Academic Half Day – Heme Onc Emergencies
Facilitator Guide

Case 1

You are on the night float intern and you get a page from a nurse saying that a patient on the 7Wollman team has a fever. You glance at your sign out and see:

Ms. A Ensee is a 62-year-old woman admitted for chemo induced nausea and vomiting. She completed her third cycle of adjuvant epirubicin and cyclophosphamide chemotherapy for breast cancer 8 days ago.

Vitals are: T 38.8 °C (100.8 °F), BP 110/60 mm Hg, HR 90/min, RR 16/min, SpO2 98%. You ask them to get a rectal temperature and it is 101.4.

1. **How do you triage this call? What information do you want to know?**

- Subjective
  - N/V nearly resolved
  - Denies all infectious symptoms (hx should focus on identifying source of infection)
- Examination
  - Normal exam: should focus on identifying source of infection (ex:look for central venous catheter, chemo ports, mucositis)
- Morning labs that day:
  - Hgb 9.2 g/dL
  - WBC 0.65 x 10^9/L (can also be expressed as 650 cells/mm^3, cells/uL)
  - 18% PMNs (0.12 x 10^9/L, or 120 cells/mm^3, cells/uL)
  - Platelets 112 x 10^9/L
  - Otherwise normal labs

Facilitators: get them to think about what would make this situation high risk/emergent vs not --- what is a fever and when is a fever dangerous?

- **Neutropenic fever is an emergency!** ---

2. **What is neutropenia? What is a fever?**
   - This definition is variable
   - Generally: ANC <1500
     - <1500: mild
     - <1000: moderate
     - <500: severe
   - **Definition for febrile neutropenia:** ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48hrsIDSA: single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period
3. **Should we have checked a rectal temp?**
   - No, increased risk of translocation of bacteria across the colonic mucosa

4. **What are your next steps in the management of a pt with neutropenia and fever?**

Neutropenic fever is an emergency! Each increase of 1h in the time to antibiotics raises the risk of mortality within 28 days by 18%. Recall for all patients with sepsis, this number is in the 7-12% range, even higher when neutropenic.

- IDSA recommended workup:
  - At least 2 sets of blood cultures + from any lines/ports/catheters
    - Note this is a special case for line cultures!
  - Additional workup as clinically indicated (ex: CXR if PNA sx or UA if urinary sx)
  - If pneumonia, get sputum cx.

Treatment: Must start antibiotics within 1hr of dx

- ALWAYS need anti-pseudomonal B-lactam agent
  - Cefepime, OR
  - A carbapenem (meropenem or imipenem-cilastatin, note Ertapenem does NOT cover PSA), OR
  - Piperacillin-tazobactam
- Vancomycin (or other agents active against aerobic gram-positive cocci) **not** recommended as standard part of the initial empiric antibiotic regimen for febrile neutropenia (common misconception)
- GNR bacteremia most frequently identified infection, although documented only 25-30% of the time
  - due to translocation of bowel flora due to epithelial breakdown in the setting of high dose chemotherapy

5. **How would your antibiotic selection change if your assessment revealed the following?**
   a. **Dyspnea, cough, right basilar crackles + consolidation on CXR?**
   b. **Purulent drainage at site of central venous catheter?**
   c. **Skin erythema and tenderness?**
   d. **Oral mucositis?**

All warrant addition of GPC coverage, probably with vancomycin.

- Vancomycin (or other agents active against aerobic gram-positive cocci) **not** recommended as standard part of the initial empiric antibiotic regimen for febrile neutropenia (common misconception)
- Should be considered for specific clinical indications

TABLE 11. Indications for the Addition of a Gram-Positive Antibiotic in the Empirical Management of Febrile Neutropenia
Hypotension or hemodynamic instability
Sepsis syndrome
Radiographically documented or strongly suggested pneumonia
Known colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant streptococci
Blood cultures positive for gram-positive bacteria
Skin or soft tissue infections
Severe mucositis
Previous use of fluoroquinolones as prophylactic therapy
Suspected catheter-related infection

6. **How would you adjust anti-microbials in the following scenarios?**
   a. **3 days later, remains hemodynamically stable, afebrile, all cultures are negative.**
      i. In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery
      ii. Empiric antibiotics should be continued until ANC is >500 cells/mcL as long as fever has resolved
      iii. If an infection is documented, antimicrobials should be de-escalated and continued for the duration appropriate for that infection
   b. **5 days later, hemodynamically stable, febrile to 101F despite broad spectrum antibiotics, all cultures remain negative.**
      i. Add GPC coverage if not already done and add empirical antifungal coverage
         - Antifungals should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen with no identified fever source OR hemodynamic instability
   c. **2 days later, the patient remains febrile at 101, HR 103, becomes hypotensive to 82/51 despite 2L IVF boluses, RR 22, 90% on RA. Repeat lactic acid has gone from 2.0 to 3.6 and they are becoming more confused. What is the diagnosis now? What is their qSOFA score?**
      i. Septic shock
      ii. The qSOFA=3 (AMs, RR 22 or greater, systolic BP <100)
      iii. Reminder that hemodynamic instability in setting of severe neutropenia is an indication to broaden to include GP coverage and antifungals.

Case #2

While on night float in the MSD when the nurse notifies you that one of the patients is having episodes non-sustained V-tach. You glance at your sign out and see:

Mr. Eurik is a 23 yo male who has been diagnosed with ALL. He started induction chemotherapy this morning.

Vitals are: 98.8 °F, BP 120/72 mm Hg, HR 100/min, RR 20/min, SpO2 98%

1. **How do you manage this call?**

Gather additional hx as learners ask:

- GET A 12-lead EKG!
- Subjective
    - Nausea, numbness and tingling in hands and feet, muscle cramps (hypocalcemia)
- Exam – normal
- Tele – frequent runs of NSVT lasting from 3-10 seconds
- Labs (obtained overnight at time of evaluation)
    - Na 142, K 6.5, Cl 106, CO2 24, BUN 27, Cr 2.2, Glucose 107
    - Ca 6
    - PO4 8
    - Mg 1.8
    - Uric acid 13
    - Baseline normal renal panel

Basic differential for VT: **electrolyte abnormalities**, ischemia, hypoxia

Facilitators: key here is recognizing that this patient has a high risk for electrolyte abnormalities due to risk of tumor lysis syndrome in someone who just started chemo for a proliferative leukemia.

Report of VT should raise strong suspicion for electrolyte abnormalities in this young patient and guide further investigation.

2. **What lab abnormalities do you expect to see in tumor lysis syndrome?**

- Hyperuricemia - released from purine breakdown from DNA in dying tumor cells
- Hyperphosphatemia - released from phosphate backbone of DNA of tumor cells
- Hyperkalemia - recall high intracellular K+, released from dying cell cytoplasm
- HYPOcalcemia - calcium chelates the phosphate being released in the serum and reduces concentration of free calcium

3. **Does this patient have tumor lysis syndrome? How do you diagnose TLS?**

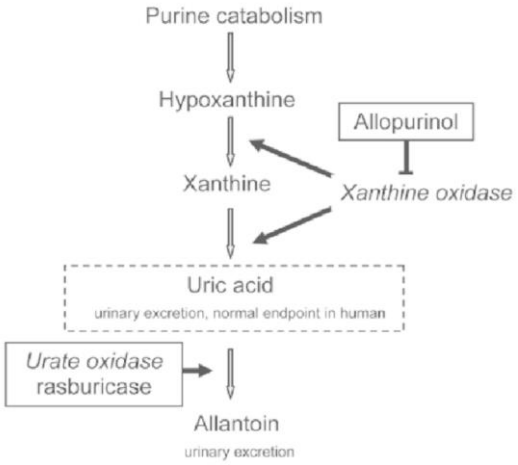
- TLS can be characterized as either lab TLS or clinical TLS
    - Cairo-Bishop definition of laboratory TLS
        - development of at least 2 of the lab abnormalities OR ≥ 25% change in 2 values from baseline value
    - Cairo-Bishop definition of clinical TLS
        - Clinical TLS is defined as laboratory TLS + one or more signs of end organ damage that was not directly or probably attributable to a therapeutic agent

Laboratory tumor lysis syndrome
Uric acid ≥8 mg/dL (≥476 μmol/L) or 25% increase from baseline
Potassium ≥6.0 mEq/L (≥6.0 mmol/L) or 25% increase from baseline
Phosphorus ≥4.5 mg/dL (≥1.45 mmol/L) or 25% increase from baseline
Calcium ≤7 mg/dL (≤1.75 mmol/L) or 25% decrease from baseline
Clinical tumor lysis syndrome
Presence of laboratory tumor lysis syndrome and one or more of the following criteria
Creatinine ≥1.5 times the upper limit of normal
Cardiac arrhythmia
Seizure
Sudden death

4. **How do you acutely manage Mr. Eurik's TLS? Which problem is going to kill him first?**
    a. Treat electrolyte abnormalities!
        i. Hyperkalemia
            - Immediate treatment: calcium (usual doses calcium gluconate 1-2 g or calcium chloride 500-1000 mg infused over 2-3 minutes), 10 units IV insulin + 1 amp D50
        ii. Hypocalcemia / Hyperphosphatemia
            - For asymptomatic patients no intervention is recommended
            - Symptomatic hypocalcemia should be treated with calcium at the lowest doses required to relieve symptoms.
            - Administration of calcium theoretically raises risk of calcium-phosphate precipitation, worsening crystalline nephropathy. Phosphate binders can be started.
    b. Aggressive IV Fluids &/or diuresis
    c. Rasburicase 3mg (fun fact rasburicase generates hydrogen peroxide which causes significant oxidative stress and individuals with G6P deficiency can get severe hemolytic anemia with rasburicase)
    d. Allopurinol (does not decrease uric acid already produced) - really more of a prophylactic agent
    e. Initiation of renal replacement therapy if indicated
    f. Monitor electrolytes q4-6 hours

Facilitators: can discuss metabolic pathway of TLS is there is time (probably not though)

-
- Treatment of established TLS requires rasburicase (urate oxidase)
- Urate oxidase metabolizes uric acid into allantoin which is much more soluble



5. **Who is at risk of TLS and how can tumor lysis syndrome be prevented?**

Because TLS can be fatal, the main principles of management are by identification of high-risk patients and initiation of preventive therapies!

- Must assess risk for TLS:

- Although TLS has been reported with virtually every type of tumor, it is typically associated with bulky, rapidly proliferating, chemo-sensitive tumors
    - Most common in aggressive/acute heme malignancies and high-grade lymphomas (ie: Burkitt's)
    - Most commonly occurs after initiation of anticancer therapy but may occur spontaneously
    - *Facilitators: emphasize that this list is fluid and not for memorization. Key is to know that different markers are used to stratify risk and that preventative strategies are based on level of risk. NO need to go through all, just understand concept.*

Risk category	Malignant disease	Prophylaxis
Low-risk disease	Solid tumor[c] Multiple myeloma CML CLL[d] Indolent NHL Hodgkin lymphoma AML (WBC <25,000/μL and LDH <2 × ULN)	Monitoring (daily laboratory tests) Intravenous hydration (3 L/m^2 daily) Consider allopurinol
Intermediate-risk disease	AML (WBC 25,000-100,000/μL) AML (WBC <25,000/μL and LDH ≥2 × ULN) Intermediate-grade NHL (LDH ≥2 × ULN) ALL (WBC <100,000/μL and LDH <2 × ULN) Burkitt lymphoma (LDH <2 × ULN) Lymphoblastic NHL (LDH <2 × ULN)	Monitoring (laboratory tests every 8-12 h) Intravenous hydration (3 L/m^2 daily) Allopurinol for up to 7 d
High-risk disease	ALL (WBC ≥100,000/μL and/or LDH ≥2 × ULN) Burkitt lymphoma (stages III/IV and/or LDH ≥2 × ULN) Lymphoblastic NHL (stages III/IV and/or LDH ≥2 × ULN) IRD with renal dysfunction and/or renal involvement IRD with elevated uric acid, potassium, and/or phosphate	Monitoring (laboratory tests every 6-8 h) Intravenous hydration (3 L/m^2 daily) Rasburicase (consider 3 mg fixed dose)

- Prevention:
    - Low risk --> IV hydration
        - goal to maintain UOP ≥ 2 ml/kg/h
        - Discuss avoiding LR or normosol due to potassium content
    - Intermediate risk --> IVF + allopurinol up to 7 days
    - High risk --> IVF + rasburicase

---------- BREAK ----------

Case #3

Mr. Roids is a 75yo male who presented to the ER complaining of shortness of breath and cough for 2 months. His symptoms have been worsening. He is now dyspneic with ambulation and his cough is productive of blood-tinged sputum. On review of systems, the patient reports fatigue, 20lb unintentional weight loss over the last 2 months, back pain, weakness, and falls. His back pain is worsened by movement. He has a 70 pack-year history of smoking and does not take any medications.

In the ED the patient is unable to urinate. A foley catheter is placed and > 400 cc of urine is obtained within the first 15 minutes.

Vitals: T 97.9, BP 135/77, HR 95, RR 18, SpO2 95% on 2 L O2

Additional details if they ask:

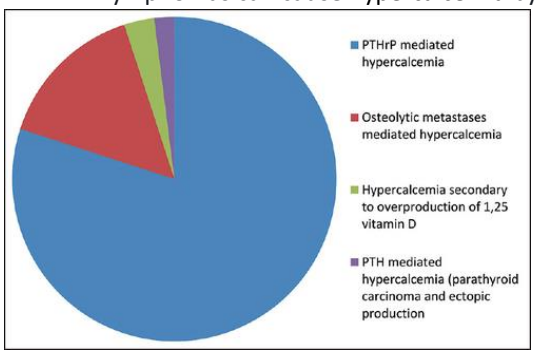
- Exam
    - Clothes are ill-fitting and appear too large

- He can lift his legs off the bed, but he is unable to oppose any force
- Hyperreflexia of patellar and achilles reflexes
- Increased tone in lower extremities
- Lower extremity sensation of light touch is diminished bilaterally up to his umbilicus
- Toes are upgoing bilaterally

1. **What do you think of this presentation? What are your worried about and what orders will you be placing?**
    a. High suspicion for pulmonary malignancy with vertebral metastases and cord compression.
    b. Sequence of symptoms for malignant spinal cord compression:
        i. back pain 1st à motor symptoms à sensory symptoms à bowel/bladder dysfunction
        ii. Back pain can precede weakness by weeks to months
    c. ~20% of cases of malignant spinal cord compression (MSCC) are among patients with no previously established diagnosis of malignancy
        i. malignancies that are most strongly associated with MSCC are breast, lung, and prostate cancer (accounting for 21%, 23%, and 18% of cases of MSCC, respectively)
    d. Reflexes are brisk if the lesion impinges on the spinal cord
        i. If compression is in the lumbar region leading to compression of the cauda equina, hypoactive reflexes would be expected.
    e. Total spine MRI W&WO contrast within 24 hours is recommended
        i. Spinal metastases are rarely localized to a single region, necessitating whole spine MRI
        ii. CT myelogram is an alternative
    f. Steroid therapy can reduce pain, improve neurologic findings, and prolong ambulatory period if patient is already ambulatory
        i. Dexamethasone 10mg IV STAT then 4mg q6

2. **MRI reveals thoracic vertebral lesions at T11 and T12, concerning for metastatic disease, with tumor extension into the spinal canal with compression of the thecal sac and mild signal change and cord edema. There is >50% collapse of these vertebral bodies. What do you do next?**
    a. Key here is to recognize that there is evidence of spinal cord instability both on history (pain that worsens with movement) and due to MRI findings
        i. The Spinal Instability Neoplastic Score (SINS) can be used as a guide to determine if surgery is indicated for spinal instability. This score includes clinical features such as pain with movement, but it also incorporates imaging findings.
            1. pain with movement
            2. deformity on exam
            3. vertebral body collapse on imaging
            4. infiltration of posterior vertebral elements
            5. location of metastases at junctions (occiput-C2, C7-T2, T11-L1, L5-S1)
    b. This patient has pain with movement and multiple radiographic features of spinal instability
        i. In addition to dexamethasone, an emergent surgical consultation is indicated.
    c. Primary determinant of the efficacy of therapy is the patient's neurologic status at time treatment
    d. If prognosis is <3 months, no surgery is indicated
    e. Some patients may also need significant pain control
3. **Prior to ordering MRI, you order some routine labs which show he has an elevated Cr of 1.4 from 1.0 and his calcium is measured at 13.2. What clinical signs/symptoms can you expect with hypercalcemia?**
    a. Lethargic/altered if very high
    b. Signs of hypovolemia, +orthostatic vitals, hypotension, dry MM, increased skin turgor, AKI
4. **What other lab do we need to determine his true calcium and why do we correct it?**
    a. Albumin – 40-45% of Calcium is bound to albumin, so measuring only the serum level may not reflect true free calcium levels (ionized calcium can be sent but expensive and poorly standardized between labs)

5. **If his albumin is measured at 2.6, calculate his true calcium.**
    a. 14.3 (use MDcalc)
6. **What is the mechanism of his hypercalcemia?**
    a. Hard to say at this point, could be PTHrP or could be osteolytic from metastatic lesions in bone
        i. Osteolytic bone metastases are usually the cause of HCM in breast cancer and myeloma, although the incidence of hypercalcemia in these patients may be decreasing with the prophylactic use of bisphosphonates.
        ii. Paraneoplastic production of PTHrP may occur in localized tumors without widespread bone metastases.
        iii. Lymphomas can cause hypercalcemia by overproduction of 1,25-dihydroxyvitamin D
    b.



1. **What do you expect his PTH and 1,25 hydroxy Vitamin D levels to be?**
    a. PTH – low, should be suppressed by high serum calcium
    b. 1, 25 hydroxy vitamin D – should be low-normal, PTHrP does NOT activate 25 vitamin D to become 1,25 like PTH does, so should be low-normal
        - Malignancies such as ovarian cancer can produce ectopic parathyroid hormone

2. **How do you manage hypercalcemia?**
    a. Must characterize the hypercalcemia
        i. Mild: 10.5 to 11.9 mg/dL
        ii. Moderate: 12 to 13.9 mg/dL
        iii. Severe: ≥ 14 mg/dL
    b. Treatment of the underlying etiology/malignancy is always the primary goal of therapy.
        i. If mild, asymptomatic, work up first and find etiology
        ii. If mod/severe + sx, requires prompt attention, may need inpatient management
    c. Treatment of severe hypercalcemia:
        i. Correction of hypovolemia --- hypercalcemia pts are very dehydrated due to polyuria and calcium induced diuresis
            - Aggressive*** IVF repletion (range from 200-300 cc/hour with goal UOP 100-150 cc/h)
              ***use caution required if comorbidities present such as heart failure.
        ii. Loop diuretics: controversial because calcium causes diuresis in itself
            - MAY be used with hydration to increase calcium excretion in pts with volume overload. MAY also prevent volume overload during therapy.
        iii. Calcitonin 4 IU/kg q12h for 48hrs will lower by calcium by 1-2 mg/dL within a few hours, but tachyphylaxis rapidly develops
            - Works by increasing renal excretion of calcium and reducing bone resorption
        iv. Bisphosphonates: zoledronic acid 4 mg IV x1 dose is the most common
            - Inhibit osteoclast mediated bone resorption. Effect seen in 2-3 days.
        v. Denosumab or renal replacement therapy can be considered if refractory to ZA
            - monoclonal antibody that binds RANKL à prevents RANKL from activating RANK receptor on the osteoclast surface à limits osteoclast formation and function

Case #4

A 37 yo male with no PMH presents 2 weeks after a viral illness with fatigue, malaise, poor appetite and yellowing of the eyes. ROS notable for easy bruising. Vitals are all within normal limits. Exam shows scattered bruises throughout, but otherwise unremarkable. Initial work-up in the ED notable for Hb of 7.8, platelet count of 7k, Cr elevated to 1.4. Transaminases are normal, he has an indirect bilirubin of 4.8 and a total bilirubin of 6.2.

1. **What is on your differential at this point and what would you like to order?**
    a. Ddx - All the MAHA's (microangiopathic hemolytic anemia) including TTP, HUS, DIC, autoimmune hemolytic anemia, viral BM suppression
    b. Orders – LDH + haptoglobin to assess for hemolysis, PT/INR and PTT to assess coagulopathy, reticulocyte count to assess BM response, slide to examine for schistocytes, and ADAMTS 13 level
2. **His LDH returns >200 with undetectable haptoglobin. You page your friendly hem/onc fellow to review the slide with you and see numerous (>3 schistocytes per HPF). What is the diagnosis and where does this patient go in the hospital? What do you do while the ADAMTS is pending?**
    a. Diagnosis->TTP (can use PLASMIC score on mdCALC to assist when it is unclear)
    b. Needs to go to MSD or ICU to get line for PLEX
    c. Difficult because you have to empirically start PLEX before ADAMTS13 level has returned (takes 5-7 days to come back), this is why PLASMIC score is so helpful.
    d. Left untreated, mortality for TTP around 90% (CANT MISS IT)
3. **What is happening at the cellular level?**
    a. TTP –95% are acquired deficiency of ADAMTS13 enzyme leads to ultralarge von willebrand factor
        i. These ultralarge VWF multimers accumulate and attach to endothelial wall in microvasculature
        ii. Platelets adhere to these multimers, form platelet rich microthrombi which occlude the microvasculature (consume platelets leading to thrombocytopenia)
        iii. Occlusions in microvasculature shear passing RBCs resulting in schistocytes (and anemia) as well as organ dysfunction (AKI, cardiac, neurologic)
4. **Why does PLEX work to treat this condition?**
    a. Removes circulating autoantibody against ADAMTS13