Rapid Fire Heme Cases for the Hospitalist

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DISCLOSURES

- Research funding: Biogen Idec, Genentech/Hoffman-LaRoche, Shire/Takeda
- Advisory Board: Bayer, Genentech, Shire/Takeda, Sigilon, Uniqure
- Consulting: Aspa, I-mAb, Sunovion

Today's Agenda

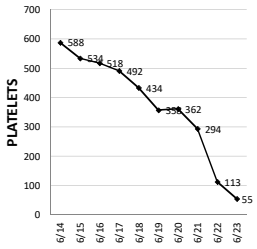
- Case-based boards-based
- Thrombocytopenia
- Anemia
- RBC Transfusion Guidelines

60yo woman with DM and HTN admitted for dyspnea

- HPI: 4 days dyspnea, T 98.2F, BP 140/86, O2 sat 89% RA, breath sounds decreased at bases, +1 LE edema
- BNP 8320, trop T <0.01, creatinine 1.9
- CXR: Bilateral infiltrates (pulmonary edema)
- Echo: LVEF 55%, RV dysfunction
- V/Q scan: Mismatched perfusion defects consistent with bilateral PE

60yo woman with DM and HTN admitted for dyspnea

- Submassive PE: RV failure, but normal BP
- IV furosemide and heparin drip
- Clinical improvement
- HD #6: Right calf pain and swelling
- Doppler U/S: Right femoral/popliteal DVT



*What is the next step?

- A. Transfuse platelets
- B. Place IVC filter
- C. Stop heparin, start bivalirudin
- D. Catheter-directed thrombolysis
- E. Check a d-dimer

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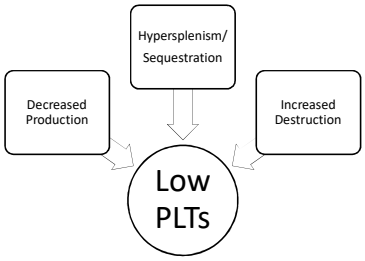
Thrombocytopenia: DDx



Thrombocytopenia: Work-up

- Peripheral blood smear:
  - Pseudo-thrombocytopenia: Platelet clumping
  - Microangiopathic hemolytic anemia (MAHA): Schistocytes
  - Sepsis: Toxic granulation, vacuoles
  - Myelophthisic (marrow invasion): Tear drops, left-shift
- DIC panel
- PF4 (HIT) Ab
- HIV, hepatitis, EBV, CMV
- ANA, lupus anticoagulant
- Ultrasound: Spleen size

When Do I Order Anti-PLT Ab?

NEVER

4 T's for HIT syndrome

- Thrombocytopenia:
  - PLTs fall >50% → 2 pts
  - PLTs fall 30-50% → 1 pt
  - PLTs fall <30% → 0
- Timing:
  - Onset 5-10d from heparin start → 2 pts
  - Onset >10d → 1 pt
  - Onset <5d → 0
- Thrombosis:
  - New clot or skin necrosis → 2 pts
  - Progressive or suspected → 1 pt
  - None → 0
- Other causes:
  - None → 2 pts
  - Possible → 1 pt
  - Definite → 0

- Total:
  - <3: Low suspicion
  - 3-5: Intermediate suspicion
  - >5: High suspicion
- If intermediate or high:
  - D/C all heparin **including flushes**
  - **Reverse warfarin with vitamin K**
  - **Start direct thrombin inhibitor** (bivalirudin or argatroban)
  - Check anti-PF4 Ab

Negative predictive value: 99%

J Thromb Haemost 2006;4:759-65

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Heparin-Induced Thrombocytopenia

- Risk factors:
  - Heparin > enoxaparin
  - Orthopedic > cardiac surgery > medical patients
- Diagnosis:
  - **4-T score: Negative predictive value 99%**
  - Anti-PF4 Ab: sensitivity >97%, specificity 74-94%
  - SRA: Sensitivity 95%, specificity 95%
- Risk of VTE continues for >1 month
  - **Anticoagulate 4-6 weeks if no clot**
  - Anticoagulate at least 3 months with clot
  - Start warfarin after PLTs are stable or >150k

My 4 T's for Thrombocytopenia

- Thrombocytopenia:
  - PLT <5: ITP, meds, bone marrow disorders (MDS, leukemia, aplastic anemia)
  - PLT <50: TTP/HUS
  - PLT 40-150: HIT, hypersplenism, infections
  - Any PLT count: Meds
- Timing of decline:
  - Acute: Meds, infection, HIT (5-10 days)
  - Subacute: Leukemia, ITP
  - Chronic: MDS, ITP
- Thrombosis: HIT syndrome, APLS, malignancy, DIC, (ITP!)
- Other causes of thrombocytopenia: ITP vs. other

66yo woman with DM, HTN, pneumonia: Thrombocytopenia

- HPI: Fevers, malaise, and productive cough
- PMHx: DM, hypertension
- MEDS: Insulin, lisinopril
- Exam: Appears unwell, lethargic, T 101.4F, BP 70/30, HR 120, O2 sat 90% RA, crackles at left base, trace ankle edema
- IV fluids, norepinephrine gtt, cefotaxime, levofloxacin, and vancomycin, enoxaparin
- 3rd hospital day: Platelets fell from 340k to 90k
- WBC 11.3, HCT 34%, MCV 88, PLT 90k, PT 12.6, INR 1.0, PTT 32, fibrinogen 290, BUN 30, creat 1.2

*66yo woman with DM, HTN, pneumonia: Thrombocytopenia

- What is the most likely cause of her thrombocytopenia?
- A) HIT
- B) ITP
- C) DIC
- D) Drug-induced thrombocytopenia
- E) MDS

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Drug-Induced Thrombocytopenia

- Suspect: Antibiotics especially…
  - TMP-SMX, penicillins, cephalosporins, vancomycin
  - Quinine, quinidine
  - Oxaliplatin, gemcitabine
  - Carbamazepine, phenytoin
  - Heparin
- Consider drug-specific platelet antibodies
- Onset: 1-2 weeks
- Recovery: Within 1 week (possibly up to 4 weeks)

36yo woman with no PMHx: Thrombocytopenia

- HPI: URI previous week, then developed rash
- PMHx: None
- MEDS: None
- Exam: Afebrile, 110/80, HR 80, O2 sat 98% RA, petechiae and ecchymoses
- WBC 7.6, HCT 38%, MCV 88, PLT 2k, PT 12.6, INR 1.0, PTT 32, fibrinogen 290, BUN 30, creat 1.2
- Smear: Confirms severe thrombocytopenia

*36yo woman with no PMHx: Thrombocytopenia

- WBC 7.6, HCT 38%, MCV 88, PLT 2k, PT 12.6, INR 1.0, PTT 32, fibrinogen 290
- What treatment should be tried first?
  - A) Dexamethasone
  - B) Prednisone
  - C) Rituximab
  - D) Plasmapheresis
  - E) Stem cell transplant

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ITP: Key Points

- Isolated thrombocytopenia: WBCs and RBCs are normal
- Diagnosis of exclusion
- WARNING: Wet purpura
- Chronic, relapses common
- Dexamethasone 40mg PO daily x4 days is standard of care

RCT: Dexamethasone better than prednisone

- Dex 40mg PO x4d vs. prednisone 1mg/kg x4wks, then taper
- n=192

- Response Rate:
  82.1% vs 67.4%, *P* = .044
- CR (PLT >100k):
  50.5% vs 26.8%, *P* = .001
- Time to response:
  3d vs 6d, *P* < .001
- Sustained response:
  40.0% vs 41.2%, *P* = .884

Blood 2016;17:296-302

ITP: Treatment

- Steroids: Dexamethasone 40mg PO daily x4d
- IVIG
- Rituximab (anti-CD20 mAb): Targets B-cells
- TPO agonists: Romiplostim, eltrombopag, avatrombopag
- Splenectomy
- Fostamatinib: Syk inhibitor → inhibits macrophage clearance

- Not necessarily in this order

Anemia by MCV

Microcytic	Normocytic	Macrocytic
Iron deficiency	Anemia of CKD	Megaloblastic anemia
Thalassemia	Anemia of Inflammation	Alcohol/liver disease
Anemia of Inflammation	Acute blood loss	Reticulocytosis
Lead poisoning	Mixed	Meds: Hydroxurea, AZT, MTX, TMP-SMX, phenytoin, valproate, azathioprine, imatinib
		MDS/AML, aplastic anemia

Anemia

Low Retic count & Normal Bili/LDH	**High Retic count & Normal Bili/LDH**
Hypoproliferative Anemia	Blood Loss
Low Retic count & High Bili/LDH	**High Retic count & High Bili/LDH**
Ineffective Erythropoiesis	Hemolytic Anemia

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Hemolytic Anemia

- Lux: "Failure of the red cell membrane"

INTRAVASCULAR	EXTRAVASCULAR
RBC destruction within vessel	RBCs removed by spleen/liver
DIC	Warm autoimmune HA
TTP/HUS	Cold agglutinin disease
Drug-induced HA	Drug-induced HA
PNH	Thalassemia
PCH	Hereditary spherocytosis
ABO mismatch transfusion rxn	Delayed transfusion rxn
G6PD, sickle cell, infections	G6PD, sickle cell, infections

Schistocytes
Helmz bodies
Bite cells
Sickle cells
Spherocytes
Agglutination
Target cells
Helmz bodies
Bite cells
Sickle cells

Case: 32yo woman with fever and rash

- HPI: Fever started 3 days ago, she noticed a rash on her arms and legs today
- Exam: T 38.4C, mild scleral icterus, petechiae
- WBC 8.2, HCT 27, MCV 94, PLT 12
- PT, PTT, fibrinogen normal
- Retics 9%
- BUN 31, creat 1.4

Case: 32yo woman with fever and rash

- What is the most likely diagnosis?
  - A) Iron-deficiency anemia
  - B) ITP
  - C) Thrombotic microangiopathy (TMA)
  - D) Acute liver failure
  - E) Acute promyelocytic leukemia (APML)

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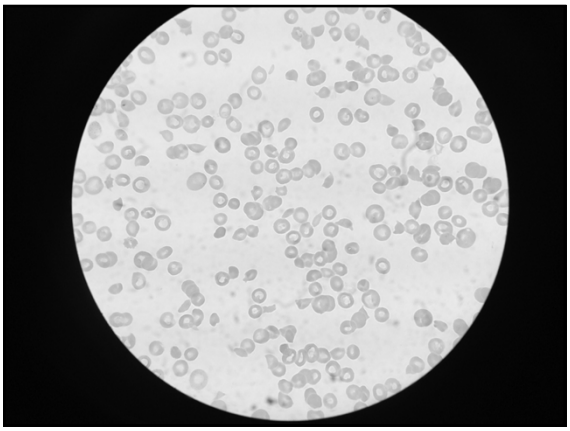

TTP/HUS

The "Classic" Pentad:

- **SCHISTOCYTES = MAHA (microangiopathic hemolytic anemia)**
- **THROMBOCYTOPENIA**

- Neurologic abnormalities
- Acute kidney injury
- Fever

- High LDH
- Normal coags

TTP: Treatment

TTP is uniformly fatal without plasmapheresis

NEJM 1991;325(6):393-7

TTP: Key Points

- Mobilize troops:
  - Examine smear for schistocytes
  - STAT page Hematology & Blood Bank for plasmapheresis
  - Dialysis-bore central line
  - Don't rest until pheresis starts!
- ADAMTS13 activity and inhibitor level PRIOR TO PHERESIS

Anemia

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Low Retic count & High Bili/LDH	**High Retic count & High Bili/LDH**
Ineffective Erythropoiesis	Hemolytic Anemia

Ineffective Erythropoiesis

- Erythropoiesis with early cell death
  - Can look like hemolysis, but without retics
- Etiology:
  - B12 and Folate Deficiency
  - MDS
  - Thalassemia

Case: 66yo man with dyspnea

- HPI: Exertional dyspnea worsening over 3 weeks, occasional lightheadedness
- PMHx: Osteoarthritis
- Meds: Naproxen, aspirin 81mg

Case: 66yo man with dyspnea

LAB TEST	**8 Months Earlier**	**Now**
WBC	6.3	8.1
RBC	4.8	2.4
Hb	13.2	7.5
HCT	41%	22.5%
MCV	93	81
PLT	188	480
Retic count		1.1%
Creatinine		0.9

Case: 66yo man with dyspnea

- What is the most appropriate treatment for this patient?
  - A) EPO injection
  - B) Iron PO supplement
  - C) IV iron
  - D) pRBC transfusion
  - E) Hydroxyurea

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Pearl: Believe ferritin

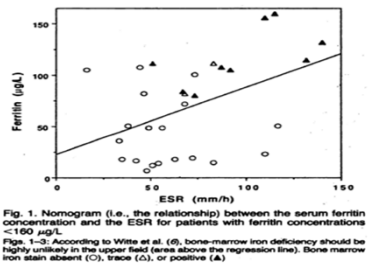
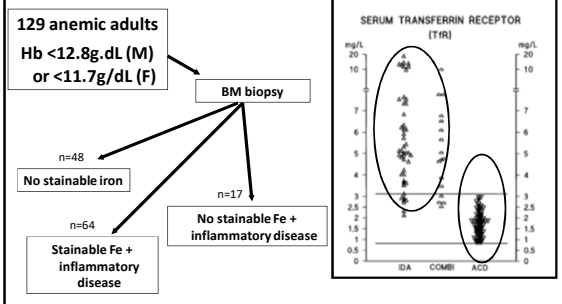


Fig. 1. Nomogram (i.e., the relationship) between the serum ferritin concentration and the ESR for patients with ferritin concentrations <160 µg/L.
Figs. 1–3: According to Witte et al. (6), bone-marrow iron deficiency should be highly unlikely in the upper field (area above the regression line). Bone marrow iron stain absent (○), trace (△), or positive (▲)

Patients with chronic diseases (RA, IBD, infections, other)

Clin Chem 1991;37:560-3

Serum Transferrin Receptor



Punnonen et al. Blood 1997;89:1052

Iron-deficiency Anemia

- Ferritin is the best!
- Mentzer index = MCV/RBC
  - Iron deficiency M.I. > 13
  - Thalassemia M.I. < 13
- Iron deficiency causes reactive thrombocytosis
- IV iron for rapid response, PO intolerance, malabsorption
- Safe in pregnancy: Iron sucrose, ferric gluconate, iron dextran
- Endoscopy?
- Iron must be repleted (ferritin >100) before using EPO

RBC Transfusion Threshold RCTs

STUDY	THRESHOLDS	N	OUTCOMES
ICU NEJM 1999	Restrictive: Hb <7 Liberal: Hb <10	838	No difference in 30-day mortality (restrictive better in less severe patients or age <55)
TRISS (Transfusion Requirements in Septic Shock) NEJM 2014	Restrictive: Hb <7-7.5 Liberal: Hb <10-10.5	1005	No difference in mortality and ischemic events
Severe acute upper GI bleeds NEJM 2013	Restrictive: Hb <7 Liberal: Hb <9	921	Restrictive: Reduced transfusions and adverse events and improved 6-week survival
TRIGGER: Severe acute upper GI bleeds Lancet 2015	Restrictive: Hb <8 Liberal: Hb <10	936	No differences in bleeding, thrombosis, ischemic events, infections, mortality, QUALY

RBC Transfusion In Cardiac Surgery: Controversy Laid to Rest

STUDY	THRESHOLDS	N	OUTCOMES
TRACS: Elective cardiac surgery JAMA 2010	Restrictive: HCT <24 Liberal: HCT <30	512	No difference in 30-day mortality and inpatient complications
TITRe2: Elective cardiac surgery NEJM 2015	Restrictive: Hb <7.5 Liberal: Hb <9	2007	No difference in 3-month ischemic events, infections, hospital LOS Liberal: 30-day mortality rate lower (1.9% vs. 2.6%) – secondary outcome
TRICS III: Moderate-high-risk cardiac surgery NEJM 2017 NEJM 2018	Restrictive: Hb <7.5 Liberal: Hb <8.5 (non-ICU) or <9.5 (ICU)	5243	No differences in 1-month and 6-month mortality, ischemic events, readmission, coronary revascularization – primary outcome

Summary: RBC Transfusions

- Many RCTs, meta-analyses, systematic reviews support **RESTRICTIVE RBC transfusion**:
- Transfuse if Hb <7-8
- Saves RBC Units and $$$
- No difference in outcomes
- Unresolved questions in cancer surgery patients, elderly, and orthopedics

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