Rethinking Common Labs: Pearls for the Hospitalist (plus some zebras)

David Krakow, MD

Director of Hospital Medicine

Emory University Hospital

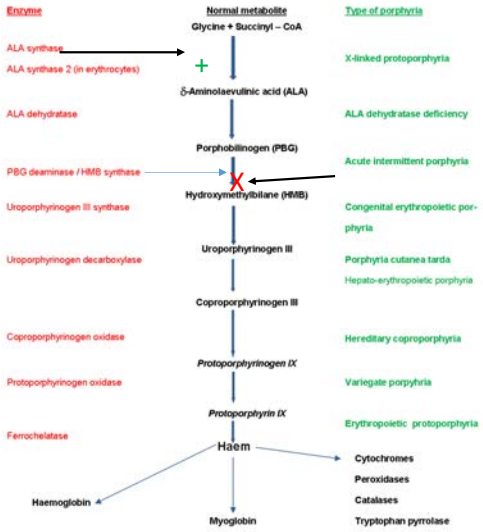
Assistant Professor of Medicine

No disclosures

28 F with multiple ER visits for acute N/V/abd pain. Pain is severe, diffuse, lasting several days and requires opiates. Intermittent lower ext weakness. Labs reveal hyponatremia. Workup unrevealing. Most recent episode followed new diet.

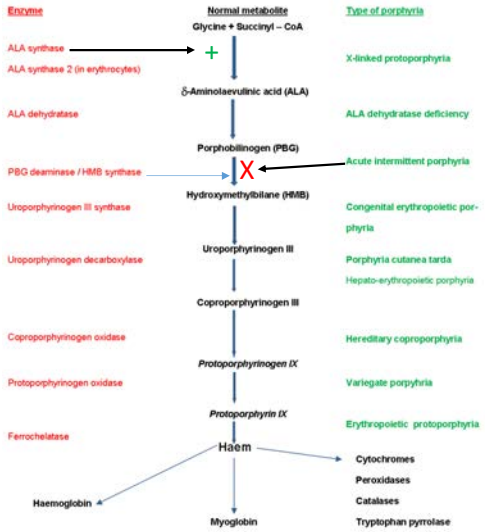
- WHAT DISEASE SHOULD BE IN YOUR DDX?

Acute Porphyria- focus on AIP



- Acute porphyria- ALAD, AIP, HCP, VP
- AIP is acute intermittent porphyria
- All 4 acute porphyrias(AIP is prototype) present similarly. **Neuropathic pain including abd pain and often weakness and hypona**.
- AIP is autosomal dominant with variable penetrance.
- Upregulation of ALAS1 leads to increase ALA and PBG. ALA is molecule that cause symptoms.
- ALAS1 is present in liver. CYPs require heme. Anything that stimulates CYPs will upregulate ALAS1 and more ALA, PBG will be produced leading to symptoms in patient's with AIP.
- ALAS1 stimulators: drugs, progesterone (luteal phase), decreased caloric intake, acute illness, smoking and ETOH.
- Always review meds for patients with AIP.

Acute Porphyria



- For AIP diagnosis send spot urine porphobilinogen (PBG). This test is nearly 100% sensitive and is 100% specific for acute porphyria (AIP is prototype) in setting of acute symptoms. ALA would be elevated in ALAD. Send urine total porphyrins as well because rarely urine (PBG) is normal if collected soon at the tail end of the attack.
- RBC PBG deaminase activity can be used to test for AIP in asymptomatic state and will be ½ normal in 90% cases.
- Acute porphyria tests: urine: PBG, ALA, total porphyrins. Plasma and fecal porphyrins. RBC PBGD enzyme activity
- Tx: IV D5/D10 until IV hematin available then hematin 4 mg/kg qd for at least 4 d. Inhibits ALA synthase. Stop offending meds that stimulate ALAS1
- Pb poisoning mimics acute porphyria. Pb blocks ALA dehydratase.↑ALA is thought to be the toxic metabolite that causes pain, neuropathy.
- Red/brown/purple urine is from oxidized porphobilinogen and from porphyrins
- Givosiran down regulates ALAS1. Given month to decrease frequency of AIP attacks

Acute Porphyria

- 28 F with multiple ER visits for acute N/V/abd pain. Pain is severe, epigastric, colicky, lasting several days and requires opiates. Intermittent lower ext weakness. Labs reveal hyponatremia. Workup unrevealing. Most recent episode followed EtOH ingestion.

- If you could send only 1 test which would it be?

  a. urine porphyrins

  b. 24 hour urine porphobilinogen (PBG)

  c. spot (random) urine porphobilinogen (PBG) with urine creatinine

  d. plasma porphyrins

Acute Porphyria

- 28 F with multiple ER visits for acute N/V/abd pain. Pain is severe, epigastric, colicky, lasting several days and requires opiates. Intermittent lower ext weakness. Labs reveal hyponatremia. Workup unrevealing. Most recent episode followed EtOH ingestion.

- If you could send only 1 test which would it be?
  - a. urine total porphyrins
  - b. 24 hour urine porphobilinogen (PBG)
  - c. **spot (random) urine porphobilinogen (PBG) with urine creatinine**
  - d. plasma porphyrins

ANION GAP

GOLDMARK – The new MUDPILES...

- **G**lycols - Ethylene/propylene glycol
- **O**xoproline
- **L**- lactate
- **D**- lactate
- **M**ethanol
- **A**spirin. Salicylates
- **R**enal failure
- **K**etoacidosis- AKA, DKA, starvation ketosis.

Mehta. Lancet, 2008

ANION GAP

60 yo malnourished pt admitted to ICU with sepsis from SBE and spinal abscess. Placed on acetaminophen 1000 mg QID for back pain.

- On Hosp day #4 , AG increases from 8 to 16.
- LFTS/lactate/ serum β-hydroxybutyrate all nl. No urine ketones
- What test to order?

Check 5-oxoproline level (also known as pyroglutamic acid)

- Dx: 5-oxoproline AG metabolic acidosis

GOLDMARK – The new MUDPILES...

- **G**lycols - Ethylene/propylene glycol
- **O**xoproline
- **L**- lactate
- **D**- lactate
- **M**ethanol
- **A**spirin. Salicylates
- **R**enal failure
- **K**etoacidosis- AKA, DKA, starvation ketosis.

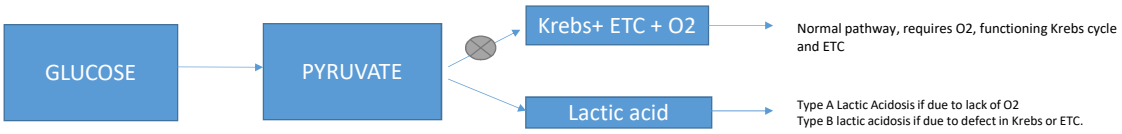
ANION GAP

55 F with extensive bowel resection for SBO 10 y ago. Over past 6 mo family notes episodic confusion after consuming large pasta meals. Pt admitted with confusion.

- AG= 20; lactate= 1 mmol/L (nl)
- What test is next?
- D- Lactate 7 mmol/L (elevated)- send out
- Dx: D- lactic acidosis due to short gut.
- Standard lactate (lactic acidosis) lab is L-Lactate
- SB malabsorption → excess carbs in colon → bacteria ferment to D- lactate.
- Rx oral antibiotic

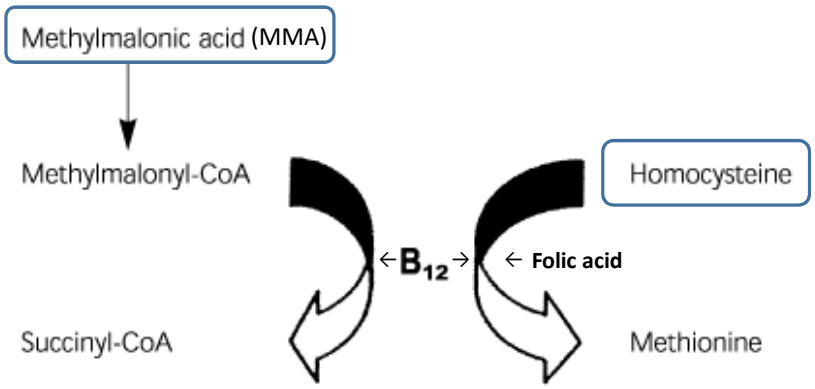
GOLDMARK – The new MUDPILES...

- **G**lycols - Ethylene/propylene glycol
- **O**xoproline
- **L**- lactate
- **D**- lactate
- **M**ethanol
- **A**spirin. Salicylates
- **R**enal failure
- **K**etoacidosis- AKA, DKA, starvation ketosis.



- 32 yo with HIV on AZT. Lactate 12 mmol/L. *ARV's may poison the ETC.*
- 45 yo DM with AKI with SCr 8 mg/dl. Lactate 13. *On metformin 1000 bid*
- 23 yo hyperemesis gravidarum. Confusion. 30lb wt loss. Lactate 14. *Thiamine undetectable*
- 67 yo metastatic RCC. Lactate 16. *Neoplasm related lactic acidosis.*
- 19 yo runner uses topical analgesic. Confused. Lactate 9. *Salicylate toxicity.*
- 45 yo rescued from house fire. Lactate 17. *Cyanide toxicity.*

B12



deficiency	homocysteine	MMA
folate	↑	nl
B12	↑	↑

B12 deficiency

- 72 yo with pancytopenia, AST 200 U/L, ALT 100U/L, LDH 800 U/L, T bili 3.5 mg/dL, indirect 3.0. hyperseg PMNs. MCV 120 fL. Ineffective hematopoiesis(bone marrow hemolysis) Dx?

Textbook B12 deficiency

- 81 yo with atrophic gastritis. + macrocytic anemia. MCV 118. Intrinsic factor ab + and parietal cell ab +. Dx?

Pernicious anemia- 3 tests: intrinsic factor ab, parietal cell ab, gastrin

- 22 yo vegan with leg weakness and paresthesias. Abuses " whippits"- nitrous oxide. Dx?

Subacute combined degeneration of the cord.
-posterior cord (position and vibration sense)
-lateral corticospinal tract (motor, spasticity)

B12 deficiency

- 67 yo on metformin. B12 is 167 (ref >190 ng/L)

Metformin causes b12 deficiency

- 23 yo with abd pain, SBO. B12 177 ng/L.

Dx: Crohn's. B12 absorbed in TI

- 34 yo with blistering rash, fatigue. B12 150 ng/L, ferritin 8 mcg/L, vit D 25-OH is 6 ng/mL. Dx?

Celiac. Rash is DH, check celiac ab panel, tissue transglutaminase IgA. Duodenal biospy.

Anemia

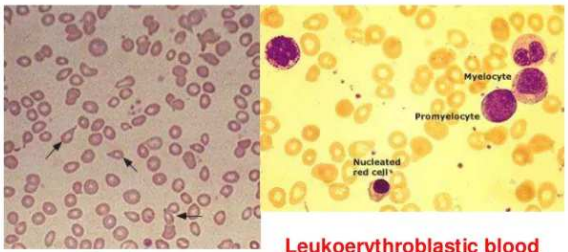
- **Anemia DDX: marrow defect, hemolysis or blood loss**
- **DDX: marrow defect**
- Nutritional (B1, B6, folate, iron, B12, malnutrition in general)
- Decreased erythropoietin (ESRD, inflammation, autoantibody)
- Endocrine- hypothyroidism, hypogonadism, adrenal insufficiency
- Sideroblastic anemia- defect hemoglobin synthesis. Ringed sideroblasts on BMBX. + pappenheimer bodies- peripheral smear. MDS, Cu def , ETOH, meds (linezolid)
- Primary bone marrow problem:
- 1. myelophthisic anemia- due to marrow infiltration. Peripheral smear= "leukoerythroblastic"= nucleated RBC, myelocytes, tear drop RBCs. Causes includes primary myelofibrosis or marrow infiltration from tumor (e.g., breast or prostate cancer) or infection (e.g., TB). Autoimmune connective tissue disease can cause marrow fibrosis and a myelophthisic anemia.
- 2. MDS, leukemia, aplastic anemia (pancytopenia from bone marrow failure), pure red cell aplasia
- **DDX: Hemolysis**
- **A. Congenital -** 1. hemoglobinopathy- sickle cell, thalassemia 2. membrane- hereditary spherocytosis 3. enzyme- G6PD deficiency
- **B. Acquired**
- 1. autoimmune- warm AIHA, cold agglutinins, paroxysmal cold hemoglobinuria(PCH). Alloimmune (transfusion reaction, delayed or acute)
- 2. MAHA- micro/macroangiopathic HA- prosthetic valve malfunction, march, AVM, TMA (MAHA + thrombocytopenia)
- 3. hypersplenism, liver disease (spur cell anemia)
- 4. infection- malaria, babesia, clostridium perfringens, bartonella
- 5. copper excess, Wilson's disease, rapid osmotic IVF
- 6. PNH- paroxysmal nocturnal hemoglobinuria – the only intrinsic cause of hemolysis that is acquired and not congenital.

Anemia

- 53 yo with newly diagnosed widely metastatic prostate cancer presents with fatigue. Found to have Hg 7. Peripheral blood smear reveals nucleated RBCs, myelocytes and tear drop cells. Bone Marrow biopsy reveals diffuse metastatic prostate cancer.
- This is a myelophthisic anemia from diffuse prostate cancer involvement of the marrow.
- The smear is called a leukoerythroblastic smear- immature WBC, nucleated RBC and tear drop RBC.
- Primary myelofibrosis would produce the same leukoerythroblastic smear.

Anemia- Leukoerythroblastic smear

Myelofibrosis



Teardrops

Leukoerythroblastic blood smear

Anemia- Hemolysis

- Hemolysis- suggested by increased reticulocyte, LDH, indirect bilirubin and decreased haptoglobin
- Extravascular v. intravascular- intravascular hemolysis suggested by dark urine (heme pigment, + u/a" blood"), + plasma free hemoglobin and urine hemosiderin
- Peripheral smear- spherocytes (HS, warm AIHA), schistocytes (TMA), bite/blister cells (G6PD), RBC agglutination (cold agglutinin disease), inclusions (infection)
- **DDX: Hemolysis**
- **A. Congenital -** 1. hemoglobinopathy- sickle cell, thalassemia 2. membrane- hereditary spherocytosis 3. enzyme- G6PD deficiency
- **B. Acquired**
- 1. autoimmune- warm AIHA, cold agglutinins, paroxysmal cold hemoglobinuria(PCH). Alloimmune (transfusion reaction, delayed or acute)
- 2. MAHA- micro/macroangiopathic HA- prosthetic valve malfunction, march, AVM, TMA (MAHA + thrombocytopenia)
- 3. hypersplenism, liver disease (spur cell anemia)
- 4. infection- malaria, babesia, clostridium perfringens, bartonella
- 5. copper toxicity, Wilson's disease, rapid hypoosmotic IVF (DW5)
- 6. PNH- paroxysmal nocturnal hemoglobinuria – the only intrinsic cause of hemolysis that is acquired and not congenital

1. Warm AIHA- + spherocytes, extravascular hemolysis. ddx meds (PCN), autoimmune. Coombs (DAT)+, IgG type. Ab coat RBC and are removed in spleen
2. Cold agglutinin disease- + agglutination of RBC. Intravascular hemolysis. False increase MCV. Coombs(DAT)+, C3 type. DDX: lymphoma, infection.
3. G6PD deficiency- bite cells on peripheral smear, Heinz bodies on peripheral smear (special stain, not seen on regular peripheral smear), G6PD level decrease
4. PNH- episodic intravascular hemolysis. Check peripheral blood flow cytometry for CD55, CD59 (RBC membrane proteins that are absent in PNH)
5. Thalassemia- target cells on peripheral smear

Hemolysis

45 yo with neurosyphilis on continuous IV PCN. Presents with fatigue on antibiotic day # 11.

- Hg 6 mg/dl, tbili 3.4 mg/dL (indirect 3.0), LDH 788, retics 30%, haptoglobin low. DAT+, IgG type. Smear shows spherocytes. Dx?
- *warm AIHA from PCN*

67 yo man with malfunctioning mechanical AoV. Hg 9, Tbili 4 mg/dL (indirect 3.2), LDH 1000 U/L. Smear shows schistos. Dx?

- *MAHA from AoV*

32 yo M presents with fatigue, back pain and dark urine a day after starting dapsone. Hg 6 mg/dL, LDH 1200 U/L, + bite cells on smear. Dipstick urinalysis shows "blood."Dx?

- *G6PD deficiency- Heinz body+ on special stain as well*

Hemolysis

76 yo presents with abd pain and found to have Budd Chiari. Hg 8 mg/dL, LDH 700 U/L, haptoglobin undetectable. Urine hemosiderin is positive confirming intravascular hemolysis. Flow cytometry shows absence of CD55 and CD59. Dx?

- *PNH: Rx: anti- C5 (eculizumab)*

23 yo with sickle presents with sickle pain episode. Retic 40%.

ABG: CO-Hg= 6% (carbon monoxide)

- Heme → biliverdin +CO → bilirubin.
  purple → green → yellow.

  Increase heme turnover → increase CO production.

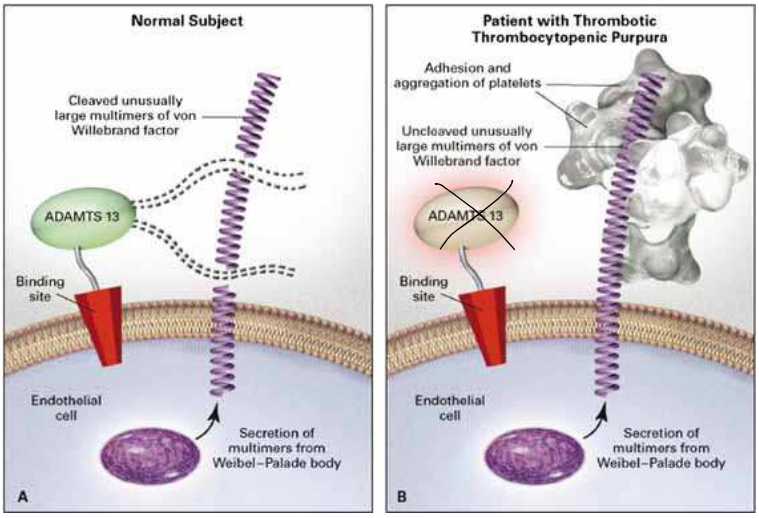
  Heme breakdown produces CO

Hemolysis- TMA

- MAHA- microangiopathic hemolytic anemia. Suggested by hemolysis with schistocytes on peripheral smear
- TMA- thrombotic microangiopathy- suggested by MAHA + thrombocytopenia. TMA pathology is microvascular thrombosis
- TMA leads to microangiopathic hemolysis by shearing of RBC passing through small blood vessels with microvascular thrombosis
- TMA leads to thrombocytopenia by platelet activation and consumption
- TTP- thrombotic thrombocytopenic purpura is prototypical TMA.
- Acquired TTP is an autoimmune disease with antibodies against the ADAMTS13 protein. This causes depletion of ADAMTS13
- ADAMTS13 protein cleaves large VWF proteins attached to endothelial cells. Large VWF proteins not cleaved (because of lack of ADAMTS13) cause microvascular thrombosis by aggregation of platelets with resultant MAHA and thrombocytopenia.
- **Evaluation for TTP:** check ADAMTS13 level and ADAMTS13 antibody. With TTP the ADAMTS13 level is usually <10% normal.
- **Treatment:**
- Start PLEX: to remove ADAMTS13 ab and large VWF and to replenish ADAMTS13 molecule with FFP as replacement fluid. FFP contains ADAMTS13
- Start prednisone and consider rituximab to decrease ADAMTS13 antibody production
- Consider caplacizumab- a monoclonal antibody that blocks VWF-platelet interaction.
- If there is no immediate access to PLEX, then give FFP prior to transfer to facility that has access to PLEX.
- FFP will provide the ADAMTS13 molecule but will not remove the anti-ADAMTS13 antibody nor the large VWF (PLEX required)
- Monotherapy with FFP is never a substitute for PLEX, only a temporizing measure.

TTP- thrombotic thrombocytopenic purpura

- MAHA is hemolysis + schistocytes
- TMA =MAHA + thrombocytopenia. TMA lesion is microvascular thrombosis.



Moake JL. N Engl J Med. 2002;347(8):589-600.

TTP

32 yo presents with confusion. Exam - petechiae. Hg 10 mg/dL, plts 45K, LDH 600 U/L, indirect bili 3 mg/dL, hapto - zero, retics 14%. peripheral smear: 12 schistos / HPF. Cr 0.9 mg/dL

TTP suspected…

TTP

Case cont'd

- ADAMTS13 level and anti-ADAMTS13 Ab drawn.
- PLEX (plasma exchange) started with FFP used as replacement fluid.
  - Rationale for PLEX (with FFP):
    - FFP replacement fluid provides the ADAMTS13
    - PLEX removes the ADAMTS13 Ab and large VWF protein
- ADAMTS13 level returns low at 3% and the anti-ADAMTS 13 Ab returns elevated. **TTP dx confirmed.**

- Tx: PLEX and prednisone, +/- rituxan to ↓ ADAMTS13 ab formation.
- Tx: Caplacizumab(anti-VWF)- monoclonal ab that binds VWF and blocks VWF platelet binding
- Tx: Caplacizumab 11 mg qs qd for 30 days after last PLEX treatment.
- TTP is the one TMA that usually does not usually present with ARF.

Primary TMA Syndromes- other than TTP

- 21 yo presents with abd pain and bloody diarrhea.

- Hg 11 mg/dL, plt 62, SCr 4 mg/dL; indirect bili 3 mg/dL, LDH 1100 U/L, haptoglobin- undetectable. + schistos on smear

- ADAMTS13, anti-ADAMTS13 ab drawn and return WNL. PLEX started after lab draw Dx?

- Shiga toxin from stool returns positive. PLEX stopped. Supportive care

- ST- HUS (hemolytic uremic syndrome)

- 55 yo drinks tonic H2O daily. Presents with anuric renal failure. Hg 9 mg/dL, plt 32. elevated indirect bilirubin, + schistos. Labs drawn and PLEX started

- ADAMTS13 level is normal and anti-ADAMTS13 ab is negative. Dx?

- Drug induced (immune) TMA – also known as DITMA from quinine.

- PLEX stopped. Supportive care

Primary TMA Syndromes	vs	TMA mimics
• TTP- hereditary and acquired • HUS (Shiga Toxin TMA) • DITMA- Drug induced TMA. Immune vs dose dependent • Complement Mediated TMA- inherited or acquired mutation in alternative complement pathway • Metabolism TMA- inherited mutation in MMACHC gene. Can appear like B12 def. Elevated plasma MMA and homocysteine • Coag TMA- inherited mutation in TM, plasminogen, DKGE		- Also presents with MAHA and thrombocytopenia. Treat underlying cause. • Pregnancy- HELLP • Malignant HTN • DIC • Neoplasm • CTD- lupus, APLS, Scleroderma renal crisis (SRC) • Stem cell transplant

TMA

- 28 yo 39 wk pregnant F presents with oliguric AKI with Scr 5.5 mg/dL, plts 68K, LDH 600, elevated indirect bilirubin and schistos on peripheral smear. HELLP is considered and fetus is delivered emergently. 1 day after delivery no improvement: Scr 6.7 mg/dL and plts 45K. ADAMTS13 labs drawn. PLEX started. No improvement. ADAMTS13 returns normal.

- Complement medicated TMA. Rx: Eculizumab (anti- complement antibody). High index of suspicion. Early addition of Eculizumab can preserve renal function. Vaccinate against Neisseria if time allows.

Eosinophilia

- Eosinophilia- defined as absolute eosinophil count (AEC) ~ >300 cells/ mcl
- Hypereosinophilia (HE)- defined as:
  1. AEC > 1500 on 2 occasions separated by > 1 month

     and/or

  2. evidence of tissue hypereosinophilia (e.g., bone marrow with >20% eos)
- Hypereosinophilic Syndrome (HES)- is HE + eosinophil mediated tissue damage
- Primary HES- underlying clonal neoplasm
- Secondary HES- any cause of HE with tissue damage. For example, Loeffler's myocarditis from Strongyloides infection.

Eosinophilia- etiology

- NAACP

- Neoplasm- Primary hypereosinophlic syndrome, lymphoma, leukemia
- Addison, AI, asthma, allergies
- CVD- Churg-Strauss (CSS) is eGPA(eosinophilic granulomatosis with polyangiitis)
- Parasites- strongyloides, toxocara, schistosomiasis, filariasis, hookworm, trichinella
- Other- ABPA, cholesterol emboli, eosinophilia myalgia syndrome, DRESS
- Other- GI dzs (e.g, eosinophilic esophagitis) Skin (E.fasciitis)

- 35 yo with asthma with foot drop, dark urine. Peripheral eos= 35%. ANCA+. Dx? eGPA
- 23 yo with CF with migrating infiltrates. Eos- 18%. IgE 1050 kU/L. Dx? Tx? ABPA. Pred and voriconazole
- 56 yo on pre-op testing for renal transplant has unexplained eosinophilia of 12%. Must check strongyloides ab. If positive then treat with ivermectin.

Eosinophilia

- NAACP

- Neoplasm- hypereosinophlic syndrome, lymphoma, leukemia

- Addison, AI, asthma, allergies

- CVD- Churg-Strauss (CSS) is EGPA(eosinophilic granulomatosis with polyangiitis)

- Parasites- strongyloides, toxocara, schistosomiasis, filariasis, hookworm, trichinella

- Other- APBA, cholesterol emboli, eosinophilia myalgia syndrome, DRESS

- Other- GI dzs (e.g, eosinophilic esophagitis) Skin (E.fasciitis)

- Immune suppression (e.g. prednisone) in pt with occult strongyloides can lead to strongyloides hyperInfxn syndrome and death.

- 24 yo with malaise, nausea, weight loss and hyperpigmentation. CBC shows eos 16%. Am cortisol =1 mcg/dL. Dx?

  Adrenal Insufficiency

- 67 yo s/p LHC (cardiac cath) last wk. Has ARF, livedo reticularis, and peripheral eosinophilia of 13%. Dx?

  Cholesterol emboli causing AKI

Coagulopathy

Coagulopathy

Interpretation of coagulation proteins

- Liver produces vit K **dependent** factors 2,7,9,10
- Liver produces vit K **independent** factor 5
- Endothelial cells make factor 8

Coagulopathy - liver failure, Vit k deficiency, DIC?

INR 3	Factor 2 (liver:vit K dep)	Factor 7 (liver: vit K dep)	Factor 5 (liver:vit K indep)	Factor 8 (endothelial)
Cirrhosis/liver failure	↓	↓	↓	nl/↑
Vit K deficiency	↓	↓	nl	nl/↑
DIC	↓	↓	↓	↓

	CASE	Factor 2 (> 80%)	Factor 7 (> 80%)	Factor 5 (>80%)	Factor 8 (>80%)	
Dx?	32 yo acetamin OD, INR 4.	12% (↓)	16% (↓)	19% (↓)	120%	Liver failure
Dx?	45 yo severe malnut. INR 2.5	20% (↓)	22% (↓)	93%	102%	Vitamin K def
Dx?	54 yo admitted with sepsis. INR 3	14% (↓)	18% (↓)	14% (↓)	19% (↓)	DIC