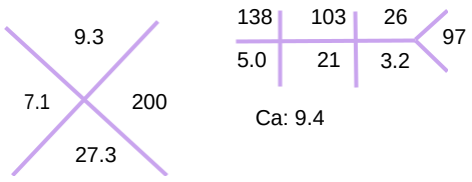
- ***Your team has a blank copy of the table listed below, discuss what lab results they would suspect for each of the listed conditions.***

	ITP	TTP	HUS	HIT	DIC
Thrombocytopenia:	Yes	Yes	Yes	Yes	Yes
Increased PT/INR:	No	No	No	+/-	**YES**
MAHA:	No	**YES**	**YES**	No	Yes
Fibrin/Fibrinogen:	Normal	Normal	Normal	Normal	**ABNL**
Ok to give Platelets:	Yes	No	No	No	Yes
Clots?	-	+++	+++	**++++**	++
Bleeding?	-	+	+	**-**	**++++**
Treatment	IVIG, Steroids	Plasmapheresis	Supportive, abx can worsen	D/c Heparin	Supportive, Cryo if fibrinogen <100

Case #4: 82 y/o Caucasian woman with hypertension, hyperlipidemia, lumbar spinal stenosis, hypothyroidism, CKD (b/l Cre 3) who presents for follow up. She has had recent problems with hyperkalemia, necessitating discontinuation of losartan that she was taking for HTN. She complains of not feeling good, mild exertional dyspnea, and low energy.

Meds: Amlodipine 10 mg daily, Levothyroxine 50 mcg daily, Pravastatin 20 mg daily

Labs



MCV: 80

1. **What additional tests should be ordered to evaluate the anemia?** Iron ***78*** (Normal 80-200)

   TIBC ***260*** (normal 250-435)
   Iron Sat ***20***% (normal 18-50%) Ferritin ***60***

   Reticulocyte count ***1%***
   B12 ***Normal***

   Folate ***Normal***

   Colonoscopy → 5yrs ago that was normal. No history to suggest chronic blood loss. Important to consider in the elderly as source of chronic blood loss

2. **What is the most likely cause of her anemia?**

   Anemia of kidney disease

   - Discuss pathophysiology of anemia in kidney disease:
     - Erythropoietin is produced in the renal cortex. When there is a reduction in functionin renal mass there is a decrease in erythropoietin production.
       - Expect normochromic, normocytic anemia with signs of underproduction (low retic count)
     - The modest increase in serum creatinine level underestimates the severity of kidney injury in this frail, older adult patient with reduced muscle mass.

3. **What treatment can be considered and what are the risks?**

   - Could consider EPO treatments recognizing that there is a black box warning:

     "For patients with CKD who are not on dialysis, one should consider starting ESA treatment only when the Hgb level is <10 g/dL and reduce or stop the ESA dose if the Hgb level exceeds 10 g/dL. For patients on dialysis, one should initiate ESA treatment when the Hgb level is <10 g/dL and reduce or interrupt the ESA dose if the Hgb level approaches or exceeds 11 g/dL"
   - Studies demonstrate an improved quality of life BUT

*TREAT Trial (ESRD Hg 13.5-14.5 v. 9.5-11.5) increased risk of fatal/non-fatal stroke with darbepoetin (HR 1.92)
*Increased incidence of thrombotic events, diastolic hypertension, and access thrombosis

- If treating with Epo, will also require iron replacement therapy to keep up with increased RBC production