# HEME MALIGNANCY FACULTY QUESTIONS:

## Plasma Cell Disorders

*Basics of monoclonal gammopathy testing*

1. Plasma cell disorders such as myeloma make a monoclonal gammopathy, which is:
    a. A direct measurement of myeloma cells in the blood
    b. A measurable abnormal immunoglobulin protein that myeloma cells produce
    c. A measurement of myeloma-mediated damage, like blood calcium or creatinine levels
    d. None of the above

    Answer: B

2. True or false: in renal insufficiency, we should adjust our expected normal range for the serum free light chain tests.
    Answer: true. The normal SFLC ratio in renal insufficiency is 0.37-3.1.

3. The combination of serum protein electrophoresis, serum immunofixation, and serum free light chains is roughly how sensitive for a diagnosis of myeloma?
    a. 20%
    b. 50%
    c. 80%
    d. 98%

    Answer: D. Lack of monoclonal gammopathy by those three blood tests indicates a very low post-test probability for a diagnosis of multiple myeloma, i.e. it's a fairly reliable test to "rule out" multiple myeloma.

*MGUS and smoldering multiple myeloma*

1. A patient is incidentally noted to have an M-spike of 1.3 g/dL on SPEP. Immunofixation reveals IgG subtype, and he has normal kappa:lambda light chain ratio. Which of the following tests should you order to ensure that he does not have either smoldering multiple myeloma or multiple myeloma?
    a. CBC, Creatinine, Calcium, urinalysis, NM bone scan, and bone marrow biopsy
    b. CBC, Creatinine, Calcium, urinalysis, whole body low-dose CT, and bone marrow biopsy
    c. CBC, Creatinine, Calcium, urinalysis, whole body low-dose CT
    d. CBC, Creatinine, calcium, and urinalysis

    Answer: D. This patient has low-risk MGUS defined by M-spike of less than 1.5 g/dL, IgG subtype, and normal serum free light chain ratio (Kyle et al. NEJM 2018). Because he has low-risk disease, bone marrow biopsy and skeletal imaging are not indicated. Answer a is additionally incorrect because nuclear medicine bone scan looks for new bone laid down, and since multiple myeloma does not activate osteoblasts, the bone scan will be negative. Instead, we can use either a skeletal bone survey or whole-body low-dose CT to identify lytic lesions. Clinical practice is moving toward whole-body low-dose CT, which is available at UNC.

2. True or false: there is a higher incidence of MGUS among whites as compared to African Americans.
   Answer: false. There is a 2-3x higher incidence of MGUS among African Americans as compared to whites. Landgren et al. Leukemia 2009.

3. The risk of progression of non-IgM MGUS to multiple myeloma or other hematologic malignancy is
   a. 1% per year
   b. 2% per year
   c. 5% per year
   d. 10% per year

   Answer: A. Non-IgM MGUS has a 1% risk per year of progression to multiple myeloma or another hematologic malignancy (AL amyloidosis, Non-Hodgkin lymphoma, plasmacytoma). IgM MGUS has a 2% annual risk of progression for the first ten years and then a 1% annual risk thereafter, and it may progress to Non-Hodgkin lymphoma, Waldenstrom macroglobulinemia, CLL, or AL amyloidosis. Kyle et al. NEJM 2018.

4. A patient with IgM MGUS is at highest risk of progression to
   a. AL amyloidosis
   b. Chronic lymphocytic leukemia
   c. Multiple Myeloma
   d. Non-Hodgkin Lymphoma
   e. Waldenstrom macroglobulinemia

   Answer: D. IgM MGUS has a 2% risk of progression per year for the first 10 years, then 1% risk of progression per year thereafter. IgM MGUS arises from CD20+ lymphoplasmacytic cells that have not yet undergone switch recombination. It is most likely to progress to Non-Hodgkin Lymphoma (50% of cases), followed by Waldenstrom macroglobulinemia (32%), CLL (9%), and AL amyloidosis (9%). When progression does occur, it is rare to progress to multiple myeloma, occurring in less than 1% of cases. This is in contrast to non-IgM MGUS (i.e. IgG MGUS and IgA MGUS), which has a 1% risk of progression per year and most commonly progresses to multiply myeloma (87% of cases). Kyle et al. NEJM 2018. Time stamp: 12:35.

5. The annual rates of progression of smoldering myeloma to multiple myeloma for the first 5 years, the next five years, and after 10 years, respectively, are:
   a. 20%, 10%, 5%
   b. 10%, 3%, 1%
   c. 1%, 5%, 10%
   d. 5%, 10%, 20%

   Answer: B. The rates of progression of smoldering myeloma is 10% per year for the first five years, 3% per year for the second five years, and 1% per year after 10 years. Kyle et al NEJM 2007.

6. The three factors that help stratify the risk of progression of smoldering multiple myeloma are 1) bone marrow plasma cells > ____%, 2) M-spike >__ g/dL, and 3) involved/uninvolved free light chain ratio >__.

Answer: 20, 2, 20. This is known as the Mayo "20/2/20" risk stratification. A bone marrow plasma cell >20%, M-spike >2 g/dL, and involved/uninvolved free light chain ratio > 20 are each independent risk factors that can predict progression of smoldering multiple myeloma to multiple myeloma. Lakshman et al, Blood Cancer J 2018.

7. A 67-year-old female with poorly controlled rheumatoid arthritis presents to her PCP with fatigue. Physical exam is remarkable for ulnar deviation of her MCPs. She has no lymphadenopathy, masses, or organomegaly. Her hemoglobin is 11.3 g/dL, MCV 89. FOBT, B12, and folate are normal. Iron studies return consistent with anemia of chronic disease. Labs also demonstrate an M-spike of 4.1 g/dL. Serum free light chains show free kappa 3 mg/dL (nl 0.3-1.94 mg/dL), lambda 1.0 mg/dL (nl 0.57-2.63 mg/dL), and kappa:lambda ratio 3 (nl 0.26-1.65). She has a normal creatinine, normal electrolytes, and denies any bone pain. A bone marrow biopsy is performed and 15% plasma cells are present. Low-dose CT reveals no lytic lesions. What is the diagnosis?
   a. MGUS
   b. Smoldering multiple myeloma
   c. Multiple myeloma

   Answer: B. Smoldering multiple myeloma is defined as serum M-spike $\geq$ 3.0 g/dL or bone marrow plasma cells 10-60%, and absence of lytic lesions, anemia, hypercalcemia, and renal insufficiency that can be attributed to the plasma cell proliferative disorder (Rajkumar et al, Lancet 2014). Although this patient has anemia, she has an alternative explanation for her anemia (anemia of chronic disease from poorly controlled rheumatoid arthritis). There are no other signs of myeloma-defining events. She should have repeat testing in 2-3 months to ensure stability. If stable, then clinical monitoring (SPEP, CBC, creatinine, calcium, serum free light chain ratio, UPEP, and urine immunofixation) can be spaced out to every 4-6 months for one year, then every 6-12 months thereafter.

8. True or false: treatment of high-risk smoldering multiple myeloma with lenalidomide has been demonstrated to improve overall survival.
   Answer: false. A recent study demonstrated a progression free survival benefit of lenalidomide treatment as compared to observation for the treatment of smoldering multiple myeloma (SMM), but too few deaths occurred to determine the impact on overall survival. Although the majority of patients with high-risk SMM will ultimately progress to active multiple myeloma, treating all patients with SMM risks exposing patients to chemotherapy who would have never needed treatment. Without a clear survival benefit, treatment of high-risk SMM with lenalidomide remains controversial. For now, the standard of care for high-risk smoldering multiple myeloma remains close surveillance (Lonial et al, J Clin Oncolo 2019). There are many ongoing clinical trials that are looking to answer whether patients with high-risk SMM benefit from treatment before progression to MM. Time stamp: 22:02.

*Multiple myeloma basics*

*Amyloidosis, monoclonal gammopathy of renal significance, and other rare plasma cell disorders*

1. True or false: the clinical phenotype of patients with plasma cell disorders varies dramatically based on the structure of the monoclonal protein and the behavior of the underlying cell clone.
   Answer: true

2. Nephrotic syndrome with massive albuminuria should prompt one to think of:
   a. MGUS
   b. Multiple myeloma
   c. Amyloidosis
   d. Diabetic nephropathy
   e. C and D
   f. A and C

   Answer: E. Diabetes and amyloidosis both cause glomerular injury, which often causes massive proteinuria (primarily albuminuria) long before renal function declines. That's in contrast to multiple myeloma, in which proteinuria is primarily Bence Jones (myeloma light chains), and if renal injury occurs, it's usually in the form of reduced renal function first i.e. rising serum creatinine.

3. True or false: Amyloidosis + monoclonal gammopathy = light chain amyloidosis. Workup done.
   Answer: false. That combination is suggestive of light chain amyloidosis but not definitive. 10-30% of patients with other forms of amyloidosis such as transthyretin have an unrelated MGUS.

**<u>Leukemia</u>**

*AML*

1. A 24-year-old woman with no medical co-morbidities presents to the emergency department with a one-day history of fever, altered mental status, and shortness of breath. Her vital signs on arrival were T 39.5 degrees Celsius, HR 128, BP 108/66, RR 24, SpO2 87% (improved to 98% on 3 L). Her labs demonstrate a white blood cell count of 67,000, hemoglobin 7.6 g/dL, and platelets 77x10^9/L, serum lactate of 4.5 mmol/L. Pathologist smear review reveals 55% myeloblasts. Urine toxicology is negative. CT head and CXR do not demonstrate any abnormalities. Blood cultures are pending. In addition to broad spectrum antibiotics and IVFs, what should be performed next?
   a. Initiate hydroxyurea
   b. Initiate hydroxyurea and arrange for emergent leukapheresis
   c. Transfuse 1 unit of packed red blood cells
   d. Obtain bone marrow biopsy

   Answer: B. This patient has an elevated white blood cell count with report of peripheral blasts, concerning for acute leukemia. She has signs of end-organ dysfunction based on her altered mental status and new oxygen requirement, and

therefore meets criteria for the diagnosis of leukostasis. Leukostasis is an oncologic emergency that requires immediate leukopheresis. IVFs and hydroxyurea should be initiated as well while awaiting leukopheresis. Blood transfusions should be avoided in both hyperleukocytosis and leukostasis as it can increase serum viscosity and precipitate leukostasis.

2. A 33-year-old male with no medical co-morbidities presents with a one-week history of severe fatigue and a 1-hour nosebleed. Exam is notable for palatal petechia and a petechial rash along his anterior shins. Labs show a white blood cell count of 16,000/mm^3, hemoglobin of 6.7 g/dL, and platelets of 6x10^9/L with 51% myeloblasts. His peripheral smear reveals numerous immature cells with scant cytoplasm, consistent with blasts. A bone marrow biopsy is eventually performed and confirms the diagnosis of acute myeloid leukemia with FLT-3 mutation. He is deemed to be medically fit for induction chemotherapy. Which treatment would you recommend?
    a. Azacitidine and venetoclax
    b. Cytarabine for 7 days + daunorubicin for 3 days
    c. Cytarabine for 7 days + daunorubicin for 3 days + midostaurin
    d. Hydroxyurea

   Answer: C. For a young patient with newly diagnosed AML, the standard of care is "7+3," which involves 7 days of cytarabine infusion and 3 days of daunorubicin infusion. As AML treatment becomes more personalized, we are able to tailor or therapeutic approach, so in a medically fit patient with FLT-3 mutation, we would consider adding midostaurin, a FLT 3 inhibitor, to front-line treatment of 7+3. The combination of Azacitidine (a hypomethylating agent) and Venetoclax (a BCL-2 inhibitor) have been FDA approved as front-line therapy for AML in older adults (age $\geq$ 75) or medically unfit adults who cannot tolerate intensive induction chemotherapy. Hydroxyurea is indicated in cases of leukostasis and hyperleukocytosis to rapidly lower the white blood cell count. It would not be indicated in this patient with a WBC of 16,000 and no signs of end organ damage. Furthermore, his other cells lines are already suppressed, so the addition of hydroxyurea would serve to worsen his anemia and thrombocytopenia.

3. A 77-year-old male with a PMHx of CAD, hypertension, and osteoarthritis presents to the ED with a one-day history of fever and six-week history of fatigue, dyspnea on exertion, and easy bruising. He currently lives with his daughter, who reports that he requires assistance with most IADLs but is still capable of his ADLs. Exam is notable for numerous ecchymoses. Labs demonstrate WBC 0.9 with ANC 0.5, hemoglobin 7.2 g/dL, and platelets 82x10^9/L with 25% peripheral blasts. Bone marrow biopsy confirms the diagnosis of AML, and he is interested in receiving leukemia-directed therapy. What regimen would you recommend for this individual?
    a. Azacitidine and venetoclax
    b. 7+3
    c. CPX-351
    d. Hospice referral

   Answer: A. Azacitidine and venetoclax would be appropriate treatment for this older adult with untreated AML. The combination of azacitidine, a hypomethylating

agent, and venetoclax, a BCL-2 inhibitor, was FDA approved in 2018 as first-line therapy AML in older adults and those medically unfit for intensive induction chemotherapy. There was an improvement in overall survival (14.7 months in aza-ven group vs 9.6 months in aza-placebo group per DiNardo et al). For this older gentleman, we would not recommend intensive induction with either 7+3 or CPX-351 (liposomal cytarabine + daunorubicin). While early Palliative Care involvement would be beneficial, since he is interested in treatment and there is a reasonable regimen available, hospice referral would not be appropriate at this time.
Reference: https://www.nejm.org/doi/full/10.1056/NEJMoa2012971

4. Which of the following patients require lumbar puncture with IT chemoprophylaxis?
    a. A 27-year-old female with newly diagnosed AML with monocytic phenotype
    b. A 45-year-old male with newly diagnosed AML undergoing induction who presented with WBC 55,000/mm$^3$
    c. A 57-year-old male with hypergingivitis due to extramedullary AML
    d. A 61-year-old male with newly diagnosed AML with FL3-ITD mutation, currently undergoing induction with 7+3+midostaurin
    e. All of the above

    Answer: E. A lumbar puncture with IT cytarabine as chemoprophylaxis should be performed in patients that have one or more risk factors for CNS disease. This is typically performed between day 14 and day 21 during induction. Risk factors for CNS disease include: 1) WBC $\geq$ 40,000/mm$^3$, 2) monocytic phenotype, 3) extramedullary AML, 4) FLT3-ITD mutation. Each of these patients has at least 1 risk factor for CNS disease.

*ALL*

1. A 24 yo male presents with shortness of breath and fatigue. Exam is notable for clear lungs and palpable splenomegaly. His CXR demonstrates a widened mediastinum. Labs show a white blood cell count of 35,000, hemoglobin 7.8 g/dL, and platelets 29X10^9/L. His peripheral smear reveals very immature cells with scant cytoplasm and large nuclei, concerning for blasts. What labs should be sent next to confirm the diagnosis?
    a. Flow cytometry
    b. LDH
    c. Lumbar puncture
    d. Blood cultures

    Answer: A. To confirm the diagnosis of ALL or any leukemia, you should send flow cytometry, which can be sent on peripheral blood. Flow cytometry identifies the analyzes the expression of cell surface markers and can determine if markers of immaturity are present and if of B-cell or T-cell origin. LDH may be elevated in some malignant hematologic processes, but it will not confirm the diagnosis here. Prior to treatment, all patients diagnosed with ALL should undergo a lumbar puncture to evaluate for leukemic involvement of the CNS, but this would not be the first study performed to confirm the diagnosis. If the patient was febrile, you would obtain blood cultures.

2. Which of the following are true:

a. Remission rates are high in ALL because most ALL cells are sensitive to multiple classes of chemotherapy
b. Relapses occur because ALL cells may survive in sanctuary sites, like the CNS or testes.
c. Relapses occur because leukemia stem cells do not divide as rapidly as ALL cells and are therefore less sensitive to cytotoxic chemotherapy.
d. The vast majority of adults can be cured with ALL.
e. A, B, and C are true.

Answer: E. Remission rates are high in ALL because most ALL cells are sensitive to multiple classes of chemotherapy. Relapses occur because 1) leukemia stem cells do not divide as rapidly and are therefore less sensitive to cytotoxic chemotherapy, and 2) ALL cells may survive in sanctuary sites, like the CNS or testes. This is why we often use intra-thecal chemotherapy for CNS prophylaxis. Answer d is false. Prognosis is strongly associated with age. While there is a high cure rate in children (>90%) and adolescents/young adults (60-70%), only 10-20% of older (age > 65) can be cured.

3. An 81-year-old female with a history of ischemic cardiomyopathy and HFrEF (EF 30%) is diagnosed with Philadelphia chromosome positive B-cell ALL. She lives independently, has a performance status of 2, and is interested in cancer-directed therapy. You would recommend which of the following treatment regimens:
    a. Imatinib + induction chemotherapy
    b. Imatinib + prednisone
    c. Prednisone monotherapy
    d. Hospice

    Answer: B. A tyrosine kinase inhibitor (such as imatinib or dasatinib) plus a steroid should be used for frail or older adults with Philadelphia chromosome positive ALL who are not able to tolerate intensive chemotherapy. Several studies have demonstrated that this combination is well tolerated in older adults and can induce high rates of remission.

*CML*

1. A 67 yo male presents to his primary care physician with complaint of fatigue, early satiety, and a 9-pound weight loss. Physical exam is remarkable for spleen measuring 6 cm below the left costal margin in 2 months. His labs reveal a white blood cell count of 142,000/uL, hemoglobin 11.5 g/dL, and platelet count 382 x 10^9/L. His differential cell count shows neutrophils 45% (nl 30-75%), lymphocytes 25% (nl 20-45%), monocytes 9% (nl 0-10%), basophils 9% (nl 0-2%), eosinophils 7% (nl 0-6%), myelocytes 2%, 2% metamyelocytes, 1% bands. His peripheral smear reveals an increased number of myeloid cells in varying stages of maturation with morphologically normal appearance; basophilia and eosinophilia are also present. What is the best next test to order to confirm the diagnosis?
    a. FISH for Philadelphia chromosome
    b. Bone marrow biopsy
    c. CT scan of chest, abdomen, pelvis
    d. PET-CT

Answer: A. FISH for Philadelphia chromosome or PCR for BCR-ABL fusion gene will confirm the diagnosis of CML. This patient is presenting with clinical symptoms and laboratory findings concerning for CML. While ~50% of patients with CML are asymptomatic at diagnosis, presenting symptoms may include fatigue, weight loss, early satiety, and abdominal fullness as in this case. The finding of marked basophilia in combination with leukocytosis should raise suspicion for chronic myeloid leukemia. Mild to moderate anemia is also common at presentation. To diagnose CML, we send FISH assay off of peripheral blood looking for the Philadelphia chromosome. At UNC, this typically results within 24-48 hours. We may also utilize PCR assay for BCR-ABL fusion gene, which is also used to assess treatment response. FISH and PCR may be done from both peripheral blood and bone marrow. While a bone marrow biopsy may be performed in the work up of this patient, the first test to order would be FISH from peripheral blood. Time stamp: 7:02.

2. A 71-year-old male presents to his PCP for routine evaluation and is incidentally found to have a WBC 67,000/uL. His exam shows splenomegaly, measuring 4 cm below the left costal margin. Remainder of CBC shows hemoglobin 12.1 g/dL and platelet count 312,000/uL. His differential cell count shows neutrophils 45% (nl 30-75%), lymphocytes 25% (nl 20-45%), monocytes 7% (nl 0-10%), basophils 15% (nl 0-2%), eosinophils 5% (nl 0-6%), blasts 3%. FISH assay from peripheral blood returns positive for the Philadelphia chromosome. Bone marrow shows hypercellular marrow (>90% cells) with absolute myeloid hyperplasia and 6% blasts present. What is the diagnosis?
    a. AML
    b. Chronic phase CML
    c. Accelerate phase CML
    d. Blast phase CML

   Answer: B. CML is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with normal differentiation. In the absence of treatment, CML has a triphasic or biphasic clinical course as it progresses from a chronic phase to an accelerated phase and on to terminal blast crisis (or directly from chronic phase to blast crisis in some cases). Chronic phase CML is defined by <10% blasts in the bone marrow or peripheral blood and <20% basophils. Accelerated phase is defined as 10-19% blasts in bone marrow or peripheral blood, basophilia $\geq$20%, platelets <100,000 or >1,000,000, progressive splenomegaly, or cytogenetic evolution. Blast phase is defined as $\geq$20% blasts (in blood or bone marrow) or extramedullary disease. Without treatment, chronic phase CML progress to accelerate phase CML in 3-5 years. Time stamp 8:48.

3. True or false: a patient with CML who presents with a WBC >100,000/uL is at high risk of leukostasis.
   Answer: false. In contrast to patients with acute leukemia, patients with CML are extremely unlikely to develop leukostasis, even at WBC counts as high as 500-600,000/uL. This is because in CML they have maturing granulocytes in their circulation that can travel normally through the microcirculation, whereas in acute

leukemia, rigid immature blasts can cause plugging in the microcirculation, impeding blood flow, leading to leukostasis. If a patient with CML developed symptoms of leukostasis, then this should raise suspicion for blast crisis CML. Time stamp: 12:16

4. You have decided to start a 68 yo male patient with high-risk CML on treatment. He has a history of moderate-severe COPD, but no other medical issues. Which tyrosine kinase inhibitor should you avoid?
    a. Bosutinib
    b. Dasatinib
    c. Imatinib
    d. Nilotinib

    Answer: B. Imatinib is the first tyrosine kinase inhibitor (TKI) approved for patients with CML in chronic phase. Second generation TKIs (i.e. bosutinib, dasatinib, and nilotinib) produce a faster and deeper response than imatinib, but improved overall survival has not yet been demonstrated. We typically utilize imatinib first-line in those with low-risk disease and second generation TKIs for those with high-risk disease. The side effect profile is an important consideration in determining which tyrosine kinase inhibitor (TKI) to select. Dasatinib can cause pulmonary hypertension, pleural effusions, and fluid retention, and therefore should be avoided in patients with underlying lung disease or issues with volume overload. Nilotinib can cause hepatotoxicity and can lead to metabolic syndrome, so it should be avoided in those with underlying liver disease, diabetes mellitus, or cardiovascular disease. Bosutinib can cause significant diarrhea, so it should be avoided in those with underlying GI disorders (i.e. IBD, IBS). Time stamp: 16:55

*CLL/SLL*

1. True or false: CLL is an oncologic emergency that requires immediate treatment at time of diagnosis.

    Answer: False. Although patients with CLL can present with severe leukocytosis, the risk of leukostasis is minimal, and many can be monitored over time prior to treatment. In fact, one in 3 patients with CLL will never need treatment in their lifetime. There are guidelines to help guide when to treat (International Workshop on CLL), which state that treatment should be initiated for any of the following: progressive marrow failure, autoimmune cytopenias poorly responsive to steroids/immunosuppressives, massive/progressive/symptomatic splenomegaly (>6 cm below costal margin) or LAD (>10 cm), progressive lymphocytosis (>50% increase over 2 months or lymphocyte doubling time <6 months), or constitutional symptoms due to CLL.

2. A 75-year-old Caucasian male presents to his PCP with fatigue and routine labs show WBC 145 g/dL, hemoglobin 11 g/dL, and platelets 165 g/dL. His differential shows:

| | |
|---|---|
| Neutrophils % | 15% |
| Lymphs % | 80% |
| Monocytes % | 3% |
| Eosinophils % | 1% |
| Basophils % | 1% |

| | |
|---|---|
| Absolute Neutrophils | 1 |
| Absolute Lymphocytes | 16 |
| Absolute Monocytes | 0.6 |
| Absolute Eosinophils | 0.2 |
| Absolute Basophils | 0.2 |

On physical exam, he has mild nontender swelling in his axillary lymph nodes, and his spleen is palpated 2 cm below the costal margin. Peripheral smear shows mature appearing lymphocytes with smudge cells. No blasts are noted. What would be the next step in management of this patient?

a. Obtain a bone marrow biopsy
b. Send peripheral blood flow cytometry and FISH/karyotype
c. Initiate induction chemotherapy with 7+3
d. Initiate ibrutinib

Answer: B. This patient most likely has chronic lymphocytic leukemia (CLL) based on his constitutional symptoms, severe leukocytosis with lymphocytosis (ALC $\geq$ 5), and the presence of smudge cells on his peripheral smear. This diagnosis can be confirmed with flow cytometry to evaluate for CLL markers. We would recommend obtaining FISH/karyotype to rule out mantle cell lymphoma, which can sometimes be confused for CLL. Bone marrow biopsy is not indicated in patients with CLL, who do not meet criteria for treatment. As he has minimal symptoms and relatively mild cytopenias, he does not require immediate treatment. It would be appropriate to work up his anemia further, especially with hemolysis labs, as CLL can be associated with autoimmune hemolytic anemia. Induction chemotherapy with 7+3 is the standard treatment in fit AML patients who are not being enrolled in clinic trial, but this would not be appropriate in this case. While Bruton tyrosine kinase inhibitor ibrutinib is a first-line treatment for CLL, this patient does not meet current criteria for treatment initiation.

Reference: Halleck M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification, and treatment. Annual Journal of Hematology 2019 Nov

3. A 73-year-old male with CLL currently well-controlled on ibrutinib presents to the hospital a 12-hour history of large volume hematochezia. Upon admission, his vital signs are notable for tachycardia and BP 94/56. He has a hemoglobin of 7.4 g/dL (from baseline 10 g/dL) and platelets of 100 x 10^9/L. He is planned for a colonoscopy. In addition to supportive care, what are the other important next steps in management?

a. Continue ibrutinib
b. Hold ibrutinib
c. Transfuse 1 unit of platelets
d. Answers b and c
e. Answers a and c

Answer: D. Ibrutinib causes an inhibitory effect on platelet function and can lead to an increased risk of bleeding with GI bleeding accounting in 5-10% of cases. Therefore, his ibrutinib should be held. Although this patient has only moderate thrombocytopenia, it would be appropriate to give a platelet transfusion in setting of

serious bleeding to replace his dysfunctional platelets. In general, patients should be cautioned against using NSAIDs or aspirin-containing products while on ibrutinib, and vitamin K antagonists should be avoided. Ibrutinib should be held prior to invasive procedures and should not be used in those with a history of major bleeding. Other severe side effects include atrial fibrillation (~10%), ventricular arrhythmias (0.3%). More common side effects include hypertension, myalgias/arthralgias, rash, and diarrhea.

4. True or false: patients with CLL who are initiating venetoclax are admitted to the hospital to monitor for the life-threatening toxicity of fulminant hepatic failure.
   Answer: false. Venetoclax is a Bcl-2 inhibitor that leads to programmed cell death of CLL cells. It can cause severe tumor lysis, which was found to be fatal during drug development. Therefore, patients are often admitted to the hospital for initiation of venetoclax (so called "venetoclax ramp-up") to monitor for tumor lysis syndrome, not fulminant hepatic failure. Risk of tumor lysis is based on absolute lymphocyte count (ALC) and lymph node dimensions (by cross sectional imaging). Other side effects include diarrhea, neutropenia, and thrombocytopenia.

5. True or false: CLL patients should undergo annual total body skin exams.
   Answer: true CLL patients are at a higher risk for other cancers. In addition to their age appropriate cancer screening, they should have annual total body skin exams given their very high risk of skin cancer.

*MDS*

## **Lymphoma**

*Introduction to lymphoma*

1. A 59-year-old male non-smoker presents with a several month history of weight loss, fatigue, and night sweats. Complete blood count shows a mild leukocytosis with lymphocyte predominance. Infectious work up, including HIV, hepatitis serologies, and quantiferon gold, is negative. LDH is elevated at 576 U/L. He ultimately undergoes a CT scan of the chest, abdomen, and pelvis, which diffuse lymphadenopathy, including a 2.1 cm node in the left external iliac chain, several 1 cm para-aortic lymph nodes, and a 2.3 cm lesion in the mediastinum. What is the next best step in management?
   a. Obtain a bone marrow biopsy
   b. Obtain excisional biopsy of external iliac node
   c. Obtain FNA of external iliac node
   d. Perform EBUS with biopsy

   Answer: B. This patient likely has lymphoma, which should be confirmed with an excisional lymph node biopsy. An excisional biopsy of adequate tissue sample that preserves the lymph node architecture is preferred for the diagnosis of lymphoma over a core biopsy or fine needle aspirate. FNA will be inadequate and should not be used. Samples should be sent for molecular testing (cytogenetics, FISH, and gene expression), immunophenotyping, and histopathologic studies. Additionally, the

least invasive node should be sampled; therefore, bronchoscopy with biopsy is not the correct choice. A bone marrow biopsy is not recommended at this point in the work up and is only required for staging of lymphoma if concern about marrow involvement or to confirm limited stage disease.
Reference: Masters P. Hematology and Oncology. MKSAP 17

2. A 48-year-old male presents to the hospital with rapidly enlarging neck mass. On exam, he has a 3 cm non-tender mass in the right cervical region as well as bilateral axillary nodes. PET-CT scan reveals splenomegaly as well as diffuse FDG-avid lymphadenopathy in right cervical, bilateral axillary, para-aortic and inguinal nodes. Biopsy confirms diffuse large B cell lymphoma. You are contemplating administering Rituximab along with combination chemotherapy. What test must you obtain prior to administration of Rituximab?
    a. Echocardiogram
    b. Hepatitis B surface antigen and Hepatitis B core antibody
    c. LDH
    d. Pulmonary function tests

   Answer: B. Rituximab may cause reactivation of Hepatitis B virus, and therefore, all patients who will be treated with Rituximab should be screened for hepatitis B virus with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). An echocardiogram would be appropriate prior to treatment with anthracycline-based therapy, which will likely be included in this patient's treatment, but this is not what the question stem is asking. LDH can have prognostic significance and should be checked for patients with a new diagnosis of lymphoma. Pulmonary function tests are a pre-screening test prior to administration of bleomycin, which is used to treat Hodgkin lymphoma.

3. What is the most common type of lymphoma in adults?
    a. Burkitt's lymphoma
    b. Diffuse large B-cell lymphoma
    c. Follicular lymphoma
    d. Peripheral T-cell lymphoma

   Answer: B. Diffuse large B-cell lymphoma is the most common lymphoma in adults, accounting for nearly one-third (33%) of cases. This is followed by follicular lymphoma, which accounts for 25% of cases. Both peripheral T-cell lymphoma and Burkitt's lymphoma are relatively rare, occurring in less than 6% and less than 2% of cases, respectively.

4. True or false: stage IV diffuse large b-cell lymphoma is potentially curative.
   Answer: True. In contrast to many stage IV solid tumor malignancies, stage IV diffuse large B-cell lymphoma is potentially curable. This depends on a number of different factors, and the International Prognostic Index (IPI) can be used to help predict survival in patients with aggressive non-Hodgkin lymphomas.

*Indolent Non-Hodgkin Lymphomas*

1. Which of the following is not considered an indolent Non-Hodgkin lymphoma?

a. Diffuse large B-cell lymphoma
b. Follicular lymphoma
c. Marginal zone lymphoma
d. Mucosa-associated lymphoid tissue (MALT) lymphoma

Answer: A. Follicular lymphoma, marginal zone lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma are all indolent lymphomas with follicular lymphoma representing the most common indolent NHL and the second most common NHL overall. Indolent NHL is associated with prolonged progression-free intervals (~7-10 years), but it is largely incurable. Diffuse large B cell lymphoma is an aggressive form of NHL; it represents the most common type of NHL.
Reference: Masters P. Hematology and Oncology. MKSAP 17

2. Indolent Non-Hodgkin lymphomas transform into more aggressive Non-Hodgkin lymphomas at which of the following rates:
   a. 2-3% per year
   b. 5% per year
   c. 10% per year
   d. 20-30% per year

   Answer: A. Indolent NHLs transform into more aggressive NHLs at a rate of 2-3% per year or 20-30% over 10-years. Transformed disease may be associated with progression of lymphadenopathy, development of systemic symptoms, and an elevated serum lactate dehydrogenase (LDH). The most common histology is diffuse large B-cell lymphoma.
   Reference: Freedman AS and Friedberg JW, Histologic transformation of follicular lymphoma. UpToDate. 2019 Nov.

3. True or false: Patients with localized indolent lymphoma require immediate systemic treatment.
   Answer: False. In general, indolent NHLs do not need to be treated unless certain criteria are met. Patients with advanced disease (stage III/IV) should be treated if they meet certain criteria for treatment, known as GELF criteria. For the most part, these criteria reflect symptomatic, or near symptomatic, disease. The goal of systemic therapy is complete remission, not cure. Localized disease (stage I/II) cis generally treated with radiation therapy as there is a cure rate of approximately 50%.
   Reference: NCCN guidelines. B-cell Lymphomas 2020 Feb.

4. A 44-year-old female is evaluated for a 6-week history of right neck swelling, which she states seems to regress intermittently. She denies any fevers, night sweats, fatigue, or weight loss. On physical exam, temperature is normal, blood pressure is 110/70 mmHg, and pulse is 85 beats/min. She has nontender enlarged right anterior cervical lymph node and bilateral axillary lymph adenopathy. Her complete blood count demonstrates a leukocyte count of 9000/uL with 35% neutrophils and 65% lymphs, hemoglobin 11 g/dL, and platelets 180,000/uL. LDH is normal. CT of the chest, abdomen, and pelvis shows diffuse lymphadenopathy, including in the axillary, cervical, mediastinal,

and para-aortic lymph nodes all measuring less than 3 cm. An excisional lymph node biopsy reveals follicular lymphoma. PET-CT demonstrates FDG-avidity at the same nodal sites as seen on CT scan. As this patient's oncologist, what would you recommend next?

a. Active surveillance with clinical exam with serum labs and scans
b. Initiate weekly Rituximab monotherapy
c. Initiate Bendamustine-Rituximab chemotherapy
d. Repeat PET-CT in one month

Answer: A. This patient has advanced follicular lymphoma, a type of indolent NHL. When to initiate systemic treatment in advanced indolent lymphomas is based on the GELF criteria (involvement of $\geq$ 3 nodal sites, each with a diameter of $\geq$ 3 cm; any nodal or extra-nodal mass with a diameter of $\geq$ 7 cm, B symptoms, splenomegaly, pleural effusions or peritoneal ascites, cytopenias). More simply put, treatment should be initiated if there is bulky disease which may become symptomatic, extra-nodal involvement including effusions, presence of B-symptoms, or cytopenias. At this point, this patient should undergo active surveillance with clinical exam and serum labs, including CBC, CMP, LDH, every 3 months with interval scans every 6-12 months. Surveillance scnas should consist of CT imaging, not PET-CT. Rituximab monotherapy could be considered at time of initiation of systemic therapy for elderly, frail patients or if low disease burden. Bendamustine-Rituximab would be an appropriate regimen at time of initiation of systemic therapy for this patient, since she is otherwise young and healthy and would be expected to tolerate chemotherapy.
Reference: NCCN guidelines. B-cell Lymphomas. 2020 Feb.

5. A 43-year-old Hispanic male with GERD presents with a three-month history of epigastric discomfort and a 15-pound unintentional weight loss. Physical exam is unremarkable. His complete blood count demonstrates a hemoglobin of 9.2 g/dL, leukocyte count of 9 g/dL, and platelets of 220,000/uL. CT chest, abdomen, pelvis has no abnormalities. He undergoes an upper endoscopy, which shows erythematous gastric mucosa without a discreet mass. Random biopsy reveals a polymorphous infiltrate of small cells with reactive-appearing follicles that are CD19+, CD20+, CD22+, CD5-, CD10-, and CD23-. Histology is positive for *Helicobacter pylori*. What is the next appropriate step in management?

    a. Clarithromycin, metronidazole, amoxicillin, and omeprazole
    b. R-CHOP chemotherapy
    c. Rituximab monotherapy
    d. Partial gastrectomy

    Answer: A. This patient has a gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma. Gastric MALT lymphomas are typically caused by chronic inflammation from ongoing infection with *Helicobacter pylori* in the upper gastrointestinal tract. Immunohistochemistry confirms B-cell origin (positive for B-cell markers CD19, CD20, CD22, and negative for T-cell markers, and exclusion of other small B-cell lymphomas, such as small lymphocytic lymphoma and mantle cell lymphoma, which are both CD5+, and follicular lymphoma, which is CD10+. Complete and durable remissions of gastric MALT lymphomas can often be induced with a combination of antibiotics and proton pump

inhibitors, such as “quad therapy” with clarithromycin, metronidazole, amoxicillin, and omeprazole. The other answer choices would not be appropriate for localized gastric MALT lymphoma. Radiation therapy can be considered for cases where *H. pylori* is negative, and Rituximab monotherapy is appropriate for more advanced disease.
Reference: NCCN guidelines. B-cell lymphomas. Feb 2020.

6. A 67-year-old African American man is brought to the emergency department by his wife for evaluation of progressive confusion over the last 2 days. She notes that prior to confusion, the patient reported a two-week history of headache and blurred vision. On physical exam, patient is afebrile, blood pressure is 170/86 mmHg, pulse 92/min, and respirations 16/min. Fundoscopic exam reveals dilated, segmented, tortuous retinal veins. His neurologic exam reveals nystagmus. The spleen is palpable 3 cm below the costal margin. There is no palpable lymphadenopathy.
Laboratory studies:
Hemoglobin 7.4 g/dL
Leukocyte count 7400/uL
Platelet count 130,000/uL
Blood urea nitrogen 18 g/dL
Sodium 136 mEq/L
Creatinine 0.9 mg/dL
Calcium 9.8 mg/dL
Total protein 12.2 g/dL
Urinalysis 3 leukocytes/hpf, negative for leukocyte esterase, nitrites, or erythrocytes.
Serum protein electrophoresis and immunofixation assay reveals an IgM kappa M-protein level of 5.3 g/dL. Serum IgM level is 8120 mg/dL. What is the next most appropriate step in management?
    a. Nitroprusside infusion
    b. Packed red blood cell transfusion
    c. Urgent plasmapheresis
    d. Bortezomib, dexamethasone, and rituximab

   Answer: This patient has hyperviscosity syndrome from Waldenstrom macroglobulinemia. Waldenstrom macroglobulinemia is a lymphoplasmacytic lymphoma characterized by excess production of monoclonal IgM antibodies. Clinical manifestations of hyperviscosity include dizziness, headache, blurry vision, nystagmus, vertigo, and disturbances in consciousness. A serum IgM level >6000 mg/dL is associated with a very high risk of developing hyperviscosity. Hyperviscosity syndrome due to Waldenstrom macroglobulinemia represents a medical emergency that requires urgent plasmapheresis. A nitroprusside infusion would be indicated for treatment of hypertensive emergency, which this patient does not have. If his altered mental status were due to hypertensive encephalopathy, then we would expect retinal hemorrhages, exudates, or papilledema on his fundoscopic examination. A packed red blood cell transfusion may exacerbate symptoms of hyperviscosity and should be avoided. Bortezomib, dexamethasone, and rituximab (BDR) is a first-line treatment for Waldenstrom

macroglobulinemia, but hyperviscosity syndrome should be treated first with plasmapheresis before Rituximab administration, which may cause flare in patients with high IgM levels. Once the hematologic emergency is controlled, the patient should receive definitive therapy for his lymphoma.
Teaching point: Hyperviscosity due to Waldenstrom macroglobulinemia constitutes a medical emergency and requires prompt initiation of plasmapheresis.
Reference: Masters P. Hematology and Oncology. MKSAP 17

*Aggressive Lymphomas*

1. A 26-year-old male presents with a rapidly enlarging neck mass. CT scan shows bulky lymphadenopathy above and below the diaphragm. LDH is 3000. Excisional lymph node biopsy is consistent with starry sky appearance. What is the most likely oncogene involved?
    a. MYC
    b. RET
    c. P53
    d. BCL6
    e. BCL2

    Answer: A. The starry sky appearance is consistent with Burkitt Lymphoma.

2. A 68-year-old male presents with GI bleeding. Endoscopy biopsy shows malignant cells which express CD20 and CD5, overexpress cyclin D1, but do not express CD23 or CD10. What is the most likely diagnosis?
    a. Burkitt lymphoma
    b. Diffuse large B-cell lymphoma
    c. Follicular lymphoma
    d. Mantle cell lymphoma
    e. Marginal zone lymphoma

    Answer: d. Mantle cell lymphoma is CD20+, CD5+, cyclin D1+, CD10-, CD230-.

3. A previously healthy 30-year-old female with four weeks of anorexia, drenching night sweats, intermittent fevers, and left upper quadrant abdominal pain is referred to you. She had previously been seen by an urgent care physician who noted 2- to 3-cm cervical adenopathy as well as splenomegaly. The urgent care physician had referred the patient to an otolaryngologist who performed a fine-needle aspiration of one of the lymph nodes and sent monospot testing, which was negative. The FNA was a limited specimen with inflammatory cells of various morphology, but an atypical B-cell infiltrate on flow concerning for lymphoma. You confirm the presence of non-bulky cervical as well as supraclavicular adenopathy, as well as a spleen tip palpated at 4 cm below the left costal margin. What is the most appropriate next step in management?
    a. Refer back to ENT for excisional lymph node biopsy
    b. Splenectomy
    c. Supportive care and repeat monospot testing in 4-6 weeks

    Answer: a

*Hodgkin Lymphoma*

1. A healthy 24-year-old male presents with prominent non-tender lymphadenopathy in the right cervical lymph nodes. He has received 2 courses of Augmentin without clinical improvement. HIV is negative. He ultimately undergoes biopsy of the cervical lymph node, which reveals Reed-Sternberg cells admixed with a population of inflammatory cells. PET-CT demonstrates hypermetabolic lymph nodes in the right cervical chain but no other sites of disease involvement. You are planning to treat with ABVD + involved field radiation. What screening test should be done prior to administration of bleomycin?
    a. Echocardiogram
    b. Serum glucose-6-phosphate dehydrogenase
    c. Hepatitis C RNA
    d. Pulmonary function tests

    Answer: D. Bleomycin can cause pulmonary toxicity with pneumonitis that can progress to pulmonary fibrosis, clinically presenting as dyspnea, cough, crackles on lung exam. Need to order PFTs with DLCO; <u>if DLCO is abnormally low, do not give bleomycin</u>.
    Source: Bleomycin: Facts and Comparisons A to Z Drugs. Lexicomp. Updated 2/5/20

2. A 31-year-old female presents to the Emergency Department with dyspnea on exertion, a dry cough, and chest pain. CXR reveals a widened mediastinum. Follow-up CT chest shows a 9 cm anterior mediastinal mass as well as hilar lymphadenopathy. PET-CT demonstrates previously seen mediastinal mass, hilar lymph nodes, as well as hypermetabolic 2.5 cm left-sided cervical lymph nodes and hypermetabolic splenic activity. An excisional lymph node biopsy is performed of the enlarged cervical lymph node, and pathology demonstrates Reed-Sternberg cells that CD15 and CD30 positive, consistent with diagnosis of classical Hodgkin lymphoma. You are planning on treated with ABVD. Why do we require placement of a Port prior to treatment with this regimen?
    a. Bleomycin is a vesicant and can cause severe necrotic damage to muscles if there is extravasation.
    b. Doxorubicin is a vesicant and can cause severe necrotic damage to muscles if there is extravasation.
    c. Vinblastine is a vesicant and can cause severe necrotic damage to muscles if there is extravasation.
    d. All of the above are correct.
    e. Answers B and C are correct.

    Answer: E. Both doxorubicin (an anthracycline) and vinblastine (a vinca alkaloid) are vesicants that can cause severe necrotic damage to skin and muscles if extravasation occurs during infusion. Bleomycin is a typically thought to be "neutral" and causes little to no tissue damage when extravasation occurs.

3. A 44-year-old male smoker with a history of moderate COPD and obstructive sleep apnea presents with left axillary lymph node swelling. He reports an 18-pound unintentional weight loss over 3 months as well as drenching night sweats.

A biopsy of the axillary lymph node reveals Hodgkin lymphoma, and staging PET-CT shows FDG-avid lymph nodes in left axillary, supraclavicular, mediastinal regions as well as hypermetabolic splenic involvement. Given his underlying lung disease, what treatment would you recommend?

a. Adriamycin, Bleomycin, Vincristine, Dacarbazine (ABVD)
b. Adriamycin, Brentuximab Vedotin, Vincristine, Dacarbazine (BV-AVD)
c. Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP)
d. Hospice referral

Answer: B. The standard front-line option for patient with newly diagnosed advanced stage Hodgkin lymphoma is Adriamycin, bleomycin, vincristine, dacarbazine (ABVD). In a patient with underlying lung disease, you would want to avoid bleomycin given risk of bleomycin-induced pulmonary toxicity. Recall other risk factors for bleomycin toxicity include older age, patients already on oxygen therapy, and those with a history of prior thoracic irradiation. In those who are not eligible for ABVD, we recommend BV-AVD, which replaces bleomycin with use Brentuximab Vedotin, an CD30 antibody conjugated to chemotherapy molecule. BV-AVD has higher rates of neutropenic fever than ABVD, so growth factor is required with this regimen. R-CHOP is often used for patients with Non-Hodgkin lymphoma, but is not recommended for classical Hodgkin lymphoma. There is a very high rate of cure in Hodgkin lymphoma (5-year survival >80%), and therefore hospice referral would not be indicated for this patient who has an appropriate treatment option.

## General

*Hematologic malignancy emergencies*

1. A 26-year-old man presents with two weeks of rapidly enlarging neck mass, abdominal distention. His vital signs show T 39 degrees Celsius, BP 92/60, HR 122, and RR 24. He has significant cervical and axillary lymphadenopathy. Spleen is palpable 5 cm below the costophrenic margin, and you are able to feel a firm abdominal mass. His labs demonstrate WBC 65,000 (35% PMNs and 65% atypical lymphocytes), hemoglobin 10.5, platelets 110x$10^9$/uL, creatinine 3.9, LDH 12,000, phosphorus 9.9, potassium 6.6, and uric acid 18.6. A lymph node biopsy reveals Burkitt lymphoma. Which is the most appropriate immediate next step in treatment?
    a. Combination chemotherapy
    b. Corticosteroids
    c. Hemodialysis, IV normal saline, and rasburicase
    d. Radiation therapy

   Answer: C. This patient is presenting with tumor lysis syndrome in the setting of a new diagnosis of Burkitt lymphoma. Tumor lysis syndrome is an oncologic emergency that is caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation. Catabolism of the nucleic acids lead to hyperuricemia, which can precipitate in renal tubules causing obstructive uropathy. TLS is most often seen in high-grade lymphomas, such as Burkitt lymphoma, and other hematologic malignancies. Treatment focuses on intensive supportive care with aggressive IV hydration and

correction of electrolyte abnormalities. Rasburicase is a hypouricemic agent that rapidly breaks down serum uric acid, leading to immediate reduction in serum uric acid. This patient already has signs of severe acute kidney injury and therefore meets the indication for hemodialysis. Source: UpToDate article, "Tumor Lysis Syndrome: Prevention and Treatment." Larson RA and Pui C. Last updated Sep 3, 2019.

2. A 28-year-old previously healthy woman presents to the emergency department with 2 weeks of progressive fatigue, dyspnea on exertion, and easy bruising. Vitals: T 37.2°Celsius, BP 124.78, HR 112, RR 24, SpO2 84% on room air, improved to 95% on 4 L NC. Exam reveals petechiae, ecchymoses, and conjunctival pallor. She has crackles in her bilateral lung bases. No hepatosplenomegaly, lymphadenopathy, or peripheral edema is appreciated. Labs show: hemoglobin 7.4 g/dL, WBC 108,400 (ANC 400), platelets 18,000, Creatinine 1.1, BUN 24, normal PT, aPTT, fibrinogen 354 mg/dL (normal 200-400 mg/dL). Her peripheral smear reveals numerous immature cells with scant cytoplasm, consistent with blasts. Which of the following is the most appropriate next step in treatment?
    a. Blood transfusion
    b. Imatinib
    c. Induction chemotherapy
    d. Leukapheresis

   Answer: D. This patient has an elevated white blood cell count with report of peripheral blasts, concerning for acute leukemia. She has signs of end-organ dysfunction based on her new oxygen requirement and therefore meets criteria for the diagnosis of leukostasis. Hyperleukocytosis refers to the lab abnormality defined as white blood cell count greater than 100,000/uL. Leukostasis occurs as a result of increased viscosity due to white blood cell plugs in the microvasculature, leading to decreased tissue perfusion. It is an oncologic emergency that requires immediate leukopheresis. A blood transfusion may increase serum viscosity and worsen symptoms of leukostasis, so it should be avoided in the absence of another compelling indication. Imatinib is a treatment for CML, which seems unlikely in the absence of organomegaly. Furthermore, CML does not typically cause leukostasis (except in the case of blast crisis). Induction chemotherapy may ultimately be indicated, but we would need to prioritize treating her leukostasis first prior to proceeding with induction therapy. Rituximab is a monoclonal antibody directed against CD20 antigens on B-lymphocytes. While it is used in numerous hematologic malignancies, it would not be indicated for this patient with leukostasis from suspected acute leukemia. Reference: UpToDate article, "Hyperleukocytosis and leukostasis in hematologic malignancies." Schiffer CA. Last updated Nov 13, 2019.

3. A 65-year-old male with a recent diagnosis of DLBCL presents to the emergency department for high fever, chills, and rigors. He reports no other localizing symptoms. He had his first infusion of R-CHOP 7 days ago. He received pegfilgrastim on day 2. On physical exam, temperature is 39°C, blood pressure is 110/60 mmHg, pulse rate 110/min, and respiratory rate is 16/min. There is no evidence of rash or mucositis. Chest is clear to auscultation. He does not have an indwelling venous catheter. Laboratory studies show: hemoglobin 10.5 g/dL,

leukocyte count 0.7 x $10^9$L (10% neutrophils, 90% lymphocytes), platelet count 90,000. Chest radiograph is normal. Blood and urine cultures are pending. Which of the following is the most appropriate step in treatment?

a. Begin empiric cefepime
b. Begin empiric vancomycin
c. Begin empiric vancomycin and cefepime
d. Begin empiric vancomycin, amphotericin, and acyclovir
e. Wait for blood cultures to result before starting antibiotics

Answer: A. This patient meets the criteria for neutropenic fever, which is defined as a single oral temperature $\geq$ 38.4°C or temperature $\geq$ 38.0°C sustained over 1 hour in the setting of neutropenia (ANC <500 or expected to decrease to <500 during the next 48 hours). Neutropenic fever is an oncologic emergency and requires immediate treatment with empiric antibiotics that provide anti-pseudomonal coverage. Patients should be started immediately on broad spectrum antibiotics such as the fourth-generation cephalosporin, cefepime. Anaerobic coverage could be added if there was a suspicion for anaerobic infection, and we typically reserve carbapenems if there is concern for ESBL. Vancomycin is not recommended as a standard part of the initial regimen but should be added in those patients with suspected catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability. Empiric anti-fungal coverage is generally initiated in those with neutropenia who remain febrile without an identified source of infection after 4-7 days of broad-spectrum antibiotic coverage. Viral infection is not a typical cause of infection in patients with febrile neutropenia, and empiric therapy with an antiviral, such as acyclovir is not indicated. Delaying broad-spectrum antibiotic therapy until culture results places the patient at risk for overwhelming sepsis and death. Furthermore, only 30% of patients with febrile neutropenia will have a positive blood or urine culture. Reference: Masters P. Hematology and Oncology. MKSAP 17, question 124.