Question 1

A 45-year-old woman is evaluated in the emergency department for a 1-day history of abdominal pain and fever. She also reports unexpected, heavy menstrual bleeding of 1 day's duration and easy bruising of 2 days' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, the patient is oriented to person and place, but not time. Temperature is 38.1 °C (100.6 °F), blood pressure is 170/98 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Other than confusion, neurologic examination is normal. Subconjunctival hemorrhages are present. Cardiopulmonary examination is normal. Abdominal examination reveals tenderness to palpation without guarding or rebound. Pelvic examination shows blood in the vaginal vault with no cervical motion tenderness or adnexal masses.

Laboratory studies:

Hematocrit	26%
Leukocyte count	10,300/µL (10.3 × 10^9/L)
Platelet count	24,000/µL (24 × 10^9/L)
Reticulocyte count	8.3% of erythrocytes
Bilirubin, total	2.3 mg/dL (39.3 µmol/L)
Creatinine	3.2 mg/dL (283 µmol/L)
Lactate dehydrogenase	1500 U/L

Which of the following is the most appropriate diagnostic test to perform next?

16%

A ADAMTS-13 activity level

1%

B Osmotic fragility test

81%

C Peripheral blood smear

2%

D Stool Shiga toxin assay

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose thrombotic thrombocytopenic purpura.

Key Point

Thrombotic thrombocytopenic purpura is a clinical diagnosis that requires the presence of thrombocytopenia and microangiopathic hemolytic anemia, which is confirmed by schistocytes on the peripheral blood smear.

The most appropriate diagnostic test to perform at this time is a peripheral blood smear. This patient likely has thrombotic thrombocytopenic purpura (TTP). TTP should be suspected in patients who have microangiopathic hemolytic anemia, characterized by schistocytes on the peripheral blood smear and increased serum lactate dehydrogenase levels, and thrombocytopenia. A peripheral blood smear is essential to determine whether the anemia is caused by a microangiopathic hemolytic process as indicated by the presence of schistocytes. Patients may also have fever; kidney manifestations such as hematuria, elevated creatinine level, and proteinuria; and fluctuating neurologic manifestations, but the absence of these symptoms does not exclude the diagnosis.

Assays for ADAMTS-13 activity and inhibitor titer are available but are best used for prognosis rather than to guide therapy, because TTP requires immediate treatment that cannot be delayed until laboratory test results are available. Low activity levels and a positive inhibitor titer confer a higher risk for relapse.

An osmotic fragility test is used to evaluate for hereditary spherocytosis, which can produce hemolysis in the setting of an acute infection. However, hereditary spherocytosis does not cause thrombocytopenia, kidney injury, or mental status changes.

TTP can overlap with hemolytic uremic syndrome (HUS), which usually occurs in children. HUS may be precipitated by an infectious diarrheal illness, especially *Escherichia coli* O157:H7 or *Shigella* species. These bacteria elaborate a toxin that resembles antigens on renal endothelial cells and bind and cause renal cell death. It is not clinically helpful to attempt to distinguish between TTP and HUS, because many patients with HUS respond to plasma exchange, the treatment for TTP.

Question 2

A 75-year-old man arrives at the emergency department after passing three large-volume, melenic stools over a 2-hour period. Medical history is significant for atrial fibrillation and hypertension. Medications are warfarin, metoprolol, and lisinopril.

On physical examination, he is diaphoretic and the skin is cool to the touch. Temperature is 36.8 °C (98.2 °F), blood pressure is 82/64 mm Hg, pulse rate is 142/min and irregular, and respiration rate is 20/min. Oxygen saturation is 95% breathing ambient air. Cardiac examination reveals tachycardia. Pulmonary examination is normal. Peripheral pulses are thready. Rectal examination reveals melenic stool that is guaiac positive.

Laboratory studies:

Hemoglobin	8.2 g/dL (82 g/L); 12.8 g/dL (128 g/L) 3 months ago
Leukocyte count	8600/µL (8.6×10^9/L)
Platelet count	183,000/µL (183×10^9/L)
INR	7.4

In addition to intravenous vitamin K and fluid resuscitation, which of the following is the most appropriate treatment?

32%

A
4-Factor prothrombin complex concentrate

1%

B
Activated factor VII

4%

C
Cryoprecipitate

63%

D
Fresh frozen plasma

Answer & Critique

Correct Answer: A

Educational Objective: Treat a patient for major bleeding who is taking warfarin.

Key Point

Major bleeding associated with vitamin K antagonists should be treated by reversing anticoagulation with 4-factor prothrombin complex concentrate in addition to intravenous vitamin K.

The patient should be given 4-factor prothrombin complex concentrate (4f-PCC) in addition to intravenous vitamin K and fluids. He is experiencing major bleeding complicated by warfarin therapy and requires immediate anticoagulation reversal. 4f-PCC is a plasma-derived product that contains all four vitamin K–dependent coagulation factors (factors II, VII, IX, and X). Unlike fresh frozen plasma (FFP), 4f-PCC is stored at room temperature, does not require ABO typing, and can be infused quickly because of its small volume, thus reducing the time to delivery of therapy. Compared with FFP, 4f-PCC has been shown to more rapidly achieve hemostasis in patients with visible or musculoskeletal bleeding with less risk of fluid overload and no difference in thromboembolic events. This agent has therefore been approved by the FDA for urgent reversal of coagulation factor deficiencies related to vitamin K antagonist therapy for adult patients with acute major bleeding, as well as for adult patients in need of urgent surgery or an invasive procedure.

Activated factor VII (factor VIIa) has been evaluated in case series for the treatment of vitamin K antagonist–related bleeding. Although factor VIIa can correct the INR quickly in most instances, it is unclear if this is associated with achievement of optimal hemostasis considering factors II, IX, and X are not replaced with this agent. A low dose of factor VIIa may be used in conjunction with 3-factor PCCs (which contain very little factor VII) for treatment of major vitamin K antagonist–associated bleeding in situations when 4f-PCCs are not available and the patient has a contraindication to the use of FFP (for example, uncompensated heart failure).

Cryoprecipitate is rich in fibrinogen and is used to treat inherited or acquired fibrinogen deficiency or dysfibrinogenemia. It has no role in the management of vitamin K antagonist–related bleeding.

FFP can be used when 4f-PCC is not readily available. However, 4f-PCC is also less likely than FFP to induce transfusion-associated circulatory overload, an important consideration in patients with heart failure or transfusion-related acute lung injury. Furthermore, 4f-PCC goes through viral inactivation, which reduces the incidence of transfusion-transmitted infectious diseases.

Question 3

A 37-year-old woman is evaluated for a 6-month history of progressive shortness of breath. Although she remains physically active, she becomes dyspneic when walking up multiple flights of stairs or running to catch a bus. Medical history is significant for a diagnosis of a pulmonary embolism 2 years ago, which was associated with oral contraceptive use. She was initially treated with low-molecular-weight heparin followed by therapeutic warfarin for 3 months. She is a nonsmoker. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, she is afebrile, blood pressure is 128/76 mm Hg at rest, pulse rate is 72/min, and respiration rate is 15/min. Oxygen saturation is 98% breathing ambient air. Pulmonary examination reveals clear lungs. Cardiac examination is significant for a fixed, split S_2, a holosystolic murmur at the left sternal border that increases on inspiration, and a heave. Trace lower extremity bilateral edema is present. The remainder of the examination is noncontributory.

Walking up stairs at the office at a moderate pace, she becomes short of breath after two flights of stairs, oxygen saturation decreases to 92%, and pulse rate increases to 145/min.

A chest radiograph is normal, showing no parenchymal abnormalities. Transthoracic echocardiography shows right atrial and ventricular dilation and moderate tricuspid regurgitation but no other valvular abnormalities.

Which of the foll owing is the most appropriate diagnostic test to perform next?

A Pulmonary CT angiography	49%
B Serum D-dimer test	9%
C Venous Doppler ultrasonography of the legs	3%
D Ventilation-perfusion (V/Q) lung scan	39%

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose chronic thromboembolic pulmonary hypertension in a patient with a previous pulmonary embolism.

Key Point

Ventilation-perfusion lung scanning is appropriate for determining chronic thromboembolic pulmonary hypertension in patients with a history of pulmonary embolism and persistent or progressive dyspnea.

A radionuclide ventilation-perfusion (V/Q) lung scan is the preferred and recommended initial study to evaluate for possible chronic thromboembolic pulmonary hypertension (CTEPH), which is likely in this patient. CTEPH is defined as a mean pulmonary artery pressure of greater than 25 mm Hg, with normal pulmonary capillary wedge pressure, left atrial pressure, and left ventricular end-diastolic pressure. It typically occurs within 2 years following a pulmonary embolism (PE), affecting 3.8% of patients, although only about 50% of these have a history of clinically detected PE. Patients with CTEPH often present with persistent shortness of breath or progressively worsening dyspnea, especially on exertion. For a patient in whom pulmonary hypertension is suspected, a V/Q scan can help determine if the patient's pulmonary hypertension is due to obstruction of medium-sized or larger pulmonary arteries (as is characteristic of CTEPH), because V/Q mismatches would be seen. In nonthromboembolic pulmonary hypertension, a V/Q scan would be normal. If the V/Q scan suggests CTEPH, confirmatory right heart catheterization with pulmonary artery pressure measurements and pulmonary arteriography is indicated.

Pulmonary CT angiography (CTA) is not sensitive for diagnosing chronic PE and often appears normal despite chronic perfusion defects, primarily because CTEPH involves chronic changes in the pulmonary vasculature owing to organization of thrombus and recanalization and is not associated with distinct intraluminal filling defects. V/Q scanning is more sensitive for detecting these changes, with a reported sensitivity of CTEPH detection of more than 96% compared with 51% with CTA.

Serum D-dimer testing is not a sensitive marker to detect CTEPH. The pulmonary changes associated with CTEPH involve organization of clots and are not clearly associated with active thrombosis. Therefore, D-dimer levels are unable to provide diagnostic information.

Similarly, venous Doppler ultrasonography would be helpful in evaluating for active thrombosis in the legs but would not provide helpful diagnostic information for evaluation of pulmonary hypertension.

Question 4

A 48-year-old woman is evaluated for fatigue and intermittent abdominal discomfort of 2 months' duration and occasional dark urine. Medical and family histories are unremarkable. Her only medication is an oral contraceptive pill.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 125/74 mm Hg, pulse rate is 68/min, and respiration rate is 13/min. Pallor is observed, and abdominal tenderness is present on palpation. No icterus, bruising, or splenomegaly is noted.

Laboratory studies:

Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	3000/µL (3×10^9/L) with a normal differential
Platelet count	125,000/µL (125×10^9/L)
Reticulocyte count	8% of erythrocytes
Bilirubin, total	Normal
Direct antiglobulin (Coombs) test	Negative

A bone marrow biopsy shows 20% cellularity. Flow cytometry reveals erythrocytes lacking CD55 and CD59. Abdominal ultrasonography shows portal vein thrombosis.

Which of the following is the most likely diagnosis?

A
Aplastic anemia

B
Myelodysplastic syndrome

C
Myeloproliferative neoplasm

D
Paroxysmal nocturnal hemoglobinuria

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose paroxysmal nocturnal hemoglobinuria.

Key Point

Findings diagnostic of paroxysmal nocturnal hemoglobinuria include hemolytic anemia, hypocellular bone marrow, and lack of CD55 and CD59.

The most likely diagnosis is paroxysmal nocturnal hemoglobinuria (PNH). PNH is an acquired clonal stem cell disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. Mutations in the *PIG-A* gene lead to the reduction or absence of glycosylphosphatidylinositol, an important erythrocyte-anchoring protein. Hemolysis is caused by the absence of decay-accelerating factor (CD55) and the membrane inhibitor of reactive lysis (CD59), which are glycosylphosphatidylinositol-dependent complement regulatory proteins. Diagnosis of PNH is based on flow cytometry results, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes.

The patient does not have aplastic anemia (AA). Although AA often has small PNH clones present, thrombosis and hemolysis are not features of this disease. In patients with AA, however, annual screening for the presence of PNH clones by flow cytometry is recommended.

The myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis. Although MDS may present with a hypocellular bone marrow approximately 10% of the time, thrombosis and hemolysis are not typical symptoms. MDS usually presents with anemia or pancytopenia and a hypercellular marrow with dysplastic changes in cell precursors.

Myeloproliferative neoplasms (MPNs) can present with splanchnic thrombosis and should be considered in the differential diagnosis of unusual blood clots. However, the peripheral blood counts do not suggest MPN (no cell lines are elevated), and hemolysis is not a prominent clinical feature. Additionally, the marrow in MPNs is typically hypercellular or fibrotic.

Question 5

A 36-year-old woman is evaluated in the emergency department for a 1-month history of intermittent abdominal pain, a 1-week history of abdominal swelling, and a 4.5-kg (10 lb) weight gain. She rarely drinks alcohol. Her only medication is an oral combination contraceptive pill.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 115/76 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. Tender hepatomegaly and tense ascites are noted on abdominal palpation. No jaundice or spider telangiectasias are observed.

Laboratory studies show a hemoglobin level of 11.5 g/dL (115 g/L), leukocyte count of 12,000/µL (12×10^9/L), and platelet count of 335,000/µL (335×10^9/L). A viral hepatitis screening panel and pregnancy test are both negative.

Abdominal Doppler flow ultrasonography shows hepatic vein thrombosis and elevated estimated portal pressures.

Which of the following diagnostic tests is most likely to explain the cau se of this patient's condition?

A
Antiphospholipid antibody

B
Factor V Leiden

C
JAK2 V617F activating mutation

D
Prothrombin gene mutation (G20210A)

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose Budd-Chiari syndrome associated with *JAK2 V617F* activating mutation.

Key Point

A *JAK2* activating mutation occurs in approximately half of patients with idiopathic Budd-Chiari syndrome.

Testing for the *JAK2 V617F* activating mutation is the most appropriate next step. This patient presents with acute portal hypertension caused by thrombosis of the hepatic veins, or Budd-Chiari syndrome (BCS), which is one of the few noncirrhotic causes of portal hypertension. Clinically, this syndrome can present acutely as fulminant hepatic failure or subacutely with tender hepatomegaly and rapid-onset ascites, as in this patient. Upon discovery of the *JAK2* activating mutation in 2005, it became apparent that up to half of patients with idiopathic BCS had an acquired mutation in *JAK2*, without overt suggestion of a myeloproliferative neoplasm. Therefore, testing for *JAK2* is part of the diagnostic testing protocol that includes consideration of paroxysmal nocturnal hemoglobinuria in the differential diagnosis of splanchnic vein thrombosis.

Antiphospholipid antibodies have been associated with BCS, but they are notoriously nonspecific, and much of the literature concerning antiphospholipid antibodies was written before more specific acquired causes were discerned. Diagnosis of antiphospholipid antibody syndrome requires persistent elevation of antibodies in association with a clinically consistent clot. Because deep venous thrombosis (DVT) and pulmonary embolism (PE), arterial thrombosis, and placental clots are more commonly associated with antiphospholipid antibody syndrome than splanchnic vein thrombosis, testing for this disorder is not indicated until other more likely diagnoses are excluded.

Factor V Leiden most characteristically presents as DVT, with or without PE. Less commonly, patients may experience cerebral, mesenteric, and portal vein thrombosis.

Patients with the prothrombin gene mutation (G20210A) are at increased risk for DVT and, less commonly, cerebral vein thrombosis. In patients with splanchnic vein thrombosis, testing for the more common *JAK2* mutation is the most appropriate initial step.

Question 6

A 24-year-old man is evaluated in the emergency department for prolonged and severe bleeding 3 days after undergoing hemorrhoidectomy. He reports continually bleeding and soaking through four bath towels. Medical history is significant for prolonged bleeding following wisdom tooth removal. Family history is notable for a brother who experienced heavy bleeding with tooth extraction and a maternal grandfather who died of an intracerebral hemorrhage at age 32 years. He takes no medications.

On physical examination, the patient appears pale. Temperature is 36.7 °C (98.1 °F), blood pressure is 90/55 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Continued rectal bleeding is observed, with no clear source on anoscopy.

Laboratory studies:

Hematocrit	17%
Leukocyte count	12,000/µL (12×10^9/L)
Platelet count	380,000/µL (380×10^9/L)
Activated partial thromboplastin time (aPTT)	45 s
Prothrombin time	12.2 s
aPTT following 1:1 mixing study with normal plasma	32 s

Which of the following is the most appropriate diagnostic test to perform next?

A
Bleeding time

B
Factor VIII level

C
Factor XI level

D
Lupus anticoagulant

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose hemophilia A.

Key Point

Hemophilia A results from factor VIII deficiency and hemophilia B from factor IX deficiency; both produce a prolongation of the activated partial thromboplastin time that fully corrects in a mixing study.

The patient should undergo factor VIII testing. He has had abnormal bleeding following a surgical procedure and dental extractions. The activated partial thromboplastin time (aPTT) is prolonged but corrects fully in a 1:1 mixing study. This could occur with clotting factor deficiencies VIII, IX, and XI; however, this patient's bleeding disorder appears to be familial. Because his maternal grandfather may have had a bleeding disorder resulting in intracerebral bleeding at a young age, and his brother had abnormal bleeding, the likely inheritance pattern is X-linked recessive; only hemophilia A and B are inherited in this fashion. Hemophilia A results from factor VIII deficiency and hemophilia B from factor IX deficiency; both produce a prolongation of the aPTT that fully corrects in a mixing study. Persons with severe hemophilia have less than 1% factor VIII or IX activity; they will have severe recurrent hemarthroses as well as retroperitoneal and intramuscular bleeding. Central nervous system hemorrhage is especially hazardous and is a leading cause of death. Mild hemophilia may present in adulthood and is characterized by posttraumatic or surgical bleeding.

The bleeding time test is performed by blotting away excess blood, which tests primary hemostasis rather than fibrin formation. The bleeding time is prolonged in patients with platelet dysfunction, von Willebrand disease (vWD), thrombocytopenia, and anemia. The bleeding time will be abnormal in this patient because of his anemia and will not assist in establishing the diagnosis.

Patients with factor XI deficiency will have a prolonged aPTT, as in this patient, but the inheritance pattern is autosomal recessive, not X-linked. Additionally, bleeding is not spontaneous, tends to be milder in degree, and typically affects mucocutaneous surfaces. It is highly unlikely to cause an intracerebral hemorrhage in a younger person, such as this patient's grandfather.

The antiphospholipid syndrome is defined by the presence of antiphospholipid antibodies and typical clinical manifestations. This disorder may occur as an independent syndrome (primary antiphospholipid syndrome) or secondary to underlying systemic lupus erythematosus. Antiphospholipid antibodies include anticardiolipin, anti-?$_2$-glycoprotein I, and the lupus anticoagulant. The lupus anticoagulant does prolong the aPTT, but the aPTT will not correct in a 1:1 mixing study. Lupus anticoagulant is also more likely to lead to abnormal thrombosis rather than bleeding.

Question 7

A 52-year-old man is evaluated for orthopnea and dyspnea on exertion of 4 weeks' duration. Twelve weeks ago, he developed chronic abdominal pain, diarrhea, and weight loss. Two weeks ago, he developed new-onset eczema and nonhealing, painful sores inside his mouth. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient appears ill and uncomfortable. Temperature is 36.4 °C (97.5 °F), blood pressure is 138/88 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. He has diffuse erythroderma and multiple oral aphthous ulcers. On cardiac examination, prominent jugular venous distention, an S_4 gallop, and a grade 2/6 holosystolic murmur are noted. On pulmonary examination, crackles are auscultated. Palpation of the abdomen elicits generalized tenderness without guarding. Lower extremity edema is present to the knee.

Laboratory studies:

Hemoglobin	13.5 g/dL (135 g/L)
Leukocyte count	18,000/µL (18 × 10^9/L) with 50% lymphocytes, 10% eosinophils, and 40% neutrophils
Platelet count	155,000/µL (155 × 10^9/L)
Troponin I	Negative

Electrocardiography shows low QRS voltage in all leads without evidence of ischemic changes. Echocardiography shows restrictive left ventricular filling, increased echogenicity of the endomyocardium, and moderate mitral regurgitation.

A peripheral blood smear demonstrates mature eosinophils. Secondary causes of eosinophilia have been excluded.

Which of the following is the most likely diagnosis?

A Acute eosinophilic leukemia
B Chronic myeloid leukemia
C Hypereosinophilic syndrome
D Systemic mastocytosis

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose hypereosinophilic syndrome.

Key Point

An elevated eosinophil count (>1500/µL [1.5 × 10^9/L]) without a secondary cause and evidence of organ involvement are diagnostic of hypereosinophilic syndrome.

The most likely diagnosis is hypereosinophilic syndrome (HES). This patient presents with cardiac complications of HES, an elevated eosinophil count (>1500/µL [1.5 × 10^9/L]) without a secondary cause, and evidence of organ involvement. The causes of eosinophilia are described in the CHINA mnemonic (connective tissue diseases, helminthic infection, idiopathic [HES], neoplasia, allergy). The most common organs affected by HES include the skin, lungs, gastrointestinal tract, and heart. HES may or may not be associated with mutations in the tyrosine kinase receptor gene, but such involvement is important to identify, because treatment with imatinib is effective in such cases.

Acute eosinophilic leukemia is characterized by increases in immature eosinophils in blood and bone marrow and infiltration of tissues with immature eosinophils. Like HES, cardiac dysfunction can develop, but findings of an acute leukemic syndrome are pronounced and include anemia, thrombocytopenia, and infection.

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by myeloid proliferation. In chronic-phase CML, the leukocyte count is high, the hemoglobin level is low or normal, and the platelet count is normal or high. CML may be associated with an absolute eosinophilia, but tissue or organ dysfunction is not common. Detection of the (9;22) translocation by routine cytogenetics or fluorescence in situ hybridization or of the *BCR-ABL* fusion transcript by reverse transcriptase-polymerase chain reaction is diagnostic.

Systemic mastocytosis with eosinophilia is characterized by urticaria pigmentosa, a unique identifying clinical finding. Urticaria pigmentosa findings include pruritic yellow to red or brown macules, papules, plaques, and nodules. The most common noncutaneous findings are gastrointestinal and include symptoms such as abdominal pain, diarrhea, nausea, and vomiting.

Question 8

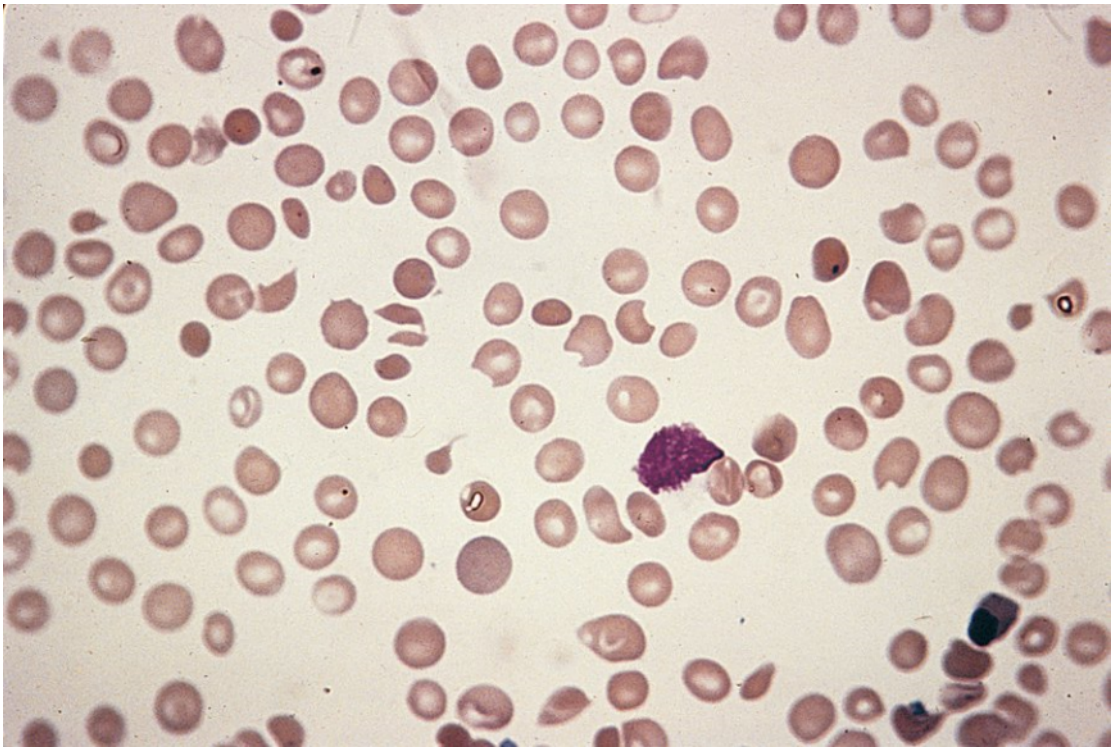
A 35-year-old woman is evaluated for worsening thrombocytopenia; she is pregnant at 36 weeks' gestation. Medical history is significant for immune thrombocytopenic purpura. Previous platelet counts during this pregnancy have been 80,000 to 100,000/µL (80-100 × 10^9/L). Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 165/110 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. Abdominal examination reveals mild right upper quadrant discomfort on palpation. Reflexes are normal, and no clonus is observed. She has lower extremity edema to the level of the knees bilaterally.

Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Platelet count	21,000/µL (21 × 10^9/L)
Alanine aminotransferase	480 U/L
Aspartate aminotransferase	600 U/L
Creatinine	1.2 mg/dL (106.1 ?mol/L)
Urinalysis	3+ protein

A peripheral blood smear is shown.



Which of the following is the most appropriate management of this patient's thrombocytopenia?

A

Emergent delivery

B

Intravenous immune globulin

C

Plasma exchange

D

Prednisone

Answer & Critique

Correct Answer: A

Educational Objective: Manage thrombocytopenia in pregnancy.

Key Point

Immediate delivery of the fetus is the best management approach for pregnant women experiencing thrombotic microangiopathy of pregnancy.

The most appropriate management for this patient's thrombocytopenia is immediate delivery of the fetus, because she has HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome. Although she has a history of immune thrombocytopenic purpura (ITP), and her platelet counts have been low throughout the pregnancy, her markedly decreased platelet count is worrisome and could indicate development of another condition. Worsening anemia, right upper quadrant pain, hypertension, proteinuria, and elevated liver enzymes are more consistent with a microangiopathy of pregnancy (HELLP syndrome, preeclampsia, thrombotic thrombocytopenic purpura [TTP]) rather than worsening ITP. Her clinical picture is more consistent with preeclampsia (new-onset hypertension at >20 weeks' gestation) with proteinuria or the HELLP syndrome. The relationship between preeclampsia and HELLP syndrome is unclear; HELLP syndrome occurs in 10% to 20% of women with preeclampsia but occasionally in some patients without hypertension or proteinuria. The primary treatment for both conditions, particularly in advanced pregnancy, is urgent delivery. Platelet counts tend to recover quickly after delivery; persistent thrombocytopenia several days after delivery should raise concern for another diagnosis, such as thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS).

Administering intravenous immune globulin is not indicated as a treatment for thrombocytopenia associated with preeclampsia and HELLP syndrome.

Plasma exchange can be undertaken if TTP is present earlier in the pregnancy before delivery is a viable option, but would not be a preferred treatment strategy in a patient in whom delivery is appropriate. Plasma exchange would be indicated if thrombocytopenia persisted after delivery and TTP-HUS were diagnosed.

Glucocorticoids such as prednisone are not indicated for microangiopathy of pregnancy. Additionally, if used as a treatment for ITP, prednisone typically takes 48 to 72 hours for effectiveness. Therefore, treatment with prednisone would not be appropriate in this patient.

Question 9

A 44-year-old man is evaluated in follow-up for an episode of unprovoked left proximal leg deep venous thrombosis 3 months ago. Following initial anticoagulation with low-molecular-weight heparin, he began treatment with warfarin. INR testing done every 3 to 4 weeks has shown a stable therapeutic INR. He has mild left leg discomfort after a long day of standing, but it does not limit his activity level. He tolerates warfarin well. Family history is unremarkable, and he takes no other medications.

On physical examination, vital signs are normal. He has mild edema of the left leg below the knee, with postthrombotic pigmentation. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

A
Continue anticoagulation indefinitely

B
Discontinue warfarin in another 3 months

C
Discontinue warfarin now

D
Discontinue warfarin and perform thrombophilia testing

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Answer & Critique

Correct Answer: A

Educational Objective: Determine duration of anticoagulation in a patient with venous thromboembolism.

Key Point

Long-term anticoagulation therapy is recommended for patients with unprovoked proximal leg deep venous thrombosis or pulmonary embolism who have low or moderate bleeding risk.

This patient should continue anticoagulation therapy indefinitely. Because his venous thromboembolism (VTE) was unprovoked, he is at relatively high risk for recurrence if he stops anticoagulation. Based on his history, stable INR values, absence of comorbidities, and age, his bleeding risk is low. He also does not have a strong preference to discontinue anticoagulation. The decision to treat him for an extended period of time is consistent with the American College of Chest Physicians guidelines, which suggest extended anticoagulant therapy in patients with unprovoked proximal leg deep venous thrombosis (DVT) or pulmonary embolism who have low or moderate bleeding risk. Re-evaluation of this indication based on periodic risk/benefit assessments, new clinical study data, and new anticoagulation drug availability is appropriate.

Short-term anticoagulant therapy (3 months) is suggested for patients with VTE associated with a major transient risk factor, such as major surgery, trauma, or immobility; patients with unprovoked distal leg DVT; and patients with unprovoked proximal leg DVT who are at high risk for bleeding. Therefore, 3 months of therapy, or extending treatment to 6 months, would not be optimal treatment for this patient with an unprovoked proximal DVT.

Because identification of an inherited thrombophilia often does not change treatment decisions in a patient with VTE (does not reliably predict risk of recurrence or influence duration of recommended anticoagulation), evidence-based guidelines recommend against routine thrombophilia testing. In this patient with an unprovoked proximal DVT, the recommendation for long-term anticoagulation would not be altered by the results of such testing, thus, it would not be helpful. Testing may be indicated, however, in patients with VTE at intermediate risk for recurrence by traditional predictors in whom finding a strong thrombophilic risk might alter therapeutic decisions.

Question 10

A 28-year-old woman is evaluated for a 1-week history of progressive dyspnea and fatigue. She was diagnosed with Hodgkin lymphoma 2 months ago and is receiving chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). She takes no other medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 134/82 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Conjunctival pallor is noted but no scleral icterus. The lungs are clear to auscultation, and the cardiac examination is normal. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	6.8 g/dL (68 g/L)
Leukocyte count	1300/µL (1.3×10^9/L)
Platelet count	83,000/µL (83×10^9/L)
Cytomegalovirus IgG antibody	Positive

A peripheral blood smear shows pancytopenia but is otherwise unremarkable.

Which of the following is the most appropriate erythrocyte transfusion product for this patient?

A
Leukoreduced

B
Leukoreduced, cytomegalovirus-negative

C
Leukoreduced, irradiated

D
Leukoreduced, washed

Answer & Critique

Correct Answer: C

Educational Objective: Treat anemia in a patient with Hodgkin lymphoma.

Key Point

Leukoreduced and irradiated erythrocytes should be used when transfusing select patients who are immunocompromised to reduce the risk of transfusion-associated graft-versus-host disease and febrile nonhemolytic transfusion reaction.

The patient should receive leukoreduced, irradiated erythrocytes. She has pancytopenia with symptomatic anemia likely because of her chemotherapy. Her bone marrow erythrocyte production cannot be efficiently increased because of her cancer treatment, so an erythrocyte transfusion is clinically indicated. However, immunocompromised patients (those with severe, inherited T-cell immunodeficiency syndromes or Hodgkin lymphoma or recipients of allogeneic or autologous hematopoietic stem cell transplantation, purine analog–based chemotherapy [fludarabine, cladribine, deoxycoformycin], alemtuzumab, or rabbit antithymocyte globulin therapy) are at increased risk of developing transfusion-associated graft-versus-host disease (ta-GVHD). ta-GVHD occurs when the recipient's immune system is unable to eradicate contaminating donor lymphocytes in the transfused erythrocyte or platelet product; the transfused lymphocytes mount an immune response toward the recipient that may result in a maculopapular skin rash, gastrointestinal symptoms, cough and dyspnea, and pancytopenia due to marrow aplasia. Irradiation of the cellular product inactivates contaminating lymphocytes and prevents this complication. ta-GVHD may also occur when partial HLA matching occurs, in which the recipient is heterozygous for an HLA haplotype for which the donor is homozygous. In such a situation, the recipient's immune system will not recognize the donor lymphocytes as foreign and will fail to mount an immune response. As such, all HLA-matched products require irradiation (that is, HLA-matched platelets for patients with platelet transfusion refractoriness owing to alloimmunization), regardless of the competency of the recipient's immune system.

The patient would benefit from leukoreduced erythrocytes, thus minimizing the risk of febrile nonhemolytic transfusion reactions, as well as HLA alloimmunization and subsequent platelet transfusion refractoriness. Although leukoreduction alone likely reduces the risk of ta-GVHD, it does not eliminate the risk of this complication.

This patient has a positive cytomegalovirus (CMV) IgG antibody and thus has already been exposed to this infectious agent. Therefore, a CMV-negative product is not required. Furthermore, the current generation of prestorage leukocyte filters has significantly decreased the risk of CMV transmission as a result of erythrocyte and platelet transfusion. As such, not all transfusion centers use CMV-negative products for recipients who are CMV seronegative.

Washed erythrocytes are considered for patients with a history of severe allergic reactions to transfusions, which this patient does not have.

Question 11

A 70-year-old man is admitted to the hospital for fatigue and malaise of 3 weeks' duration and easy bruising and fever of 1 week's duration. Medical and family histories are unremarkable. He takes no medications.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 128/83 mm Hg, pulse rate is 115/min, and respiration rate is 13/min; BMI is 28. Conjunctivae are pale. Splenomegaly is noted and lower extremity petechiae are observed.

Laboratory studies show a hemoglobin level of 7.3 g/dL (73 g/L), a leukocyte count of 20,000/µL (20 × 10^9/L), and a platelet count of 14,000/µL (14 × 10^9/L). Bone marrow examination reveals 35% lymphoblasts. A peripheral blood smear demonstrates immature cells identified as lymphoid blasts by flow cytometry. Cytogenetic testing using fluorescence in situ hybridization is positive for t(9;22).

In addition t o dexamethasone, which of the following is the most appropriate treatment?

A
Asparaginase

B
Dasatinib

C
Daunorubicin

D
Vincristine

Answer & Critique

Correct Answer: B

Educational Objective: Manage Philadelphia chromosome–positive acute lymphoblastic leukemia in an older patient.

Key Point

Tyrosine kinase inhibitor therapy, such as dasatinib, provides a significant advance in the treatment of older patients with Philadelphia chromosome–positive acute lymphoblastic leukemia.

This patient has acute lymphoblastic leukemia (ALL), and the most appropriate treatment is dasatinib with dexamethasone. Diagnosis requires the presence of 25% or more lymphoblasts on bone marrow examination. Cytochemical stains and flow cytometry can help distinguish ALL from acute myeloid leukemia (AML) and B-cell from T-cell ALL. The prognosis for an older patient with ALL has traditionally been poor, with Philadelphia chromosome [t(9;22)] positivity indicating worse outcomes. Twenty-five percent of all adults with ALL and up to 50% of those older than 70 years are positive for t(9;22). With the advent of tyrosine kinase inhibitor (TKI) therapy, medications like imatinib and dasatinib have become the backbone of therapy for Philadelphia chromosome–positive ALL and can be used alone or with chemotherapy. The most significant advance in the treatment of older patients with Philadelphia chromosome–positive disease is TKI therapy. The results of dasatinib and dexamethasone therapy are better than those for traditional chemotherapy, with less toxicity. For older patients who have Philadelphia chromosome–negative ALL, no clear standard cytotoxic chemotherapy regimen exists. However, TKI therapy can provide disease control for greater than 1 year with much less toxicity.

Based on encouraging progress in intensive pediatric regimens, asparaginase has been incorporated into care for adolescents and young adults with ALL. However, use in older adult patients does not improve outcomes and multiplies toxicity.

Anthracyclines (such as daunorubicin), vincristine, and dexamethasone are part of traditional chemotherapy for pediatric and adult patients with ALL; however, results in older patients are disappointing. Therefore, none of these medications would be the best treatment option for this older patient. Combination regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) can cure adults with ALL, but are too toxic for

use in elderly populations. The paradox of ALL in older adults is that although less aggressive regimens are less toxic, they compromise the ability to control the leukemia.

Question 12

A 38-year-old man is evaluated in the hospital for increasing right leg pain and swelling. He experienced a right femur fracture 2 days ago and underwent surgical repair. Medical history is unremarkable, but family history reveals his mother experienced a pulmonary embolism at age 66 years while receiving breast cancer treatment, and a maternal uncle had a “leg clot” at age 82 years. Medications are as-needed oxycodone and prophylactic-dose enoxaparin.

On physical examination, vital signs are normal. The right leg shows increased circumference of 2 cm at the midcalf compared with the left. The surgical site is clean and dry.

Laboratory studies show normal activated partial thromboplastin and prothrombin times.

Doppler ultrasonography shows a right proximal leg deep venous thrombosis.

Which of the following is the most appropriate thrombophilia testing for this patient?

A
Antiphospholipid antibodies

B
Factor V Leiden

C
Prothrombin gene mutation

D

No thrombophilia testing

Answer & Critique

Correct Answer: D

Educational Objective: Determine indications for thrombophilia testing in a patient with a first thromboembolic event.

Key Point

Thrombophilia testing is not indicated in patients who develop a venous thromboembolism in the setting of a major transient risk factor (major surgery or trauma or prolonged immobility), because results would not influence duration or intensity of anticoagulation therapy.

No thrombophilia testing is indicated in this patient. No evidence indicates that identification of a thrombophilia in this patient would influence the duration or intensity of anticoagulant therapy. Consequently, the American Society of Hematology recommends against thrombophilia testing in patients who develop a venous thromboembolism (VTE) in the setting of a major transient risk factor (surgery, trauma, or prolonged immobility). The appropriate duration of anticoagulation for this patient with VTE due to recent trauma and major surgery is 3 months, regardless of identification of a thrombophilia. It is unclear which patients benefit from thrombophilia testing. It may be appropriate to consider evaluation for a strong thrombophilia in a patient with VTE who is at intermediate risk for recurrent VTE by traditional recurrence risk factors. These are patients with a thromboembolism associated with minor VTE risk factors, such as women with hormone- or pregnancy-associated VTE or men or women with VTE associated with minor immobility or minor surgery. Finding a strong thrombophilia in these patients may be one of the indications for long-term anticoagulation.

Antiphospholipid antibodies (APLAs) impart a greater risk of arterial and venous thromboembolism. Although the prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be elevated in patients with APLAs, they are not adequately sensitive or specific to indicate the presence or absence of this cause of thrombophilia. If antiphospholipid syndrome is suspected, APLA tests (lupus anticoagulant, anticardiolipin antibodies, and anti-?$_2$-glycoprotein I antibodies) should be ordered, independent of whether the PT and aPTT are normal or prolonged. Testing for any of these conditions is not indicated in this patient.

If thrombophilia testing is indicated, evaluation should be based on the circumstances, location, and extent of the thrombosis, possibly with input from a coagulation subspecialist. Factor V Leiden

and the prothrombin G20210A mutation are the most common inherited thrombophilias and are associated with a mildly increased risk for VTE.

Question 13

A 23-year-old man is admitted to the hospital with an acute vaso-occlusive pain episode. He reports pain in his back and legs with no respiratory or abdominal symptoms and rates his pain 10/10. Medical history is significant for homozygous sickle cell anemia (Hb SS). He has vaso-occlusive pain episodes approximately every 2 months. He typically receives erythrocyte transfusions for symptomatic anemia one to three times per year. Medications are folic acid and hydroxyurea.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 115/70 mm Hg, pulse rate is 96/min, and respiration rate is 20/min. Oxygen saturation is 96% breathing ambient air. Scleral icterus is observed. A grade 2/6 early systolic murmur is heard at the base of the heart. Lungs are clear. No hepatosplenomegaly or tenderness is noted on abdominal examination.

Laboratory studies show a hemoglobin level of 7 g/dL (70 g/L), a mean corpuscular volume of 110 fL, and a serum creatinine level of 0.4 mg/dL (35.4 µmol/L).

A chest radiograph is normal.

Hydration and incentive spirometry are initiated.

Which of the following analgesic regimens is most appropriate for this patient?

A
As-needed ketoprofen and morphine

B
As-needed morphine

C
Scheduled meperidine

D
Scheduled morphine

Answer & Critique

Correct Answer: D

Educational Objective: Manage an acute, uncomplicated vaso-occlusive pain episode with opioids.

Key Point

During hospitalization, opioid analgesia is most effectively delivered by regularly scheduled opioid administration or by patient-controlled analgesia pumps.

The most appropriate pain regimen for this patient is scheduled morphine. Pain is the most common complication of sickle cell disease (SCD) and may be the initial presenting symptom in patients who subsequently develop more severe complications, such as acute chest syndrome (ACS) or multiorgan failure. Patients commonly have musculoskeletal symptoms, but vaso-occlusion can occur in any organ system. No reliable physical or laboratory findings serve as useful surrogate markers for excluding vaso-occlusion; therefore, managing a painful episode in SCD is based on symptoms. Management of an uncomplicated painful episode includes hydration, nonopioid and opioid analgesia, and incentive spirometry to avoid ACS. Morphine and hydromorphone are the opioid analgesics of choice. During hospitalization, opioid analgesia is most effectively delivered by regularly scheduled opioid administration or by patient-controlled analgesia pumps that include a basal rate and a demand option.

Meperidine is generally avoided because of its short half-life and lowered seizure threshold.

NSAIDs such as ketoprofen may be useful in the outpatient management of a painful vaso-occlusive crisis in patients with stable kidney function, but are probably inadequate as single agents for patients with severe pain requiring hospitalization. In addition, randomized studies have demonstrated no benefit of adding an NSAID to an opioid for the treatment of acute vaso-occlusive crisis in hospitalized patients.

Question 14

A 25-year-old woman is evaluated for a 3-hour history of pleuritic chest pain and mild shortness of breath. She is pregnant at 16 weeks' gestation. Her symptoms began acutely; she reports no other symptoms or previous problems during the pregnancy. Medical and family history is unremarkable. Her only medication is a prenatal vitamin.

On physical examination, she is afebrile, blood pressure is 125/88 mm Hg, heart rate is 80/min, and respiration rate is 15/min. Oxygen saturation is 97% breathing ambient air. Lungs are clear, and cardiac examination is normal. She has a distended, pregnant abdomen. Trace bipedal edema is noted, and the left midcalf circumference is 1.5 cm larger than the right. The remainder of the physical examination is unremarkable.

A chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

A
CT pulmonary angiography

B
D-dimer test

C
Lower extremity venous duplex ultrasonography

D
Ventilation-perfusion lung scan

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose suspected pulmonary embolism in a pregnant woman.

Key Point

The preferred initial diagnostic test to perform in a pregnant patient with possible pulmonary embolism is lower extremity venous duplex ultrasonography to assess for the presence of deep venous thrombosis, which, if present, would obviate the need for radiation and contrast exposure associated with other diagnostic studies.

This patient, who is pregnant and has a clinical suspicion for pulmonary embolism (PE), should undergo lower extremity venous duplex ultrasonography. Because anticoagulant therapy for PE and deep venous thrombosis (DVT) is similar, diagnosing a DVT noninvasively through ultrasonography would allow immediate initiation of therapy and avoid fetal exposure to radiation and contrast, which are involved in other studies for diagnosing PE. However, a normal lower extremity study for DVT does not exclude the presence of a PE in a patient with a reasonable pretest probability based on clinical features, such as this woman. If her ultrasound is normal, a ventilation-perfusion (V/Q) lung scan is the next preferred modality. If a V/Q scan is unavailable, CT pulmonary angiography is the next diagnostic choice.

Unfortunately, no validated clinical prediction rules exist for assessing pretest probability of PE in pregnant women. Additionally, D-dimer levels are normally elevated during pregnancy. Therefore, D-dimer testing has minimal clinical utility in evaluating for the presence of PE or DVT.

Bibliography

Question 15

A 42-year-old woman is evaluated for thrombocytopenia. She was admitted to the hospital 1 week ago for newly diagnosed acute myeloid leukemia. She has been receiving leukoreduced, irradiated erythrocyte and platelet transfusions since admission. Yesterday, her platelet count was 8000/μL (8×10^9/L). A platelet count checked 30 minutes after a random, donor-pooled platelet transfusion was 11,000/μL (11×10^9/L). This morning, her platelet count was 6000/μL (6×10^9/L). Thirty minutes after a random, donor-pooled platelet transfusion, the platelet count is 9000/μL (9×10^9/L). She has had four uncomplicated pregnancies and deliveries. Medications are daunorubicin, cytarabine, cefepime, posaconazole, valacyclovir, and ondansetron.

On physical examination, vital signs are normal. No splenomegaly is present. Ecchymoses are seen at previous venipuncture sites. She has scattered petechiae over the lower extremities. The remainder of the examination is normal.

Peripheral blood smear reveals no schistocytes or platelet clumps.

Which of the following is the most appropriate management?

A
Transfuse ABO-matched platelets

B
Transfuse HLA-matched platelets

C
Transfuse washed platelets

D
Observation

Answer & Critique

Correct Answer: B

Educational Objective: Treat platelet transfusion refractoriness.

Key Point

Patients experiencing platelet transfusion refractoriness because of alloimmunization should receive HLA-matched platelets.

This patient should receive HLA-matched platelets. She meets criteria for platelet transfusion refractoriness, defined as an increase in the platelet count less than 10,000/µL (10×10^9/L) measured 10 to 60 minutes after transfusion on at least two separate occasions. Nonimmune causes include sepsis, fever, disseminated intravascular coagulation, splenomegaly, and medications that decrease platelet half-life. This patient has no features suggesting a nonimmune cause. She is most likely alloimmunized from her previous pregnancies. Such patients are ideally treated with HLA-matched platelets. A systematic review demonstrated improved 1-hour posttransfusion platelet counts with HLA typing. However, the effects on 24-hour platelet counts were more varied, and the impact of this practice on bleeding and mortality is unclear. If HLA-matched platelets are not available, other strategies can be used, including transfusion of HLA-compatible platelets, in which the transfused platelets are missing the antigen to which the patient's alloantibodies are directed, or platelet crossmatching, in which the patient's serum is incubated with donor platelets.

ABO-matched platelets lead to a slightly higher platelet increment in patients who are not alloimmunized but are not likely to have a significant impact on someone who is truly alloimmunized.

Washed platelets are typically reserved for patients who have had severe allergic reactions to platelet transfusion (such as patients who are IgA deficient).

Studies have shown that prophylactic platelet transfusion for a platelet count less than 10,000/µL (10×10^9/L) is superior to platelet transfusions administered at the onset of clinical bleeding, thus decreasing the incidence of clinically significant bleeding. As such, observation without platelet transfusion is inappropriate.

Question 16

A 56-year-old man is evaluated in the hospital for acute onset right lower extremity pain and swelling. He was admitted to the hospital 2 days ago with hematemesis and underwent emergent upper endoscopy with band ligation of extensive esophageal varices. He received 2 units of packed red blood cells. Medical history is significant for alcoholic cirrhosis. He stopped drinking alcohol 18 months ago. His only outpatient medication is propranolol.

On physical examination, he is alert and oriented. He is afebrile, blood pressure is 128/76 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. Splenomegaly is present. The right calf is 4 cm in circumference larger than the left. The remainder of the physical examination is noncontributory.

Laboratory studies:

Activated partial thromboplastin time	39.3 s
Hemoglobin	10.3 g/dL (103 g/L)
Platelet count	78,000/µL (78 × 10^9/L)
Prothrombin time	16.3 s

A lower extremity Doppler ultrasonography reveals a right leg proximal deep venous thrombosis (DVT).

Which of the following is the most appropriate management of this patient's DVT?

A
Argatroban

B
Inferior vena cava filter placement

C
Intravenous heparin

D
Rivaroxaban

Answer & Critique

Correct Answer: B

Educational Objective: Manage a patient with acute venous thromboembolism who experienced a major bleeding episode.

Key Point

In patients who cannot safely undergo anticoagulation therapy for venous thromboembolism, such as those with recent bleeding, an inferior vena cava filter should be used until the bleeding risk resolves.

Inferior vena cava (IVC) filter placement is indicated; this patient cannot safely undergo anticoagulation because of his recent major gastrointestinal bleed. He is at increased risk for bleeding owing to the presence of a coagulopathy, likely secondary to his liver disease, and thrombocytopenia, likely due to hypersplenism from an enlarged spleen resulting from portal hypertension. Despite having prolonged coagulation parameters, patients with liver disease are not “autoanticoagulated” and may experience venous thromboembolism (VTE), because procoagulant and anticoagulant protein production is deficient in unpredictable ratios, making it nearly impossible to predict if the patient is most at risk for bleeding or thrombosis. Because of this, anticoagulation in patients with liver disease should be undertaken with caution because of the risk for bleeding. This patient's bleeding risk is very high because of the recent episode of bleeding varices. When IVC filters are necessary, retrievable filters are strongly recommended rather than permanent filters. Whether IVC filters are beneficial for patients with pulmonary embolism (PE) despite appropriate therapeutic anticoagulation is unclear; a possible indication is massive PE with poor cardiopulmonary reserve. No evidence supports the use of IVC filters in the primary prophylaxis of VTE. If the bleeding risk resolves, a conventional course of anticoagulant therapy is recommended with consideration of filter removal.

Considering this patient's risk for bleeding, no anticoagulant (such as heparin, argatroban, rivaroxaban) can safely be given. Additionally, rivaroxaban and argatroban are partially cleared by the liver and are contraindicated in severe liver disease.

Question 17

A 30-year-old woman is evaluated in follow-up for anemia diagnosed during a recent evaluation for symptoms of fatigue. She reports no shortness of breath, dizziness, or chest pain. Medical history is notable only for heavy menses. Family history is remarkable for anemia in her mother. Her only medication is an iron supplement. She is white.

On physical examination, the patient appears well. Temperature is 36.9 °C (98.4 °F), blood pressure is 100/60 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 25. No lymphadenopathy or organomegaly is identified, and the remainder of her physical examination is unremarkable.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Mean corpuscular volume	68 fL
Platelet count	400,000/µL (400 × 10^9/L)
Reticulocyte count	6% of erythrocytes
Bilirubin, total	2.0 mg/dL (34.2 µmol/L)
Lactate dehydrogenase	300 U/L
Iron studies	
Ferritin	450 ng/mL (450 µg/L)
Iron	60 µg/dL (11 µmol/L)
Total iron-binding capacity	300 µg/dL (54 µmol/L)
Hemoglobin electrophoresis	
Hemoglobin A	94% (slightly low)
Hemoglobin A_2	4% (increased)
Hemoglobin F	2% (increased)

Hemoglobin S	0% (normal)

Numerous target cells are seen on a peripheral blood smear.

Which of the following is the most likely diagnosis?

A
Anemia of chronic disease

B
Iron malabsorption

C
α-Thalassemia

D
β-Thalassemia

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose ?-thalassemia.

Key Point

Hemolytic anemia, microcytosis, and target cells are typical of ?-thalassemia, which is associated with slightly increased hemoglobin A_2 and some residual hemoglobin F.

This patient's most likely diagnosis is ?-thalassemia intermedia. She has erythrocyte parameters typical for thalassemia (hemolytic anemia, microcytosis, target cells), a common genetic disorder caused by a mutation in one or more ?-globin or ?-globin genes leading to a quantitative deficiency in the synthesis of that globin chain. The imbalance in globin-chain synthesis leads to impaired production of hemoglobin and ineffective erythropoiesis, with intramedullary hemolysis and often chronic anemia. ?-Thalassemia and ?-thalassemia are usually differentiated by hemoglobin electrophoresis, with ?-thalassemia associated with a slightly increased hemoglobin A_2 and some residual hemoglobin F. Because of this patient's increased hemoglobin A_2 level, she most likely has ?-thalassemia. Because of the low-level hemolysis associated with either type of thalassemia, patients with thalassemia (and other chronic hemolytic anemias) can commonly have low folate levels even if dietary intake is inadequate, leading to worsening of chronic anemia.

Although most patients with ?-thalassemia intermedia are anemic at baseline, most are physiologically adjusted to a hemoglobin level between 7 and 10 g/dL (70-100 g/L). This is not an anemia associated with chronic inflammation.

The patient's iron studies do not indicate iron deficiency; in fact, her ferritin level is elevated, which is often seen in thalassemia. Therefore, she is unlikely to be experiencing iron malabsorption.

Question 18

A 68-year-old man is evaluated for a 3-year history of dyspnea on exertion. He experiences no headaches or blurred vision. Medical history is notable for a stroke 2 years ago. He is a smoker with an 80-pack-year smoking history. Medications are hydrochlorothiazide, lisinopril, aspirin, and simvastatin.

On physical examination temperature is 36.7 °C (98.0 °F), blood pressure is 145/84 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Oxygen saturation breathing ambient air is 88%. He has facial plethora. He has no carotid bruits. Cardiac sounds are distant. Pulmonary examination reveals distant breath sounds with scattered wheezing. No hepatosplenomegaly is palpated. No digital clubbing is observed.

Laboratory studies show a hemoglobin level of 18.2 g/dL (182 g/L), leukocyte count of 8000/µL (8×10^9/L) with a normal differential, and platelet count of 225,000/µL (225×10^9/L). Erythropoietin level is 30 mU/mL (30 U/L).

The patient is advised to quit smoking.

Which of the following is the most appropriate next step in management?

A
Bone marrow biopsy

B
JAK2 V617F testing

C
Phlebotomy

D
Supplemental oxygen

Answer & Critique

Correct Answer: D

Educational Objective: Evaluate erythrocytosis.

Key Point

Secondary erythrocytosis can be caused by hypoxemia, so patients may benefit from oxygen supplementation.

The patient should receive supplemental oxygen. He probably has secondary erythrocytosis due to hypoxic lung disease and may benefit from oxygen therapy based on his documented hypoxemia (arterial P_{O_2} ?55 mm Hg [7.3 kPa] or arterial oxygen saturation ?88%). The erythropoietin level is elevated owing to hypoxemia, causing an erythrocyte mass. No splenomegaly is present on physical examination, and the lung examination suggests COPD.

Because of the patient's elevated erythropoietin level and hypoxemia, a bone marrow biopsy is not required to exclude polycythemia vera (PV). No leukocytosis, basophilia, or thrombocytosis is seen on laboratory studies, all of which are common in PV.

The *JAK2 V617F* activating mutation defines PV, and 95% of PV harbors this mutation, with the other 5% presenting with variations of the mutation. No *JAK2*-negative PV exists. However, *JAK2* testing is expensive and is not required when a clear cause of secondary erythrocytosis is apparent.

The appropriate management of secondary erythrocytosis is control of the underlying cause. In most circumstances, therapeutic phlebotomy is not recommended for secondary erythrocytosis, because the increased erythrocyte mass is compensating for an unmet tissue oxygenation need.

Question 19

A 73-year-old woman is evaluated for increasing dyspnea on exertion and left buttock pain of 1 week's duration. She reports pain with standing straight or sitting down. She has no history of trauma. Family history is unremarkable, and she takes no medications.

On physical examination, the patient is pale and displays significant distress by bending over and grasping the back of the chair. Temperature is 36.6 °C (98.1 °F), blood pressure is 140/80 mm Hg, pulse rate is 108/min, and respiration rate is 19/min. A 10-cm hematoma is noted on the left buttock with tracking down the back of the thigh, with smaller ecchymoses scattered over her arms and shins. She has no bleeding of the gums or nose. A stool sample is guaiac negative.

Laboratory studies:

Hematocrit	35%
Leukocyte count	9100/µL (9.1×10^9/L)
Mean corpuscular volume	89 fL
Platelet count	310,000/µL (310×10^9/L)
Activated partial thromboplastin time (aPTT)	90 seconds
Prothrombin time	10.3 seconds
aPTT following 1:1 mixing study with normal plasma	45 seconds
Factor VIII activity	3% (normal, 50%-150%)
Factor VIII inhibitor	Markedly elevated

Which of the following is the most appropriate management?

A
Administer desmopressin

B
Administer factor VIII

C
Administer recombinant activated factor VII

D Measure lupus anticoagulant

Answer & Critique

Correct Answer: C

Educational Objective: Manage acquired hemophilia.

Key Point

Recombinant activated factor VII is used to treat the bleeding episodes of acquired hemophilia associated with high titers of inhibitor.

The patient should be given recombinant activated factor VII (VIIa). She is an older adult with no bleeding history and no family history of bleeding disorders who now has intramuscular and cutaneous bleeding, which suggests an acquired bleeding disorder. Acquired hemophilia (acquired factor VIII deficiency) causes bleeding with an isolated prolongation of the activated partial thromboplastin time (aPTT). It is associated with the postpartum state, malignancy, or autoimmune conditions, but 50% of cases are idiopathic. Patients have no history of bleeding, but bleeding at presentation can be severe. Unlike congenital hemophilia, bleeding in acquired hemophilia tends to be mucocutaneous and intramuscular. Factor VIII levels are reduced, and mixing study results show unsuccessful correction consistent with an inhibitor. Test results for the lupus anticoagulant are negative.

Patients with low titers of inhibitor (measured in Bethesda units) may be treated with factor VIII concentrates. Patients with high inhibitor titers (>5 Bethesda units) require treatment with recombinant factor VIIa or prothrombin complex concentrates designed to activate factor X and secure hemostasis independent of factor VIII and the intrinsic pathway. Patients may require immunosuppression for inhibitor eradication.

Mild bleeding associated with low inhibitor titers may be treated with desmopressin. However, this patient's hematocrit is low, she has tachycardia possibly related to volume depletion, and her inhibitor level is elevated, making desmopressin a less suitable treatment than recombinant factor VIIa.

Lupus anticoagulants can interfere with the coagulation cascade, causing a prolongation of the aPTT or prothrombin time not corrected by a mixing study. Although they prolong in vitro coagulation tests, they are associated with an increased risk for venous and arterial

thromboembolism, not a bleeding tendency. This patient's cutaneous and intramuscular bleeding is inconsistent with the presence of a lupus anticoagulant.

Question 20

A 52-year-old man is evaluated in follow-up. He was admitted to the hospital 2 weeks ago with a new diagnosis of acute myeloid leukemia. He has received induction chemotherapy with daunorubicin and cytarabine. Medical history is remarkable for an urticarial reaction to a platelet transfusion that resolved promptly with diphenhydramine. Other medications are posaconazole, valacyclovir, and cefepime.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 132/72 mm Hg, pulse rate is 84/min, and respiration rate is 18/min. Oxygen saturation is 94% breathing ambient air. Oropharyngeal examination is unremarkable. He has scattered petechiae over both ankles and an ecchymosis at the insertion site of his central venous catheter.

Laboratory studies show he is neutropenic and has a platelet count of 12,000/μL (12×10^9/L).

Which of the following is the most appropriate management of this patient's thrombocytopenia?

A
Transfuse leukoreduced, irradiated platelets

B
Transfuse leukoreduced, irradiated, HLA-matched platelets

C
Transfuse leukoreduced, irradiated, washed platelets

D
Recheck platelet count in 24 hours

Answer & Critique

Correct Answer: D

Educational Objective: Manage thrombocytopenia in a patient with acute myeloid leukemia.

Key Point

Clinically stable patients with chemotherapy-induced thrombocytopenia who are not bleeding do not benefit from platelet transfusion when the platelet count is 10,000/µL (10×10^9/L) or greater.

The platelet count should be rechecked in 24 hours. Although this patient is significantly thrombocytopenic, phase III clinical trial data do not support the use of prophylactic platelet transfusions for patients with acute myeloid leukemia (AML) whose platelet count is 10,000/µL (10×10^9/L) or higher. Randomized studies have been published comparing a platelet transfusion threshold of 10,000/µL (10×10^9/L) to 20,000/µL (20×10^9/L) in stable patients with AML undergoing induction or consolidation chemotherapy; all have demonstrated equivalent outcomes with respect to clinically significant bleeding, need for erythrocyte transfusions, and mortality during induction chemotherapy. Therefore, these data support and guidelines recommend a threshold of 10,000/µL (10×10^9/L) for prophylactic platelet transfusion in hospitalized patients with thrombocytopenia due to decreased bone marrow production. Patients with acute promyelocytic leukemia (APL), fever, clinically significant bleeding, or a need for invasive procedures were not evaluated in these studies and are typically transfused at a threshold of 20,000/µL (20×10^9/L).

Transfusion of leukoreduced, irradiated platelets would be appropriate if the patient's platelet count decreases to less than 10,000/µL (10×10^9/L). HLA-matched platelets would only be used if the patient had a history of platelet transfusion refractoriness attributed to platelet alloantibodies. Washing of platelets leads to loss of platelet numbers and function and is reserved for patients with a history of a severe allergic reaction to a transfused blood product (such as anaphylaxis in a patient with IgA deficiency).

Question 21

A 77-year-old woman is evaluated for frequently fluctuating INRs (<1.8 to >3.5) while taking warfarin therapy. She has undergone INR testing every 1 to 2 weeks and frequent warfarin dose adjustments. She reports a consistent dietary intake. Medical history is notable only for recurrent deep venous thrombosis. She takes no other medications.

On physical examination, vital signs are normal, as is the remainder of the examination.

Which of the following is the most appropriate next step in management?

A
Daily low-dose vitamin K supplementation

B
Genetic testing for cytochrome P-450 2C9 and vitamin K epoxide reductase complex-1 polymorphisms

C
Genetic testing for factor V Leiden

D
Warfarin cessation and aspirin initiation

Answer & Critique

Correct Answer: A

Educational Objective: Manage warfarin therapy with vitamin K supplementation.

Key Point

In some patients with fluctuating INRs while taking warfarin, daily supplementation with low-dose vitamin K (100-150 µg/d) can stabilize the INR.

The patient should begin daily low-dose vitamin K supplementation. In 2007, a double-blind randomized trial compared the effects of low-dose vitamin K (100-150 µg/d) and placebo on INR stability in 70 patients receiving chronic warfarin therapy. Vitamin K supplementation resulted in 19 of 35 patients achieving the predefined criteria for stable control of anticoagulation compared with only 7 of 35 patients receiving placebo. It was hypothesized that low-dose vitamin K reduced the day-to-day variation in dietary vitamin K intake in patients with unexplained INR fluctuations.

Polymorphisms in the genes transcribing enzymes involved in the metabolism of vitamin K antagonists, such as cytochrome P-450 2C9 and vitamin K epoxide reductase complex-1, contribute to the variability in dose requirements among patients but do not explain day-to-day or week-to-week INR fluctuations in individual patients. Therefore, genetic testing would not be helpful in this situation.

A factor V Leiden mutation would not explain INR fluctuations. The only thrombophilia that might cause INR fluctuations over time is the presence of a lupus anticoagulant; however, such frequent fluctuations as this patient is experiencing would not be expected with any thrombophilia. Thus, a thrombophilia evaluation would not be indicated.

Aspirin alone will not provide the same protective benefit as warfarin for this patient with recurrent deep venous thrombosis.

Question 22

A 24-year-old woman is evaluated in the emergency department for dyspnea on exertion and severe fatigue. Medical history is significant for sickle cell anemia, with a hospital admission for acute chest syndrome last year. She reports that her 4-year-old son had a high fever 1 week ago. She takes stable doses of hydroxyurea and a folic acid supplement.

On physical examination, she appears breathless and pale. Temperature is 38.4 °C (101.1 °F), blood pressure is 95/61 mm Hg, pulse rate is 104/min, and respiration rate is 14/min. Scleral icterus is observed. Lungs are clear. Cardiac examination reveals tachycardia with a prominent flow murmur.

Laboratory studies:

Hemoglobin	3.4 g/dL (34 g/L)
Leukocyte count	14,000/µL (14×10^9/L)
Platelet count	222,000/µL (222×10^9/L)
Reticulocyte count	0.1% of erythrocytes

Which of the following is the most likely cause of this patient's findings?

A
Cytomegalovirus

B
Epstein-Barr virus

C
Influenza A virus

D
Parvovirus B19

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose the cause of an aplastic crisis.

Key Point

Parvovirus B19 infection can cause acquired pure red cell aplasia in an otherwise functionally asplenic patient with sickle cell disease.

The patient has parvovirus B19 infection. She has chronic hemolytic anemia due to sickle cell anemia and presents with severe anemia and a completely inadequate reticulocyte response 1 week after being exposed to a child with a febrile illness, which was likely caused by parvovirus B19. Hydroxyurea could lead to worsening anemia in a patient with sickle cell anemia but would not cause the acute signs or symptoms found in this patient. A subsequent bone marrow examination would demonstrate pure red cell aplasia (PRCA). Parvovirus has a tropism for erythrocyte precursors and is a known cause of aplastic crisis in patients with underlying sickle cell disease (SCD). Immune competent patients and those without chronic hemolysis have a milder hematologic response to parvovirus infection and are more likely to recover spontaneously.

Cytomegalovirus could cause constitutional symptoms and could trigger a painful crisis, but it is not associated with direct destruction of erythrocyte precursors. Cytomegalovirus may cause retinitis, gastroenteritis, or hepatitis in an immunocompromised patient, none of which are seen in this patient. Adults with SCD are functionally asplenic.

Epstein-Barr virus is unlikely owing to its lack of association with PRCA. However, viral illnesses are the frequent underlying causes that precipitate vaso-occlusive crises or acute chest syndrome in patients with SCD.

Influenza A virus is an unlikely diagnosis because the patient has no typical symptoms. Although influenza A could cause severe viral pneumonia and could lead to acute chest syndrome, its association with PRCA is not strong.

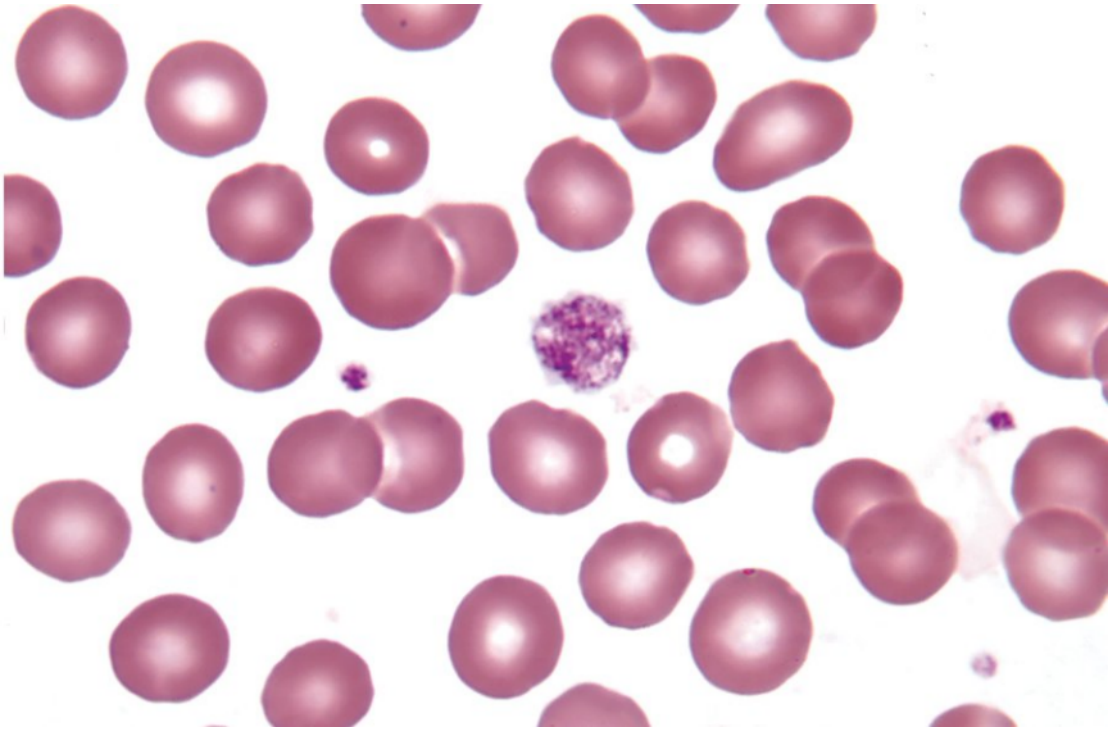
Question 23

A 35-year-old woman is evaluated for the recent onset of a rash on her legs. She has no other symptoms. She does not drink alcohol. Medications are an oral contraceptive and a multivitamin.

On physical examination, vital signs are normal. Nonpruritic, nonblanching red macules are noted on the lower extremities. Abdominal examination reveals no splenomegaly.

Laboratory study results show a hematocrit of 38%, leukocyte count of 7000/µL (7×10^9/L), and platelet count of 78,000/µL (78×10^9/L).

The peripheral blood smear is shown.



Which of the following is the most appropriate management?

A

Anti-D immune globulin

B Prednisone

C Repeat complete blood count in 1 week

D Rituximab

E Splenectomy

Answer & Critique

Correct Answer: C

Educational Objective: Manage asymptomatic immune thrombocytopenic purpura.

Key Point

Patients with immune thrombocytopenic purpura without evidence of bleeding and platelet counts greater than 30,000 to 40,000/µL (30-40 × 10^9/L) have less than a 15% chance of developing more severe thrombocytopenia requiring treatment and can be managed with careful observation.

The patient most likely has immune thrombocytopenic purpura (ITP) and should have another complete blood count performed in 1 week. Although ITP is a diagnosis of exclusion, supportive clinical findings include an otherwise normal blood count and the absence of additional organ dysfunction. Platelets on the peripheral blood smear are large because they typically have been recently released from the marrow, and the enhanced hemostatic function of these young platelets may account for less severe bleeding symptoms than those associated with other diseases with a similar platelet count. Not all patients with ITP require therapy, and monitoring for signs of bleeding or further declines in platelet counts may be appropriate. Asymptomatic patients without evidence of bleeding and platelet counts greater than 30,000 to 40,000/µL (30-40 × 10^9/L) have less than a 15% chance of developing more severe thrombocytopenia requiring treatment. In such patients, the most appropriate course of action is to provide counseling on potential bleeding symptoms and repeat the complete blood count at a designated interval, generally 1 to 2 weeks, until the course of the illness is determined.

In adults with ITP, therapy may be required for patients with platelet counts lower than 30,000 to 40,000/µL (30-40 × 10^9/L) or with bleeding. Initial therapy consists of glucocorticoids. Patients who do not respond to glucocorticoid therapy should be treated with an additional agent such as intravenous immune globulin or anti-D immune globulin or rituximab.

Splenectomy leads to a sustained remission in 75% of patients. Because of this patient's lack of symptoms and platelet count greater than 30,000/µL (30 × 10^9/L), therapy is unnecessary at this time, and the patient may be safely observed.

Question 24

A 43-year-old man is evaluated for a 2-day history of painful swelling of the left thigh just below the groin. He reports no preceding trauma, immobility, surgery, hospital stay, or long-distance airline travel. Medical history is notable for well-controlled hypertension. His only medication is losartan.

On physical examination, vital signs are normal. BMI is 28. An approximately 6-cm area of erythema and tenderness with a palpable cord is present overlying the greater saphenous vein on the proximal medial aspect of the left thigh up to the inguinal crease, consistent with superficial thrombophlebitis. Examination of the distal extremities is normal, without swelling or asymmetry. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

A
Low-dose aspirin

B
Serum D-dimer testing

C
Venous duplex ultrasonography of the left thigh

D
Warm compresses and NSAIDs

Answer & Critique

Correct Answer: C

Educational Objective: Manage unprovoked proximal leg superficial thrombophlebitis.

Key Point

Duplex ultrasonography is indicated to assess for the possibility of an associated deep venous thrombosis (DVT) in patients with isolated superficial venous thrombophlebitis (SVT), because DVT or pulmonary embolism risk increases in patients with SVT of the great or small saphenous vein, with extremity swelling more pronounced than would be expected from the SVT alone, and with progressive symptoms.

This patient should undergo venous duplex ultrasonography of the left thigh to evaluate for deep venous thrombosis (DVT) associated with his superficial venous thrombophlebitis (SVT). DVT or pulmonary embolism (PE) develops in up to 3.3% of patients with isolated SVT. The risk increases in patients with SVT of the great or small saphenous vein, with extremity swelling more pronounced than would be expected from the SVT alone, and with progressive symptoms. In these situations, such as with this patient, duplex ultrasonography is indicated to assess for the possibility of an associated DVT.

The effectiveness of low-dose aspirin to treat or prevent propagation of clots in SVT has not been established. Additionally, the use of other anticoagulants for treatment of SVT is controversial. Some evidence indicates that patients with extensive SVT may benefit from a short course of anticoagulant therapy. However, because of a lack of additional data, the specific patients for whom treatment is indicated, the optimal duration of anticoagulation, and the appropriate drug dose and choice are unknown.

D-dimer testing has no utility for differentiating superficial from deep venous thrombosis because levels may be elevated in both conditions. It would, therefore, not be useful in this patient.

Nonextensive SVT, defined as less than 5 cm in length and not near the deep venous system, may be treated with only symptomatic therapy consisting of analgesics, anti-inflammatory medications, and warm or cold compresses for symptom relief, because the risk of progression into the deep venous system and of PE is low.

Question 25

A 79-year-old woman is diagnosed with new-onset anemia during a routine examination. Medical history is significant for an ischemic stroke 8 weeks ago, which resulted in residual right-sided weakness and admission to a rehabilitation facility. At that time, her complete blood count was normal. She has been eating poorly while in the facility. Her medications are aspirin, lisinopril, and simvastatin.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 120/70 mm Hg, pulse rate is 82/min, and respiration rate is 12/min; BMI is 27. Right-sided motor strength is 3/4 and sensation is normal.

Laboratory studies:

Hemoglobin	10.1 g/dL (101 g/L)
Mean corpuscular volume	102 fL
Folate	2.5 ng/mL (5.7 nmol/L)
Homocysteine	10.2 mg/L (75.4 µmol/L)
Methylmalonic acid	Normal

Which of the following is the most likely diagnosis?

A
Folate deficiency

B
Iron deficiency

C
α-Thalassemia trait

D
Vitamin B_{12} deficiency

Answer & Critique

Correct Answer: A

Educational Objective: Diagnose folate deficiency.

Key Point

An elevated homocysteine level is 90% sensitive for folate deficiency, making this measurement the most sensitive diagnostic marker in suspected folate deficiency when the serum folate level is normal.

This patient has folate deficiency. Folate deficiency caused by decreased folate consumption occurs infrequently, because normal diets are replete with folate. However, patients with folate-deficient diets, especially those with generalized malnutrition or poor nutrition, can become folate deficient in weeks to months because of relatively limited stores of folate in the body. Other less common causes of folate deficiency include conditions such as hemolytic anemia (for example, sickle cell disease), desquamating skin disorders (for example, psoriasis), and other conditions associated with increased cellular turnover. Measuring serum folate levels is typically unreliable in diagnosing folate deficiency, because folate levels increase rapidly after a single folate-containing meal. Plasma homocysteine levels increase in folate deficiency, whereas homocysteine and methylmalonic acid levels are increased in cobalamin deficiency. An elevated homocysteine level has a sensitivity of greater than 90% in the diagnosis of folate deficiency, making homocysteine measurement a reasonable test when the disorder is suspected but the serum folate level is normal.

In addition to peripheral blood smear findings of microcytosis and anisopoikilocytosis (abnormalities in erythrocyte size and shape), patients with iron deficiency have reduced serum iron and ferritin levels, increased total iron-binding capacity, and reduced transferrin saturation (iron/total iron-binding capacity). The patient's macrocytosis and high homocysteine level make iron deficiency an unlikely cause of her anemia.

?-Thalassemia trait (or ?-thalassemia minor) is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results. The (-?/-?) variant is found in 2% to 3% of all black persons and is often mistaken for iron deficiency. The patient's new-onset macrocytic anemia is not consistent with an inherited hemoglobinopathy associated with microcytosis.

Vitamin B_{12} deficiency usually develops over several months, not weeks. Furthermore, homocysteine and methylmalonic acid levels are elevated in vitamin B_{12} deficiency, but this patient's methylmalonic acid level is normal.

Question 26

A 67-year-old man is evaluated during follow-up consultation after a diagnosis of essential thrombocythemia discovered incidentally on a routine health maintenance examination. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, he is afebrile, blood pressure is 115/72 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. Cardiac evaluation reveals a regular rate and rhythm with no murmurs.

Results of laboratory studies show a hemoglobin level of 15 g/dL (150 g/L), leukocyte count of 5600/μL (5.6×10^9/L), and platelet count of 770,000/μL (770×10^9/L). Follow-up testing confirms a diagnosis of essential thrombocythemia.

Which of the following is the most appropriate treatment?

A
Anagrelide plus low-dose aspirin

B
Hydroxyurea plus low-dose aspirin

C
Ruxolitinib

D
Warfarin

E
Observation

Answer & Critique

Correct Answer: B

Educational Objective: Treat essential thrombocythemia based on risk stratification.

Key Point

Hydroxyurea plus low-dose aspirin is the best treatment option for essential thrombocythemia when treatment is required in patients older than 60 years, those with a platelet count greater than 1 million/µL (1000 × 10^9/L), or those with a history of thrombosis.

Hydroxyurea plus low-dose aspirin is the most appropriate treatment for patients with essential thrombocythemia (ET) in whom treatment is indicated. Treatment of ET requires reduction of the platelet count; however, when and whom to treat remain controversial. Although the exact platelet count does not determine the risk for thrombosis, lowering the platelet count in patients at risk for thrombosis will decrease this risk and, possibly, the risk for secondary myelofibrosis. Patients do not require treatment if they are younger than 60 years, have a platelet count less than 1 million/µL (1000 × 10^9/L), and have no history of thrombosis. Hydroxyurea plus low-dose aspirin is the best treatment option for ET when treatment is required in patients older than 60 years, those with a platelet count greater than 1 million/µL (1000 × 10^9/L), or those with a history of thrombosis or an increased risk for thrombosis because of cardiovascular risk factors such as hypertension and diabetes mellitus. Hydroxyurea plus low-dose aspirin reduces the risk for arterial thrombosis and bleeding (regardless of the platelet count achieved) in patients with ET.

Anagrelide is another platelet-lowering agent used to manage ET, but in a randomized trial comparing anagrelide with hydroxyurea, anagrelide was found to have a less favorable side effect profile. Likewise, hydroxyurea, but not anagrelide, decreases thrombotic risk independent of platelet-count lowering.

Ruxolitinib is an inhibitor of constitutively active *JAK2 V617F*. Although 50% of patients with ET demonstrate this mutation, ruxolitinib has a therapeutic role only in alleviating the splenomegaly and systemic symptoms of primary myelofibrosis.

Warfarin has not been studied for primary prophylaxis of ET; therefore, it would not be an appropriate treatment choice for this patient.

The patient's age is an important factor in initiating therapy, making observation an inappropriate choice.

Question 27

A 78-year-old woman is evaluated for progressive fatigue and dyspnea with exertion over the past 6 months. She has otherwise felt well with no nausea, vomiting, or changes in stool. Medical history is significant for hypertension and an aortic valve replacement at age 67 years. Medications are metoprolol and warfarin.

On physical examination, the patient appears well. Temperature is 37.0 °C (98.6 °F), blood pressure is 135/55 mm Hg, pulse rate is 65/min, and respiration rate is 14/min. BMI is 28. She has mild scleral icterus. The lungs are clear to auscultation. Examination of the heart reveals a mechanical S_2, a grade 3/6 systolic murmur at the right upper sternal border radiating to the carotid arteries, and a soft diastolic murmur heard at the left sternal border. The spleen is not palpable, and no pedal edema is present. Stool guaiac testing is negative.

Laboratory studies:

Haptoglobin	32 mg/dL (320 mg/L)
Hemoglobin	6.5 g/dL (65 g/L)
Leukocyte count	5500/µL (5.5 × 10^9/L)
Mean corpuscular volume	71 fL
Platelet count	290,000/µL (290 × 10^9/L)
Reticulocyte count	2.9% of erythrocytes
Bilirubin, total	2.7 mg/dL (46.2 µmol/L)
Bilirubin, direct	1.0 mg/dL (17.1 µmol/L)
Ferritin	3.6 ng/mL (3.6 µg/L)
Lactate dehydrogenase	1200 U/L

Peripheral blood smear shows 3+ schistocytes and microcytic, hypochromic cells.

Which of the following is the most appropriate diagnostic test to perform next?

A
ADAMTS-13 assay

B
D-dimer measurement

C
Direct antiglobulin (Coombs) test

D
Echocardiography

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose macroangiopathic hemolytic anemia caused by a mechanical heart valve.

Key Point

Patients with suspected macroangiopathic hemolytic anemia caused by a mechanical heart valve should be diagnosed using transesophageal echocardiography.

This patient should be further evaluated with echocardiography; she likely has hemolysis due to her mechanical aortic valve. She has evidence of hemolytic anemia based on her low serum haptoglobin and high lactate dehydrogenase levels. The peripheral blood smear shows schistocytes, which are often found in clinical conditions in which erythrocytes are damaged in small blood vessels (microangiopathic hemolytic anemia), but schistocytes may also occur from trauma in larger blood vessels (macroangiopathic hemolytic anemia). The patient has a mechanical heart valve with a significant murmur, suggesting possible valve dysfunction, and, in the absence of other likely causes of a microangiopathic hemolytic anemia, this is likely the cause of her hemolysis. Therefore, echocardiography to identify a regurgitant jet or paravalvular leak, suggested by the murmur present in this patient, would be the most appropriate next diagnostic study. In patients with suspected valve-associated hemolysis, transesophageal echocardiography is the preferred study because of its ability to effectively visualize the aortic valve structures for this potential complication. Patients with chronic intravascular hemolysis may ultimately develop iron deficiency anemia as the heme iron released from the hemolysis passes through the kidneys and is lost in the urine.

Thrombotic thrombocytopenic purpura (TTP) is a cause of microangiopathic hemolytic anemia and should be considered in this patient. However, her normal platelet count and the slowly progressive onset of her symptoms make this diagnosis unlikely. In patients with TTP, an ADAMTS-13 assay may be helpful in estimating prognosis, but would not be an appropriate study in this patient.

Disseminated intravascular coagulation (DIC) is an acquired form of microangiopathic hemolytic anemia. Acute DIC is associated with evidence of accelerated fibrinolysis, including increased fibrin degradation products and D-dimer. However, this patient has no other clinical findings

consistent with DIC (such as bleeding or thrombocytopenia), making this an unlikely diagnosis and a D-dimer measurement unnecessary.

The direct antiglobulin (Coombs) test is used to determine an autoimmune cause of hemolytic anemia. However, neither warm nor cold autoimmune hemolytic anemia causes schistocytes as seen in this patient's blood smear, making this diagnosis unlikely. Therefore, this test would be of low diagnostic yield.

Question 28

A 42-year-old man arrives for follow-up consultation. Three months ago he developed a proximal right leg deep venous thrombosis following a skiing-related fracture of the right tibia. Although not recommended by guidelines, a thrombophilia evaluation was performed, which revealed an elevated plasma homocysteine level, and subsequent genetic testing revealed that he is homozygous for the C677T methylene tetrahydrofolate reductase (*MTHFR*) polymorphism. He is otherwise healthy, and his medical history is unremarkable. He has a 12-year-old son. There is no family history of thrombotic disorders. His only medication is warfarin.

Which of the followi ng is the most appropriate next step in management?

21%

A

Folic acid and vitamin B_{12} administration

13%

B

Indefinite continuation of warfarin

10%

C

MTHFR polymorphism testing of first-degree relatives

56%

D

Warfarin discontinuation

Answer & Critique

Correct Answer: D

Educational Objective: Manage anticoagulation in a patient with an elevated plasma homocysteine level and methylene tetrahydrofolate reductase polymorphism.

Key Point

Thrombophilia test results typically do not influence treatment duration, so testing is not indicated, especially for patients with only a single venous thromboembolism resulting from a major transient risk factor.

This patient's warfarin should be discontinued. Patients who have experienced a single venous thromboembolism (VTE) due to a major transient risk factor only require short-term anticoagulation for 3 months. This patient experienced a deep venous thrombosis following a traumatic tibia fracture. Generally, the clinical setting of a thrombotic event (unprovoked versus provoked) provides greater prognostic information regarding recurrence risk than the results of thrombophilia testing. Therefore, in most instances, thrombophilia testing results will not influence treatment duration and testing is not indicated. If thrombophilia testing is considered, it should be targeted to persons in whom finding a strong thrombophilia may influence length of anticoagulant treatment or have an impact on other family members if they also tested positive for the higher risk thrombophilia. However, consensus is limited on what defines higher risk thrombophilias.

Elevated plasma homocysteine levels are associated with an increased risk for a first venous or arterial thromboembolic event. Homocysteine levels can be lowered with folic acid, vitamin B_6, and vitamin B_{12}. However, this does not change the risk of a first thromboembolic event, which this patient has already experienced, nor of recurrent VTE.

Homozygosity for the methylene tetrahydrofolate reductase (*MTHFR*) C677T polymorphism can be associated with elevated homocysteine levels but alone is not a risk factor for VTE. Thus, no clinical indication exists for testing for the *MTHFR* polymorphism in patients or first-degree relatives.

Question 29

A 45-year-old man is evaluated following a recent diagnosis of hereditary hemochromatosis. He was screened after a relative was diagnosed with hereditary hemochromatosis. He is asymptomatic and has no clinical or laboratory evidence of liver disease, diabetes mellitus, or cardiomyopathy. Medical history is otherwise negative, and he takes no medications.

On physical examination, vital signs are normal. The examination is unremarkable.

Weekly phlebotomy is planned.

Which of the following dietary constituents should this patient be advised to avoid?

A
Calcium supplements

B
Raw or undercooked seafood

C
Red meat

D
Vitamin C–containing fruits and vegetables

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose infectious complications of iron overload syndromes.

Key Point

Vibrio vulnificus infection is associated with ingestion of raw seafood, especially oysters, and the risk of sepsis and death is increased in persons with hereditary hemochromatosis.

This patient should be advised to avoid eating raw or undercooked seafood. Patients with iron overload syndromes, including those with hereditary hemochromatosis, are at risk for a number of infections with organisms whose virulence is increased in the presence of excess iron. Although the exact mechanisms of increased susceptibility to specific infections are not known, pathogens require mobilization of tissue iron from the host, which is increased in iron overload syndromes. Additionally, excess iron appears to impair host defenses against certain infections, such as decreasing the chemotactic response and compromising the ability of phagocytic cells. The result is increased virulence among specific infectious organisms in patients with iron overload, including *Vibrio*species *(vulnificus,cholerae), Escherichia coli*, *Yersinia enterocolitica, Listeria monocytogenes*, cytomegalovirus, hepatitis B and C viruses, and HIV. Fungi include *Aspergillus fumigatus* and mucor. *V. vulnificus* infection is associated with ingestion of raw seafood, especially oysters, and the risk of sepsis and death is significantly increased in persons with hemochromatosis; therefore, these foods should be specifically avoided by these patients.

Oral calcium supplements may bind iron in the gut and inhibit iron absorption and are acceptable to take if needed for another indication. However, this inhibitory effect is small relative to the removal of iron by phlebotomy. Therefore, supplementation for treatment of hemochromatosis in those undergoing phlebotomy is not usually required.

Although red meat contains iron, and excessive meat intake should be avoided, consumption of moderate amounts of meat by those being treated with phlebotomy is reasonable for nutritional purposes. The amount of iron removed by phlebotomy far exceeds the iron content of a moderate intake of meat.

Vitamin C (ascorbic acid) may interact with tissue iron and lead to generation of oxidative radicals with the potential for tissue damage. However, the amount of vitamin C contained in fruits and vegetables is relatively low, and their consumption as part of a normal diet should not be discouraged.

Question 30

A 26-year-old woman is evaluated during consultation for concerns about a possible hypercoagulable state. Her mother was recently diagnosed with heterozygous factor V Leiden mutation following multiple episodes of venous thromboembolic disease. The patient is concerned with her own risk of thrombosis. Medical history is unremarkable, with no venous thromboembolism or abnormal bleeding. She takes no medications.

The physical examination is unremarkable.

Which of the following is the most appropriate diagnostic test?

A
Activated protein C resistance assay

B
Factor V activity level

C
Factor V Leiden genetic test

D
No testing

Answer & Critique

Correct Answer: D

Educational Objective: Manage testing of family members for factor V Leiden mutation.

Key Point

Routine testing for factor V Leiden (FVL) mutation in offspring of a patient with FVL is not indicated.

This patient should not undergo further testing for a factor V Leiden (FVL) mutation. FVL is the most common inherited thrombophilia, resulting from a point mutation in the factor V gene that causes it to be resistant to inactivation by activated protein C (APC). FVL prevalence in the United States is 3% to 8% in whites and 1.2% in blacks, but it rarely occurs in African and Asian populations. Homozygous FVL carries an 18-fold increased risk of first-time venous thromboembolism (VTE), whereas FVL heterozygosity only carries a 2.7-fold increased risk. Although this patient's mother has a known inherited thrombophilia with recurrent episodes of VTE, no evidence indicates testing for inherited thrombophilia is beneficial in an asymptomatic child, particularly with heterozygous FVL, which is not considered a strong thrombophilia.

In patients in whom testing for FVL is indicated, the presence of FVL can be detected by an APC resistance assay that assesses the ability of protein C to inactivate factor Va. This is a very sensitive study that effectively excludes FVL if normal and is the preferred initial screening test, mainly because it is typically less expensive than the FVL genetic test. An abnormal result suggests heterozygous or homozygous FVL, depending on the degree of abnormality, but should be followed by confirmatory genetic polymerase chain reaction testing of the FVL gene that assesses for the point mutation in genetic material from leukocytes from the peripheral blood.

Factor V deficiency is an extremely rare inherited disorder that causes abnormal bleeding as a result of failure of thrombin generation because of inadequate amounts of factor V. This patient has no evidence of a bleeding disorder, so testing factor levels is not indicated.

Question 31

A 43-year-old woman is admitted to the hospital for fatigue of 4 weeks' duration, easy bruising and bleeding gums of 1 week's duration, and a 1-day fever of 38.9 °C (102.0 °F).

On physical examination, the patient appears ill. Temperature is 39.4 °C (103.0 °F), blood pressure is 105/62 mm Hg, pulse rate is 115/min, and respiration rate is 22/min. She has gingival bleeding, bleeding around her intravenous insertion site, and multiple ecchymoses and petechiae. Hepatomegaly is also noted.

Laboratory studies:

Activated partial thromboplastin time	65 s
Hemoglobin	7.6 g/dL (76 g/L)
Leukocyte count	32,000/µL (32 × 10^9/L)
Platelet count	25,000/µL (25 × 10^9/L)
Prothrombin time	24 s
Fibrinogen	97 mg/dL (0.97 g/L)

A peripheral blood smear shows 80% immature blasts with prominent Auer rods phenotypically consistent with promyelocytes.

Which of the following is the most appropriate initial management?

A
All-*trans* retinoic acid

B
Chemotherapy

C
t(9;22) testing

D
t(15;17) testing

Answer & Critique

Correct Answer: A

Educational Objective: Treat acute promyelocytic leukemia.

Key Point

Immediate administration of all-*trans* retinoic acid is important in preventing early mortality in suspected acute promyelocytic leukemia.

All-*trans* retinoic acid (ATRA) should be administered as soon as possible, followed by chemotherapy, for this patient with acute promyelocytic leukemia (APL). APL is a clinically and biologically distinct variant of acute myelocytic leukemia characterized by the presence of a (15;17) gene translocation, which gives rise to the promyelocytic leukemia–retinoic acid receptor-? fusion transcript and arrest of leukemic cells at the promyelocyte stage. Adding ATRA to standard induction and consolidation chemotherapy releases the block in promyelocyte maturation and produces cure in up to 80% of patients. If APL is suspected, ATRA should be initiated without waiting for confirmation. This patient's symptoms and laboratory studies strongly suggest APL, with prominent Auer rods on the peripheral blood smear and bleeding out of proportion to thrombocytopenia. She also has biochemical evidence of disseminated intravascular coagulation, which is a defining clinical clue to APL. In addition to appropriate blood product transfusion support, early ATRA administration is required to help patients survive induction chemotherapy. The greatest mortality risk from APL accrues in the first 2 weeks, with delay in ATRA administration being one of several root causes.

Testing for the t(9;22) would not be helpful in this patient, because it would identify the Philadelphia chromosome, which only has relevance in chronic myeloid leukemia or acute lymphoblastic leukemia.

Testing for the t(15;17) would confirm a diagnosis of APL and can be accomplished in less than 24 hours using fluorescence in situ hybridization. However, enough clinical clues are already provided to strongly suspect the diagnosis, and ATRA should be initiated at the point of clinical suspicion to improve early survival.

Question 32

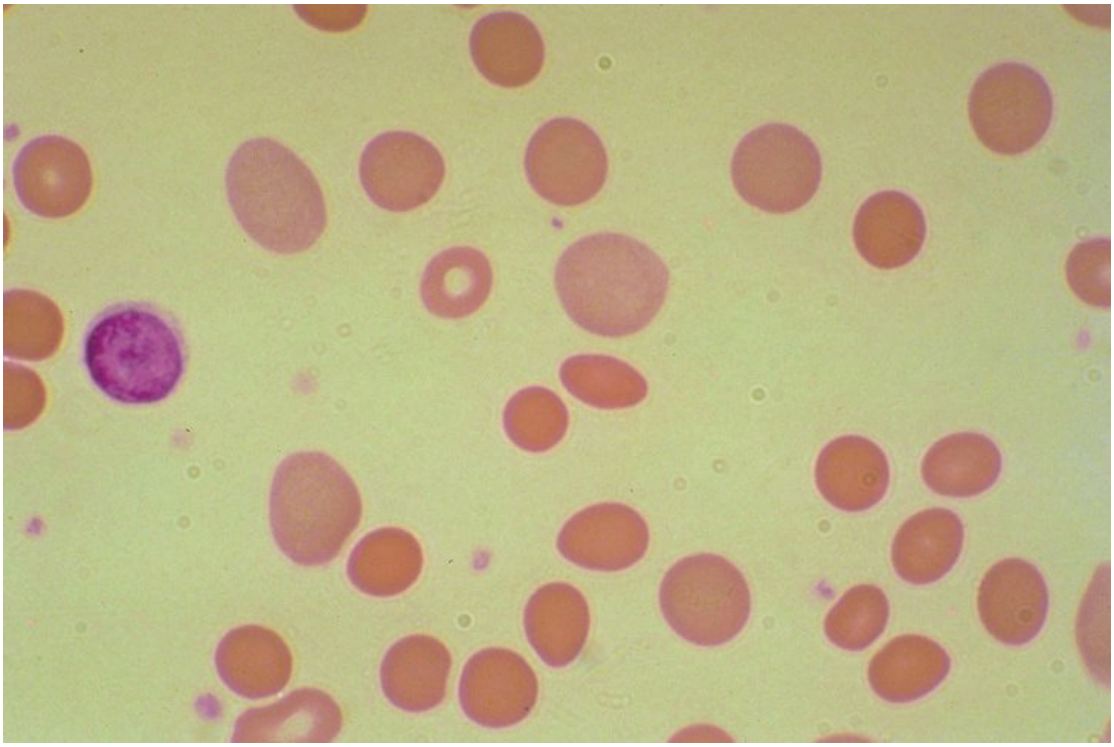
A 25-year-old woman is evaluated for worsening shortness of breath that began 2 to 3 days ago. A week before the onset of these symptoms, she developed a flulike syndrome of fever, myalgia, arthralgia, and transient facial rash. Medical history is significant for anemia. Her father also has anemia. She takes no medications.

On physical examination, the patient appears pale. Temperature is 36.9 °C (98.5 °F), blood pressure is 100/60 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. BMI is 24. Scleral icterus is noted. On palpation, her spleen is enlarged. Cardiopulmonary examination reveals tachycardia.

Laboratory studies:

Hematocrit	18%
Leukocyte count	8300/µL (8.3×10^9/L)
Platelet count	200,000/µL (200×10^9/L)
Lactate dehydrogenase	500 U/L
Direct antiglobulin (Coombs) test	Negative

A peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test?

A

Diagnostic trial of prednisone

B

Flow cytometry

C

Glucose-6-phosphate dehydrogenase activity

D

Osmotic fragility test

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose hereditary spherocytosis.

Key Point

The osmotic fragility test with 24-hour incubation is a key step in diagnosing hereditary spherocytosis.

This patient should undergo an osmotic fragility test. She most likely has hereditary spherocytosis. Inheritance is usually autosomal dominant with variable penetrance but may occasionally be sporadic. Alternations in membrane structure destabilize the erythrocyte, leading to a spherocytic shape, reduced deformability, trapping, and subsequent destruction in the spleen. Hereditary spherocytosis should be suspected in patients with a personal or family history of anemia, jaundice, splenomegaly, or gallstones. Some patients, such as this patient, may come to medical attention because of an aplastic crisis precipitated by an acute parvovirus B19 infection. Spherocytes are present on the peripheral blood smear, and the direct antiglobulin (Coombs) test (DAT) is negative. The osmotic fragility test with 24-hour incubation is a key step in diagnosis, demonstrating increased erythrocyte fragility in hypotonic saline compared with control erythrocytes.

Patients with warm autoimmune hemolytic anemia (WAIHA) may present with rapid or insidious symptoms of anemia or jaundice; mild splenomegaly is often present. Spherocytes are seen on the peripheral blood smear. The DAT is used to diagnose WAIHA. In less than 10% of patients, the DAT may be normal, in which case more sensitive diagnostic testing through a reference laboratory or blood center is required. First-line therapy for WAIHA is glucocorticoids; however, a trial period of prednisone is not indicated in this patient with a negative DAT and a family history of anemia.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal progenitor cell disorder characterized by hemolytic anemia, pancytopenia, or unprovoked thrombosis. Diagnosis is based on flow cytometry results, which can detect CD55 and CD59 deficiency on the surface of

peripheral erythrocytes or leukocytes. In the absence of pancytopenia and a history of thrombosis, flow cytometry is not indicated in this patient

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is caused by various mutations on the X chromosome and occurs more commonly in men, often in blacks. During an acute hemolytic episode, bite cells may be seen on the peripheral blood smear, and a brilliant cresyl blue stain may reveal Heinz bodies (denatured oxidized hemoglobin). These findings are not present in the patient's peripheral blood smear, so measuring the G6PD activity is not indicated.

Question 33

A 45-year-old man is evaluated in follow-up for iron deficiency anemia discovered during routine evaluation 1 week ago. His complete blood count was normal when he was last evaluated 1 year ago. He feels well, his medical history is unremarkable, and he takes no medications.

The physical examination performed 1 week ago was normal.

A fecal occult blood test is negative.

Iron replacement is initiated.

Which of the following is the most appropriate management?

A
Colonoscopy and upper endoscopy

B
Repeat iron studies in 1 month

C
Tissue transglutaminase IgA antibody assay

D
Wireless capsule endoscopy

Answer & Critique

Correct Answer: A

Educational Objective: Evaluate the cause of iron deficiency anemia with colonoscopy and upper endoscopy.

Key Point

In men and nonmenstruating women, gastrointestinal blood loss is the presumed cause of iron deficiency unless proven otherwise; because it may develop secondary to an undiagnosed colonic neoplasm, colonoscopy and upper endoscopy are recommended.

This patient should undergo evaluation by colonoscopy and upper endoscopy. Iron deficiency can result from blood loss or malabsorption. In men and nonmenstruating women, gastrointestinal blood loss is always the presumed cause of iron deficiency unless proven otherwise and may develop secondary to an undiagnosed colonic neoplasm. Colon cancer is the most commonly detected cancer causing iron deficiency anemia.

Remeasuring iron stores in 1 month will not be helpful and is not an appropriate choice without assessing the cause of the iron deficiency. In patients who receive adequate treatment for iron deficiency anemia, reticulocytosis can be expected within 7 to 10 days, and the hemoglobin level can be expected to increase in 1 to 2 days. Iron stores are not expected to normalize for 6 months.

Iron malabsorption can result from celiac disease, inflammatory bowel disease, or surgical resection (affecting the duodenum, as in gastric bypass). Some malabsorption syndromes, such as celiac disease, are not accompanied by diarrhea, steatorrhea, or weight loss. In developed nations, gastrointestinal bleeding is the most common cause of iron deficiency; iron malabsorption is much less common. Considering this patient's complete blood count was normal 1 year ago, celiac disease is an unlikely cause of iron deficiency, and screening for celiac disease with tissue transglutaminase IgA antibody is not appropriate at this time.

Wireless capsule endoscopy is an effective technology that provides visualization of the small bowel. Unlike angiography or technetium scans, wireless capsule endoscopy is effective even in the absence of active bleeding. It detects the source of occult bleeding in 50% to 75% of patients. In those with iron deficiency anemia, in whom bleeding can be episodic, capsule endoscopy is another way to investigate potential sources of blood loss after other investigations have been

unrevealing. Wireless capsule endoscopy should not precede colonoscopy and upper endoscopy as the first diagnostic tests for adult patients with iron deficiency anemia and presumed gastrointestinal blood loss.

Question 34

A 24-year-old woman undergoes routine evaluation. She is pregnant at 12 weeks' gestation. Medical history is notable for homozygous sickle cell anemia (Hb SS). She has had multiple uncomplicated painful crises treated at home with hydration, nonopioid analgesia, and incentive spirometry. She requires hospital management for these episodes approximately twice per year. She has declined the use of hydroxyurea. Her only other medication is folic acid.

On physical examination, vital signs are normal. Mild scleral icterus is noted. A grade 2/6 early systolic flow murmur is heard at the cardiac base. The examination is otherwise normal.

Laboratory results show a hemoglobin level of 7.5 g/dL (75 g/L).

Which of the following is the most appropriate management?

A
Erythrocyte transfusion to maintain hemoglobin level at 10 g/dL (100 g/L)

B
Erythropoiesis-stimulating agent

C
Exchange transfusion

D
No transfusion at this time

Answer & Critique

Correct Answer: D

Educational Objective: Manage transfusion in an asymptomatic pregnant patient with sickle cell anemia.

Key Point

In patients with sickle cell disease, including pregnant patients, transfusion is not indicated for uncomplicated pregnancy, routine painful episodes, minor surgery not requiring anesthesia, or asymptomatic anemia.

The patient should not receive an erythrocyte transfusion at this time. Erythrocyte transfusion in sickle cell disease (SCD) is appropriate only for specific indications, including stroke, symptomatic anemia, acute chest syndrome (ACS), surgical interventions, secondary prevention of stroke or ACS, and, possibly, prevention of priapism, pulmonary hypertension, and nonhealing ulcers. Transfusion is not indicated for uncomplicated pregnancy, routine painful episodes, minor surgery not requiring anesthesia, or asymptomatic anemia. Erythrocyte exchange transfusion is indicated for acute ischemic stroke, ACS with significant hypoxia, and multiorgan failure/hepatopathy as well as in persons in whom simple transfusion would increase the hemoglobin level to greater than 10 g/dL (100 g/L). Chronic transfusion can lead to iron overload, alloimmunization, and an increased risk for a delayed hemolytic transfusion reaction. Erythrocytes used in transfusion should be leukoreduced, hemoglobin S negative, and phenotypically matched for the E, C, and K antigens as well as for any known alloantibodies. Hemoglobin targets should remain less than 10 g/dL (100 g/L) to avoid hyperviscosity.

In a randomized trial, transfusion reduced the risk of pain crisis in pregnant women with SCD but showed no clear improvement in maternal mortality, perinatal mortality, or severe maternal morbidity (pulmonary embolism, chronic heart failure, ACS). Transfusion should be provided based on symptoms of anemia and not hemoglobin levels.

Erythropoiesis-stimulating agents (ESAs) are used to treat anemia in conditions in which bone marrow stimulation of erythrocyte production is inadequate, such as chronic kidney disease. However, in SCD, erythropoietin levels are typically high to augment bone marrow erythrocyte production in response to chronic hemolysis. Therefore, ESAs are not indicated for treatment of the anemia associated with SCD.

Question 35

A 73-year-old woman is evaluated in the emergency department following a fall in her home. She tripped and fell over a rug. She did not lose consciousness but is experiencing left hip pain. Medical history is remarkable for atrial fibrillation. Her only medication is warfarin.

On physical examination, the patient is afebrile, blood pressure is 137/88 mm Hg, pulse rate is 105/min and irregular, and respiration rate is 14/min. The lungs are clear to auscultation, and the cardiac examination is significant only for an irregular rate. She has mild tenderness to palpation over the left hip. No hematoma or other bleeding is evident. The remainder of the examination is unremarkable.

Laboratory studies show a normal hemoglobin level and an INR of 10.2.

Radiographs of the left hip are negative for fracture.

In addition to withholding warfarin, which of the following is the most appropriate management of this patient's anticoagulation?

A
4-Factor prothrombin complex concentrate

B
Fresh frozen plasma

C
Oral vitamin K

D

No additional therapy

Answer & Critique

Correct Answer: C

Educational Objective: Manage a supratherapeutic INR in a patient receiving vitamin K antagonist therapy.

Key Point

In patients taking a vitamin K antagonist who have an INR greater than 9 and no evidence of bleeding, oral vitamin K and withholding warfarin are indicated to rapidly reduce the INR.

This patient should be treated with oral vitamin K for a supratherapeutic INR without evidence of active bleeding. Elevation of the INR beyond the desired therapeutic range is common in patients taking vitamin K antagonists. Recommended management depends on the level of INR elevation and whether active bleeding or bleeding risk factors are present. In patients without bleeding, management involves withholding warfarin and possibly administering oral vitamin K, depending on the level of INR elevation. For a supratherapeutic INR less than 5.0, withholding warfarin and restarting at a lower dose are usually adequate. For an INR of 5.0 to 9.0, a similar management strategy is appropriate, although administration of 1 to 2.5 mg of oral vitamin K is reasonable in patients at risk for bleeding. In patients with an INR greater than 9.0, such as this patient, administration of 2.5 to 5 mg of oral vitamin K is indicated to more rapidly reduce the INR to the desired range.

In patients with serious bleeding, active reversal of anticoagulation is indicated regardless of the INR level. Use of intravenous vitamin K and 4-factor prothrombin complex concentrate (PCC) (or 3-factor PCC and fresh frozen plasma [FFP] or recombinant activated factor VII) is preferred. FFP alone is an option if factor concentrates are unavailable. These treatments are not indicated in this patient who does not have evidence of active bleeding.

Because the risk of bleeding increases with the level of INR elevation, not providing additional treatment for this patient with a significantly supratherapeutic INR would be inappropriate.

Question 36

A 52-year-old man is evaluated for low back pain of 3 months' duration that is nonradiating, progressive, and worse with ambulation. He reports no preceding injury. Medical history is notable for smoldering multiple myeloma diagnosed 1 year ago; he has been stable since that time. His only medication is as-needed acetaminophen.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 132/82 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. No focal neurologic findings are noted. He has pain to palpation of the lower lumbar spine. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 13 g/dL (130 g/L), serum creatinine level of 1.0 mg/dL (88.4 μmol/L), and serum calcium level of 9.8 mg/dL (2.5 mmol/L).

Plain radiographs of the lumbosacral spine demonstrate degenerative disk changes in the lumbar spine but no lytic lesions or fractures.

Which of the following is the most appropriate management?

A
Chemotherapy

B
MRI of the lumbar spine

C
Symptomatic treatment and routine follow-up

D
Zoledronic acid

Answer & Critique

Correct Answer: B

Educational Objective: Manage low back pain in a patient with smoldering multiple myeloma.

Key Point

An MRI or CT is more sensitive at detecting lytic bone lesions than plain radiographs in patients with multiple myeloma and should be considered when bone pain is present and plain radiographs are unrevealing.

This patient should undergo MRI of the lumbar spine. He has a diagnosis of smoldering (asymptomatic) multiple myeloma, which is defined as an M protein level of 3 g/dL or more or clonal plasma cells representing 10% or more of the total marrow cellularity on bone marrow biopsy but the absence of disease-specific signs or symptoms. Most patients with smoldering myeloma eventually develop symptomatic disease, with a median time to progression of 4.8 years. Therefore, surveillance in these patients is necessary. The CRAB (hyperCalcemia, Renal failure, Anemia, Bone disease) criteria for a diagnosis of multiple myeloma requiring therapy are commonly used to determine the need to start chemotherapy. Although this patient does not have hypercalcemia, kidney disease (renal failure), or anemia, he is experiencing unexplained lower back pain with nonspecific findings on plain radiographic imaging. Therefore, additional imaging is warranted to better determine the cause of the pain. Although plain radiography remains an important component of the initial evaluation of patients with multiple myeloma, more than 30% of trabecular bone must be lost before lytic lesions are evident by plain radiographs. MRI is a more sensitive imaging modality for detecting lytic bone lesions of myeloma, and would be the preferred next imaging study in this patient. Additional imaging techniques that may be used in multiple myeloma include CT or PET/CT.

The role of chemotherapy in patients with smoldering myeloma is unclear. Although lenalidomide and dexamethasone have been shown to delay disease progression, the optimal patient population for these agents has not been identified, and early initiation of chemotherapy for smoldering myeloma is not routinely utilized.

Although most patients with acute low-back pain may be treated conservatively without imaging, symptomatic treatment of this patient's low back pain with routine follow-up would not be

appropriate because of his diagnosis of multiple myeloma and the possibility that his back pain is secondary to disease progression.

Bisphosphonates are a key component of therapy for patients with multiple myeloma requiring therapy. Zoledronic acid has been shown to reduce the risk of skeletal-related events and improve progression-free survival. However, the patient has yet to be diagnosed with symptomatic myeloma. No role exists for the routine use of bisphosphonates for patients with smoldering myeloma.

Question 37

A 19-year-old woman is evaluated for progressive weakness and dyspnea during exercise. Medical history is notable for heavy menses since menarche that last approximately 8 days. She had abnormal bleeding with wisdom tooth extraction 5 years ago. Her mother and sister have heavy menses. Her only medication is a multivitamin.

On physical examination, she appears pale. Temperature is 36.8 °C (98.2 °F), blood pressure is 110/65 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Pale conjunctivae are noted. A grade 2/6 systolic murmur is heard at the cardiac base. The lung fields are clear. The remainder of the examination is normal.

Laboratory studies:

Hematocrit	25%
Leukocyte count	5700/µL (5.7 × 10^9/L)
Mean corpuscular volume	71 fL
Platelet count	490,000/µL (490 × 10^9/L)
Activated partial thromboplastin time	25 s
Prothrombin time	10 s

Which of the following is the most likely diagnosis?

A
Factor VII deficiency

B
Factor XI deficiency

C
Factor XII deficiency

D
Hemophilia A

E
von Willebrand disease

Answer & Critique

Correct Answer: E

Educational Objective: Diagnose von Willebrand disease.

Key Point

Symptoms of von Willebrand disease typically include easy bruising, postsurgical bleeding, and heavy menstrual bleeding in women in conjunction with normal prothrombin and normal to minimally prolonged activated partial thromboplastin times.

The patient most likely has von Willebrand disease (vWD). vWD is an autosomal codominant disorder. Von Willebrand factor (vWF) protects factor VIII from degradation, and factor VIII levels can be low enough in vWD to cause slight prolongation of the activated partial thromboplastin time (aPTT), although typically the prothrombin time (PT) and aPTT are normal. Hemorrhagic manifestations of vWD are characterized by mucocutaneous bleeding, not hemarthroses as in hemophilia. Many women with vWD have significant menorrhagia, endometriosis, and postpartum hemorrhage. Mild vWD may not be detected by the Platelet Function Analyzer-100 (PFA-100®) assay, necessitating measurement of vWF antigen and activity levels for diagnosis. Additionally, levels of vWF fluctuate in response to estrogens, stress, exercise, inflammation, and bleeding, and repeated assays may be required to make the diagnosis.

Factor VII deficiency may be inherited or acquired as a result of vitamin K deficiency or warfarin therapy. Patients with factor VII deficiency will have an abnormal prolongation of the PT but a normal aPTT, which is incompatible with this patient's findings.

Factor XI deficiency is an autosomal recessive bleeding disorder and may be associated with a prolonged aPTT and significant bleeding with surgery or trauma. Severe factor XI deficiency is much more frequent in persons of European Jewish descent. Severe factor XI deficiency will prolong the aPTT and is not associated with spontaneous bleeding or with the classic bleeding manifestations of hemophilia, such as hemarthrosis or soft-tissue bleeding, making this diagnosis unlikely.

Factor XII deficiency also produces a normal PT and markedly prolonged aPTT but is not associated with bleeding manifestations and, therefore, is not a likely diagnosis for this patient.

Factor VIII deficiency is responsible for hemophilia A, an X-linked recessive disorder. Severe hemophilia A is characterized by recurrent hemarthroses resulting in chronic, crippling degenerative joint disease unless treated prophylactically with factor replacement. Mild hemophilia may present in adulthood, characterized by posttraumatic or surgical bleeding and a prolonged aPTT. This patient's clinical presentation of mucocutaneous bleeding, normal aPTT, and apparent inheritance pattern of bleeding are not compatible with hemophilia.

Question 38

A 73-year-old woman undergoes follow-up warfarin monitoring. She takes warfarin for atrial fibrillation and her INRs have previously been stable. Five days ago, she was prescribed a 3-day course of trimethoprim-sulfamethoxazole for an uncomplicated urinary tract infection. Three weeks ago, her INR was 2.9; this morning, her INR is 8.2. She has no history of major bleeding.

On physical examination, vital signs are normal. No bruising or bleeding is evident. The cardiac examination reveals an irregular rhythm but is otherwise unremarkable.

Laboratory studies show a hemoglobin level of 13.6 g/dL (136 g/L) and platelet count of 178,000/µL (178 × 10^9/L).

Which of the following is the most appropriate management?

A
Fresh frozen plasma infusion

B
Oral vitamin K and repeat INR in 24 hours

C
Prothrombin complex concentrate administration

D
Warfarin interruption

Answer & Critique

Correct Answer: D

Educational Objective: Manage an elevated INR in a patient taking warfarin.

Key Point

In patients without evidence of bleeding whose INR is 9.0 or less while taking warfarin, the next one or two dose(s) should be withheld, but the American College of Chest Physicians recommends against the routine use of vitamin K.

Because the patient is not bleeding and is not at high risk for bleeding, interruption of warfarin therapy is appropriate. Concomitant antibiotic and warfarin use can result in INR elevation. A population-based study revealed that the over-anticoagulation risk was most strongly increased by amoxicillin, clarithromycin, norfloxacin, and trimethoprim-sulfamethoxazole. Changes in the INR were often noted in the first 3 days of antibiotic use. This patient's elevated INR is most likely related to her concomitant use of warfarin and trimethoprim-sulfamethoxazole. The appropriate treatment for patients taking warfarin whose INR is supratherapeutic depends on the absolute INR value, the absence or presence of bleeding risk factors or active bleeding, and the seriousness of bleeding, if present. Increased age, actively bleeding lesions, coagulation disorders, and use of antiplatelet drugs increase the bleeding risk while taking warfarin. If the INR is less than 5.0 and no bleeding is apparent, the next dose of warfarin is withheld and the subsequent maintenance dose is reduced. If the INR is 9.0 or less and the risk of bleeding is low, the next one or two doses of warfarin are withheld and the INR is repeated in 48 hours; in these patients who have no evidence of bleeding, the American College of Chest Physicians (ACCP) recommends against the routine use of vitamin K. If the INR is greater than 9.0, warfarin is withheld and 2.5 to 5 mg of oral vitamin K is administered.

Patients with an elevated INR and serious bleeding (or those requiring rapid anticoagulation reversal) are treated by withholding warfarin and administering 10 mg of vitamin K intravenously. For patients with critical need of anticoagulation reversal (for example, intracerebral bleeding), the ACCP recommends administration of 4-factor prothrombin complex concentrate rather than fresh frozen plas

Question 39

A 58-year-old man is evaluated in the hospital for thrombocytopenia. He recently underwent multiple orthopedic procedures for repair of traumatic injuries experienced 3 days ago. He received 12 units of packed red blood cells throughout trauma resuscitation and surgical procedures. Except for postoperative pain, the patient reports no focal symptoms. Medical history is otherwise unremarkable. Medications are as-needed acetaminophen and oxycodone for pain relief and subcutaneous unfractionated heparin for venous thromboembolism prophylaxis.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 135/85 mm Hg, pulse rate is 89/min, and respiration rate is 18/min. Multiple healing surgical incisions are clean and dry, without evidence of infection. No lower extremity edema is present. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 11.5 g/dL (115 g/L), leukocyte count of 9800/μL (9.8 × 10^9/L), and platelet count of 115,000/μL (115 × 10^9/L) (previously 160,000/μL [160 × 10^9/L]).

Which of the following is th e most appropriate next step in management?

A
4T pretest probability scoring

B
Heparin-induced platelet aggregation assay

C
Platelet factor 4 enzyme-linked immunosorbent assay

D
Serotonin release assay

Answer & Critique

Correct Answer: A

Educational Objective: Evaluate a patient for heparin-induced thrombocytopenia.

Key Point

Assessing the pretest probability of heparin-induced thrombocytopenia by using a risk scoring system, such as the 4T score, is helpful in guiding therapy in patients at low risk for it.

Performing 4T pretest probability scoring for the possibility of heparin-induced thrombocytopenia (HIT) is the most appropriate next step in management. This patient's platelet count decreased following a recent exposure to heparin, raising concern for the possibility of HIT. The 4T score is used to estimate the pretest probability of HIT based on clinical factors, including degree of thrombocytopenia, timing of the decrease in platelet count, presence of any potential sequelae of HIT (such as thrombosis), and whether another potential cause for thrombocytopenia exists. Possible point values range from 0 to 8; scores of 0 to 3 indicate low probability, 4 or 5 indicate intermediate probability, and 6 to 8 represent high pretest probability. The 4T score has been validated in a study of more than 3000 patients with a negative predictive value of 99.8% in those with low probability scores. Although specific decisions must be made for individual patients based on their clinical status, many physicians reserve further evaluation for patients with intermediate or high pretest probability scores, with close clinical observation in those with low probability scores. This patient has a 4T score of 1 based on a possible alternative explanation for his thrombocytopenia (blood transfusion), indicating a low pretest probability of HIT; therefore, observation without additional testing for HIT would be reasonable.

Confirmatory testing for antiplatelet antibodies may be done by direct antibody testing or by functional assays that test the ability of serum from patients with HIT to activate test platelets. Direct antibody testing is typically performed by enzyme-linked immunosorbent assay (ELISA) that detects antibodies directed toward heparin-platelet factor 4 complexes. The two commonly used functional assays are the serotonin release assay (SRA) and the heparin-induced platelet aggregation (HIPA) assay. SRA is considered the gold standard study for HIT with a sensitivity and specificity of more than 95%; HIPA is also very specific but has a lower sensitivity than SRA. However, no clear indication exists for confirmatory testing for HIT considering this patient's low pretest probability.

Question 40

A 65-year-old man was admitted to the hospital 10 days ago with community-acquired pneumonia requiring intubation, mechanical ventilation, and fluids and vasopressors for persistent hypotension. He has since been extubated and his blood pressure has stabilized; he no longer requires vasopressor therapy. Oxygen saturation is 90% with 3 L/min oxygen via nasal cannula. He has a resolving cough and improving fatigue. Medical history is otherwise unremarkable. Medications in the hospital are levofloxacin, heparin, and omeprazole.

Laboratory studies:

Hemoglobin	7.4 g/dL (74 g/L) (10.6 g/dL [106 g/L] on admission)
Reticulocyte count	2.0% of erythrocytes; absolute: 58,000/µL (58 × 10^9/L)
Creatinine	2.8 mg/dL (248 µmol/L) (4.5 mg/dL [398 µmol/L] on admission)
Iron studies	
Ferritin	410 ng/mL (410 µg/L)
Iron, serum	30 µg/dL (5.4 µmol/L)
Total iron-binding capacity	144 µg/dL (26 µmol/L)

Electrocardiography reveals no ST- or T-wave changes.

Which of the following is the most appropriate management of this patient's anemia?

A
Erythrocyte transfusion

B
Erythropoiesis-stimulating agent

C
Intravenous iron

D

Continue current management

Answer & Critique

Correct Answer: D

Educational Objective: Manage anemia in a critically ill hospitalized patient.

Key Point

In hospitalized patients without symptoms or end-organ damage, a restrictive treatment strategy for hemoglobin levels less than 7 g/dL (70 g/L) and targeting 7 to 9 g/dL (70-90 g/L) is appropriate.

Continuing current management is appropriate. The patient is asymptomatic and displays no end-organ compromise as a result of reduced oxygen-carrying capacity. A randomized phase III study was performed in euvolemic patients whose hemoglobin level decreased to less than 9 g/dL (90 g/L) within 72 hours of admission to an ICU. Patients were assigned to a liberal transfusion strategy targeting a hemoglobin level of 10 to 12 g/dL (100-120 g/L), in which they were transfused when their hemoglobin level decreased to less than 10 g/dL (100 g/L), or a restrictive approach, in which they were transfused for a hemoglobin level less than 7 g/dL (70 g/L) (target 7-9 g/dL [70-90 g/L]). Mortality rates were at least as good for those assigned to the restrictive transfusion approach. However, a subset analysis revealed that patients with ischemic heart disease had a trend toward higher mortality with a restrictive transfusion practice that was not statistically significant, suggesting that patients with ischemic heart disease should be evaluated on a case-by-case basis until further phase III data dictate otherwise.

Although the patient has an elevated creatinine level, this is likely the result of sepsis and appears to be improving with volume repletion and correction of hypotension. As such, there is no role for an erythropoiesis-stimulating agent (ESA). Furthermore, ESAs have not been studied for this indication.

The patient has iron indices typical of an inflammatory anemia (low serum iron, low total iron-binding capacity, normal transferrin saturation, elevated ferritin), likely due to sepsis and not iron deficiency anemia (low serum iron, high-normal to high total iron-binding capacity, low transferrin saturation, low ferritin). Therefore, intravenous iron is not indicated.

Question 41

A 45-year-old man presents to the emergency department with a 1-week history of fever, chills, hypotension, cough, progressive dyspnea, and lethargy. Medical history is remarkable for hepatitis C virus infection with cirrhosis. Medications are omeprazole and propranolol.

On physical examination, the patient is in moderate respiratory distress. Temperature is 39.2 °C (102.6 °F), blood pressure is 74/42 mm Hg, pulse rate is 144/min, and respiration rate is 26/min. Oxygen saturation is 76% breathing ambient air. He has no jugular venous distention. Chest examination reveals decreased breath sounds over the lower left lung field. Mild abdominal distention is present without a fluid wave. The spleen tip is palpable below the left costal margin.

Laboratory studies:

Activated partial thromboplastin time	42.4 s
Hemoglobin	11.8 g/dL (118 g/L)
Leukocyte count	10,500/µL (10.5×10^9/L)
Platelet count	63,000/µL (63×10^9/L)
Prothrombin time	16.6 s
INR	1.4
Fibrinogen	154 mg/dL (1.5 g/L)

A chest radiograph shows opacity of the left lower lobe and a moderate left-sided pleural effusion.

The patient is admitted to the ICU. Placement of an internal jugular central venous catheter is planned for medication administration.

Which of the following is the most appropriate next step in management before catheter placement?

A

Cryoprecipitate transfusion

B

Fresh frozen plasma transfusion

C

Platelet transfusion

D

No transfusion

Choose

Answer & Critique

Correct Answer: D

Educational Objective: Manage mild coagulopathy in a patient undergoing central venous catheter placement.

Key Point

Patients with mild coagulopathy requiring central venous catheter insertion do not need to receive fresh frozen plasma or other transfusions before the procedure.

No transfusion is needed before central venous catheter insertion. This patient has modest coagulopathy and thrombocytopenia resulting from hepatitis C–related liver disease. Previous retrospective studies have shown that central venous catheter insertion is safe in patients with a prolonged prothrombin time and INR, including those with liver disease. In a prospective audit of 580 internal jugular and subclavian vein cannulations in patients with chronic liver disease and an INR of 1.5 or greater, only one major vascular complication was noted.

Although his fibrinogen level is slightly low, cryoprecipitate is typically reserved for patients with clinically significant bleeding and a fibrinogen level less than 100 mg/dL (1.0 g/L). Cryprecipitate in the prophylaxis of bleeding for patients with low fibrinogen levels undergoing procedures has not been evaluated.

Numerous studies have shown that fresh frozen plasma (FFP) is overutilized in nonbleeding patients with mild coagulopathies, which is a significant problem given the risks associated with FFP use, including transfusion-related acute lung injury, transfusion-transmitted infection, transfusion-associated circulatory overload, allergic reactions, and hemolysis. The role of FFP in the prevention of bleeding complications for nonbleeding patients undergoing procedures is unclear. However, it is known that FFP is ineffective at correcting a minimally elevated INR (<1.85).

Most procedures and surgeries can be safely performed with a platelet count of at least 50,000/µL (50×10^9/L), although a platelet count of at least 100,000/µL (100×10^9/L) is recommended for neurosurgical intervention. Thus, a platelet transfusion is not indicated for this patient.

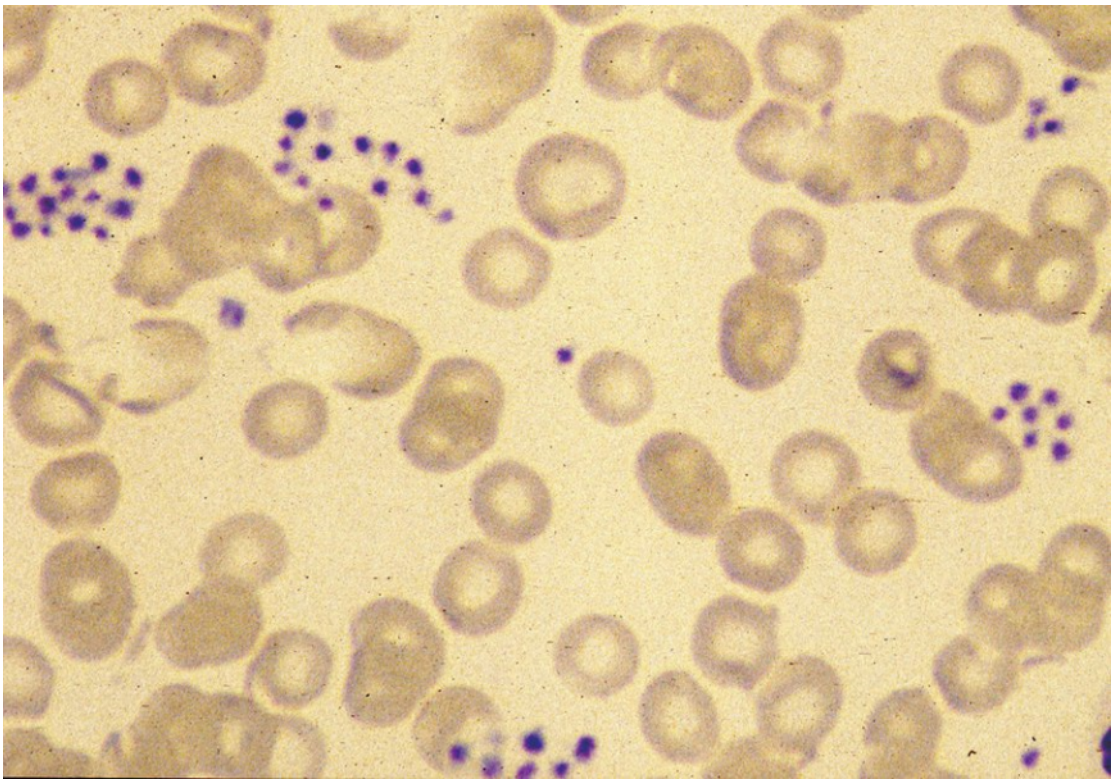
Question 42

A 35-year-old woman is evaluated following a recent diagnosis of iron deficiency anemia secondary to menorrhagia. She began an oral contraceptive to control bleeding and oral iron sulfate 6 weeks ago. She has no other medical conditions and takes no additional medications.

On physical examination, vital signs are normal. The conjunctivae are pink. No petechiae or purpura is evident. The remainder of the examination is normal.

Laboratory studies show a hematocrit level of 39%, leukocyte count of 5800/µL (5.8 × 109/L), and platelet count of 35,000/µL (35 × 109/L).

The peripheral blood smear is shown.



Which of the following is the most appropriate management?

A

Antinuclear antibody and HIV testing

B

Plasma exchange

C

Prednisone

D

Repeat complete blood count with a citrated tube

Answer & Critique

Correct Answer: D

Educational Objective: Manage pseudothrombocytopenia.

Key Point

Platelet clumping signifies pseudothrombocytopenia, which will resolve if blood is redrawn using a citrated or heparinized tube.

The patient's blood should be redrawn using a citrated tube. She has pseudothrombocytopenia as shown on the peripheral blood smear, a condition that leads to the formation of platelet clumps in vitro. This in vitro occurrence is caused by the presence of ethylenediaminetetra-acetic acid (EDTA) agglutinins, which naturally occur in approximately 0.1% of the population and lead to platelet clumping. The automated platelet counter does not recognize the clumps as masses of platelets, and the platelet count is, therefore, spuriously low. Drawing a complete blood sample into a citrate- or heparin-anticoagulated tube may resolve the clumping.

Prednisone and methylprednisolone are first-line agents for treating adults with immune (or idiopathic) thrombocytopenic purpura (ITP) who require therapy. ITP is an acquired autoimmune condition in which autoantibodies are directed against platelet surface proteins, leading to platelet destruction that may be only partially counteracted by increased bone marrow platelet production. Variants of ITP may be drug induced or part of a broader illness of abnormal immune regulation, as with systemic lupus erythematosus, HIV infection, or lymphoproliferative malignancies. Therapy may be required for patients with platelet counts lower than 30,000 to 40,000/µL (30-40 × 10^9/L) or with bleeding. Because this patient most likely does not have ITP, diagnostic testing for systemic lupus erythematosus with antinuclear antibody or HIV testing is not indicated.

Plasma exchange would not benefit this patient. Thrombotic thrombocytopenic purpura (TTP) is a process characterized by abnormal activation of platelets and endothelial cells, deposition of fibrin in the microvasculature, and peripheral destruction of erythrocytes and platelets. Most patients with the typical sporadic form of TTP have developed autoantibodies directed against the protease that cleaves the high-molecular-weight multimers of von Willebrand factor. Initial treatment consists of plasma exchange. Because this patient has platelet clumping on the peripheral blood smear and no evidence of schistocytes characteristic of TTP-associated microangiopathic hemolysis, the diagnosis of TTP is unlikely and plasma exchange is unnecessary.

Question 43

A 45-year-old woman is evaluated before surgery; she is scheduled to undergo elective hysterectomy for fibroid tumors. Her medical history is significant for type 1 von Willebrand disease (vWD), long-standing iron deficiency anemia, and heavy menstrual bleeding. Family history is notable for vWD in the patient's father, sister, and two sons. Her only medication is iron sulfate.

On physical examination, vital signs are normal. The patient has palpable lower abdominal masses along the midline consistent with fibroids.

Which of the following is the most appropriate periopera tive treatment?

A
Cryoprecipitate

B
Fresh frozen plasma

C
Recombinant factor VIII

D
Tranexamic acid

E
von Willebrand factor–containing factor VIII concentrates

Answer & Critique

Correct Answer: E

Educational Objective: Manage von Willebrand disease perioperatively.

Key Point

Patients with von Willebrand disease scheduled to undergo major surgery should be treated with factor VIII concentrates containing von Willebrand factor.

The most appropriate perioperative treatment for this patient is von Willebrand factor (vWF)–containing factor VIII concentrates. She has type 1 von Willebrand disease (vWD) and is scheduled for abdominal surgery. The best products to give are the vWF-containing factor VIII concentrates. These so-called “intermediate purity,” plasma-derived products have undergone viral inactivation (of viruses such as HIV and hepatitis B and C), and their use has not led to transmission of any serious illness. Desmopressin, which leads to release of vWF and factor VIII from endothelial cells and thus provides hemostasis, can be used for less invasive procedures. However, unless a trial of desmopressin shows a robust, sustained response, it should not be used for a major surgery.

Cryoprecipitate contains a concentrated source of factor VIII, vWF, factor XIII, fibronectin, and fibrinogen and is the treatment of choice in bleeding patients with hypofibrinogenemia from liver disease, thrombolytic therapy, or disseminated intravascular coagulation (DIC). Cryoprecipitate is not virally inactivated and is therefore not a first-line agent for this patient with vWD.

Fresh frozen plasma (FFP) contains all the blood clotting factors and is indicated for warfarin reversal in actively bleeding patients (alone or concomitantly with a 3-factor prothrombin complex concentrate), treatment of thrombotic thrombocytopenic purpura, dilutional coagulopathy during massive transfusion, and in bleeding patients with several factor deficiencies such as in DIC or liver disease. However, the concentration of vWF in FFP is too low to correct the patient's vWF levels without producing volume overload. Other risks include viral transmission, transfusion-related acute lung injury, and febrile, allergic, and anaphylactic reactions.

Recombinant factor VIII is used to treat patients with hemophilia A. Recombinant factor VIII is devoid of any vWF and would not improve hemostasis in this patient with vWD.

Fibrinolytic agents such as ?-aminocaproic acid and tranexamic acid can be used in patients with mild vWD to prevent dissolution of the hemostatic plug, particularly those associated with mucocutaneous bleeding. Prolonged use of these agents is associated with the potential for thrombosis, especially in patients with an underlying thrombophilia. Used as a single agent, tranexamic acid is unlikely to provide sufficient hemostasis for a patient undergoing abdominal surgery.

Question 44

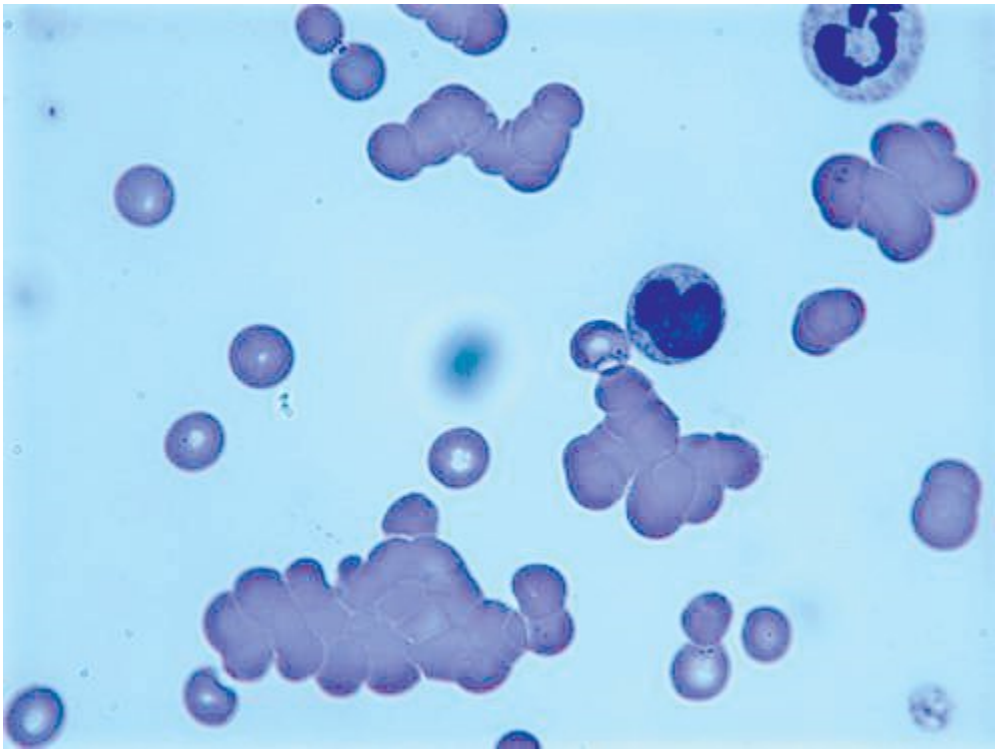
A 55-year-old man is evaluated for fatigue and gradually increasing dyspnea of 1 month's duration. He has otherwise felt well and has no other symptoms, although he reports an occasional bluish tint to his fingers while at work. He is employed as a frozen food handler in a grocery store. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient appears pale. Temperature is 37.0 °C (98.6 °F), blood pressure is 130/65 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. BMI is 26. Mild scleral icterus is noted. A grade 2/6 systolic murmur is heard at the left costal margin without radiation. The lungs are clear to auscultation. No lymphadenopathy is noted, but the spleen tip is palpable below the left costal margin.

Laboratory studies:

Hematocrit	23%
Leukocyte count	13,200/µL (13.2 × 10^9/L) with normal differential
Platelet count	355,000/µL (355 × 10^9/L)
Reticulocyte count	14% of erythrocytes
Lactate dehydrogenase	978 U/L

Peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test to perform next?

A

Direct antiglobulin (Coombs) test

B

Flow cytometry for CD55 or CD59

C

Hemoglobin electrophoresis

D

Indirect antiglobulin (Coombs) test

Answer & Critique

Correct Answer: A

Educational Objective: Diagnose cold agglutinin disease.

Key Point

Cold agglutinin disease, identified by characteristic erythrocyte clumping that disappears when a peripheral blood sample is warmed, can be confirmed by direct antiglobulin (Coombs) testing.

A direct antiglobulin (Coombs) test is the most appropriate next diagnostic step for this patient with cold agglutinin disease. Autoimmune hemolytic anemias are characterized by the presence of antibodies directed toward antigens on the surface of erythrocytes; they are further classified by the type of immunoglobulin involved and the resulting tendency of hemolysis to occur in warm or cold environments. Direct IgG optimally binds erythrocytes at temperatures of 37.0 °C (98.6 °F), causing warm autoimmune hemolytic anemia. The immune response to the bound IgG causes erythrocytes to become spherocytic, resulting in hemolysis. Direct IgM binds more effectively at temperatures colder than 32.0 °C (89.6 °F), typically in the fingers, toes, and nose, causing cold agglutinin disease. IgM-coated erythrocytes agglutinate in the microvasculature, leading to cyanosis and ischemia in the cold extremities. The IgM antibodies fix complement and then detach from erythrocytes when they return to the warmer body core. This patient likely has cold agglutinin disease because he has an acquired hemolytic anemia associated with cold exposure and supported by his peripheral blood smear, showing agglutinated erythrocytes that disappear when warmed. Cold agglutinin disease may occur as a primary disorder or may be associated with a lymphoproliferative disorder or certain infections, such as *Mycoplasma pneumoniae*or Epstein-Barr virus. The primary treatment for cold agglutinin disease is avoidance of cold exposure.

Flow cytometry to detect the absence of specific cell surface antigens (CD55 and CD59) is useful in diagnosing paroxysmal nocturnal hemoglobinuria, which is another potential cause of hemolytic anemia. However, testing for this disorder is indicated only in patients without evidence of an autoimmune cause of hemolysis. Therefore, such testing would be inappropriate for this patient.

Multiple congenital hemoglobinopathies are associated with hemolysis, although this patient's clinical picture is consistent with an acquired hemolytic anemia. Therefore, hemoglobin electrophoresis would not likely be helpful in establishing the cause of his hemolysis.

The indirect antiglobulin test detects antierythrocyte antibodies in the serum and is used primarily before blood transfusion and in prenatal testing of pregnant women. It would not provide significant diagnostic information in this patient.

Question 45

A 50-year-old man is evaluated for anemia following a diagnosis of osteomyelitis of the right foot. Complete blood counts before the osteomyelitis diagnosis have been normal. Medical history is notable for type 2 diabetes mellitus. His only medication is metformin.

On physical examination, vital signs are normal; BMI is 30. No cardiopulmonary findings attributable to the anemia are noted. The right foot has a small, deep open wound through which bone can be detected with a metal probe.

Laboratory studies:

Erythrocyte sedimentation rate	60 mm/h
Hemoglobin	8.5 g/dL (85 g/L)
Leukocyte count	15,000/µL (15×10^9/L)
Mean corpuscular volume	80 fL
Reticulocyte count	0.5% of erythrocytes
Iron studies	
Ferritin	500 ng/mL (500 µg/L)
Iron	50 µg/dL (9 µmol/L)
Total iron-binding capacity	225 µg/dL (40 µmol/L)
Transferrin saturation	30%

Appropriate antibiotics are initiated.

Which of the following is the most appropriate management of this patient's anemia?

A
Bone marrow aspiration

B
Erythropoiesis-stimulating agent therapy

C
Oral iron supplementation

D
Continue current management

Answer & Critique

Correct Answer: D

Educational Objective: Manage inflammatory anemia.

Key Point

Inflammatory anemia typically requires no treatment other than for the underlying condition.

The only management the patient requires at this time is observation. He has inflammatory anemia (previously anemia of chronic disease), which does not usually require treatment. Chronic infections such as tuberculosis or osteomyelitis, malignancies, and collagen vascular diseases are associated with anemia. In response to inflammatory states, erythropoietin production is inhibited and the erythroid precursor response to erythropoietin is blunted. Inflammation leads to increased levels of inflammatory cytokines, including tumor necrosis factor-?, interleukin (IL)-6, IL-1, and interferon, which lead to altered erythropoietin responsiveness. In particular, IL-6 causes hepatic synthesis of the small peptide hepcidin, which is pivotal in regulating iron absorption. Hepcidin causes decreased iron absorption from the gastrointestinal tract and decreased iron release by macrophages by inducing internalization and proteolysis of the transporter protein ferroportin. No laboratory test is commercially available for measuring hepcidin levels. A peripheral blood smear may be normal in patients with inflammatory anemia, or, over time, may show microcytic hypochromic erythrocytes such as in iron deficiency. Typically, inflammatory anemia is characterized by a hemoglobin level greater than 8 g/dL (80 g/L). Because of erythrocyte underproduction, the reticulocyte count is typically low for the degree of anemia. The serum iron level is initially normal but decreases over time, the total iron-binding capacity is low, and the ferritin level is typically elevated.

Although bone marrow evaluation is seldom necessary, ample stainable iron would be present. However, it is not indicated for diagnosis in classic cases of inflammatory anemia.

Erythropoiesis-stimulating agents may improve inflammatory anemia but are associated with thrombosis and other effects that impede safe use.

Iron replacement is unlikely to alleviate the patient's symptoms, because he is not iron deficient. Iron deficiency would present with a low ferritin level of less than 100 ng/mL (100 µg/L) even in the setting of chronic inflammation. Additionally, total iron-binding capacity in iron deficiency tends to

be elevated and not decreased. However, the transferrin saturation is normal in inflammatory anemia.

Question 46

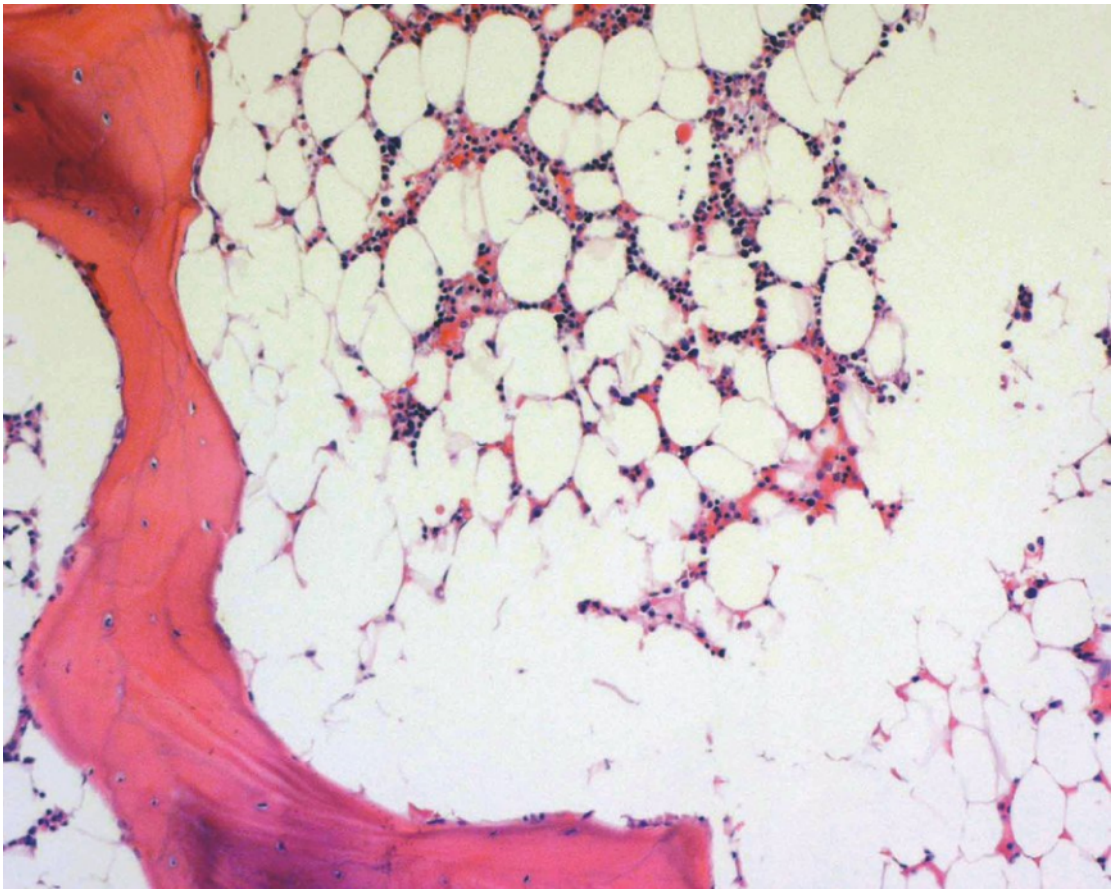
A 24-year-old man is evaluated for a 2-month history of frequent upper respiratory tract infections, easy bruising, and worsening endurance. Medical and family histories are unremarkable. He takes no medications.

On physical examination, the patient appears fatigued, but not acutely ill. Temperature is 36.7 °C (98.0 °F), blood pressure is 105/62 mm Hg, pulse rate is 108/min, and respiration rate is 14/min. Pallor and several 3- to 4-cm ecchymoses on the lower extremities are noted. He has no hepatosplenomegaly.

Laboratory studies:

Haptoglobin	40 mg/dL (400 mg/L)
Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	1000/µL (1×10^9/L) with 5% neutrophils
Platelet count	7000/µL (7×10^9/L)
Lactate dehydrogenase	150 U/L

Bone marrow aspirate demonstrates less than 5% blasts and no dysplastic changes. Results of a bone marrow biopsy are shown.



Which of the following is the most likely diagnosis?

A

Acute lymphoblastic leukemia

B

Acute myeloid leukemia

C

Aplastic anemia

D

Myelodysplastic syndrome

E

Paroxysmal nocturnal hemoglobinuria

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose aplastic anemia.

Key Point

Aplastic anemia is characterized by severe hypocellularity of the bone marrow and pancytopenia.

The patient has aplastic anemia (AA). He presents with an insidious clinical course and has severe pancytopenia. The absolute neutrophil count is only 50/µL (0.05×10^9/L). Despite severe neutropenia, AA may present with clinically unimpressive infections. This contrasts with the acute leukemias. The bone marrow biopsy demonstrating less than 10% cellularity confirms the diagnosis of aplasia. AA may occur secondary to infections or toxins. However, it usually presents without preceding insult. Such patients respond to immunosuppressive therapy, and allogeneic hematopoietic stem cell (HSC) transplantation can be curative in young otherwise healthy patients.

Acute lymphoblastic leukemia (ALL) is a reasonable consideration in this patient, because ALL is more common in adolescents and young adults. It can present with pancytopenia rather than hyperleukocytosis. However, the bone marrow biopsy excludes ALL, because leukemic blasts more typically cause marrow hypercellularity; very few blood-making cells are present on this patient's biopsy. For the same reason, acute myeloid leukemia can be excluded.

The myelodysplastic syndromes (MDS) are clonal HSC disorders characterized by ineffective hematopoiesis and a variable rate of transformation to acute myeloid leukemia. MDS can present with pancytopenia, although it occurs less commonly in younger patients. However, the bone marrow in MDS is classically hypercellular. Although hypocellular MDS exists, crossover with AA is considerable, and the decrease in marrow cellularity is not this striking.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired HSC disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. The bone marrow is usually hypocellular with PNH, but other features such as hemolysis and thrombosis are present, distinguishing it from AA. Likewise, the degree of hypocellularity is not as severe as that of AA.

Question 47

A 56-year-old woman is evaluated for an elevated serum protein level discovered during a routine examination for a life insurance policy. She is asymptomatic. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	13.4 g/dL (134 g/L)
Leukocyte count	6400/µL (6.4×10^9/L)
Platelet count	224,000/µL (224×10^9/L)
Calcium	9.6 mg/dL (2.4 mmol/L)
Creatinine	0.7 mg/dL (61.9 µmol/L)
IgA	2080 mg/dL (20.8 g/L)

Serum protein electrophoresis and immunofixation reveal a monoclonal IgA κ band measuring 1.8 g/dL. A 24-hour urine protein electrophoresis reveals 80 mg of total protein and trace monoclonal free κ light chains that are too low to quantify.

A bone marrow aspirate and biopsy reveals clonal plasma cells representing 8% of the overall marrow cellularity. A skeletal survey demonstrates no lytic lesions, osteopenia, or fractures.

Which of the following is the most appropriate diagnostic test to perform next?

A
MRI of the cervical, thoracic, and lumbar spine

B
Serum β_2-microglobulin measurement

C
Serum free light chain testing

D
Serum lactate dehydrogenase measurement

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose monoclonal gammopathy of undetermined significance.

Key Point

Risk factors for progression of monoclonal gammopathy of undetermined significance to multiple myeloma include a non-IgG M protein, an M protein level of at least 1.5 g/dL, and an abnormal serum free light chain ratio.

Serum free light chain (FLC) testing should be performed. This patient meets criteria for a diagnosis of monoclonal gammopathy of undetermined significance (MGUS), because clonal plasma cells represent less than 10% of the total marrow cellularity, and she does not meet CRAB (hyperCalcemia, Renal failure, Anemia, Bone disease) criteria for a diagnosis of multiple myeloma requiring therapy. MGUS is common, affecting 3.2% of persons 50 years or older and 5.3% of persons 70 years or older. The risk of progression to a clinically symptomatic disease is approximately 1% per year. Risk factors for progression include a non-IgG M protein, an M protein level of at least 1.5 g/dL, and an abnormal serum FLC ratio. A few FLCs (not bound to immunoglobulin) circulate normally and can be measured in serum. The FLC ratio measures the ? and ? FLCs, expressed as the ?/? FLC ratio. Persons without a plasma cell dyscrasia have normal ratios; abnormal ratios suggest a disproportionate production of a monoclonal ? or ? chain. An abnormal FLC ratio is prognostically helpful, because it suggests a more virulent plasma cell clone that may be at higher risk of transforming into overt multiple myeloma. This patient has two risk factors identified thus far (M protein level ?1.5 g/dL and an IgA M protein). Serum free ? and ? light chain level measurement and ?/? FLC ratio determination are essential parts of the evaluation of MGUS; they help delineate the risk of progression to clinically symptomatic disease and dictate the frequency of follow-up. Patients with zero, one, two, or three risk factors have a risk of progression to clinically symptomatic disease over 20 years of 5%, 21%, 37%, and 58%, respectively.

MRI imaging of the spine and whole spine MRI have not been shown to further risk stratify patients with MGUS. However, in patients with smoldering (asymptomatic) multiple myeloma, more than one focal bone lesion on MRI is associated with a greater risk of progression to multiple myeloma requiring therapy.

The ?$_2$-microglobulin and lactate dehydrogenase levels are useful tools for determining the prognosis of multiple myeloma requiring therapy but are not routinely performed in MGUS.

Question 48

A 63-year-old man is evaluated for severe mid-upper back pain following a minor fall 1 day ago. He also notes progressive fatigue of 6 months' duration and a 6.8-kg (15 lb) weight loss. Medical history is notable for an 80-pack-year smoking history, although he is currently a nonsmoker.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 112/74 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. BMI is 22. The cardiopulmonary examination is unremarkable. He has no lymphadenopathy or hepatosplenomegaly. Point tenderness to palpation is noted over the mid thoracic spine. No skin changes or peripheral edema are observed.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	4800/µL (4.8 × 10^9/L) with a normal differential
Platelet count	155,000/µL (155 × 10^9/L)
Albumin	2.8 g/dL (28 g/L)
Calcium	11.8 mg/dL (3.0 mmol/L)
Creatinine	3.1 mg/dL (274 µmol/L)
Total protein	6.3 g/dL (63 g/L)
Urinalysis	Trace protein, no blood, 0 erythrocytes/hpf, no casts
Urine protein-creatinine ratio	2300 mg/g

A chest radiograph shows no infiltrates and a normal cardiac silhouette. Radiographs of the thoracic spine reveal osteopenia with a compression fracture of T6.

Which of the following is the most appropriate diagnostic test to perform next?

A
1,25-Dihydroxyvitamin D (calcitriol) measurement

B
Intact parathyroid hormone measurement

C
Parathyroid hormone–related protein measurement

D
Serum protein electrophoresis and free light chain test

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose multiple myeloma requiring therapy.

Key Point

Combination serum protein electrophoresis and free light chain testing has a sensitivity approaching 100% for diagnosing multiple myeloma requiring therapy.

Serum protein electrophoresis and serum free light chain (FLC) testing should be performed in this patient with likely multiple myeloma; together, these have a diagnostic sensitivity approaching 100% for multiple myeloma requiring therapy. This patient has several findings suspicious for this disease as the cause of his hypercalcemia, including osteopenia with a thoracic compression fracture, anemia, and kidney dysfunction. However, kidney dysfunction can occur as a direct result of hypercalcemia, regardless of its underlying cause. An important clue in this patient is the discordance between the degree of proteinuria assessed by the urinalysis compared with the urine protein-creatinine ratio. A routine dipstick urinalysis will detect albuminuria but is relatively insensitive at detecting other urine proteins. However, a urine protein-creatinine ratio measures all proteins in the urine, including immunoglobulins, if present. This discrepancy should raise suspicion for monoclonal FLCs in the urine (Bence-Jones proteinuria) and potential cast nephropathy. Similarly, a sulfosalicylic acid test will detect all urine proteins, including light chains, and can be performed for suspected myeloma cast nephropathy. In FLC myeloma, the serum protein electrophoresis may only reveal hypogammaglobulinemia and no monoclonal band or a low-level monoclonal band because of its insensitivity at detecting monoclonal FLCs. However, the serum FLC test, an antibody-based assay that can detect low levels of FLCs, will demonstrate an elevated level of the affected monoclonal FLC and an abnormal serum ?/? FLC ratio.

Increased 1,25-dihydroxyvitamin D (calcitriol) levels may result from ingestion of calcitriol or increased 25-hydroxyvitamin D (calcidiol) activation to calcitriol as a result of underlying granulomatous disease (for example, sarcoidosis) or lymphoma, thus leading to hypercalcemia. This patient has no history of calcitriol ingestion and no physical examination or radiographic features of granulomatous disease or lymphoma. Increased calcitriol levels do not explain his anemia, osteopenia and thoracic compression fracture, or kidney dysfunction with nonalbumin proteinuria.

Primary hyperparathyroidism can present with hypercalcemia, bone mineral density loss with increased compression fracture risk, and, when hypercalcemia is severe enough or long-standing, kidney dysfunction. However, primary hyperparathyroidism is uncommonly associated with anemia and does not explain the proteinuria, so measuring the intact parathyroid hormone level is not indicated.

Hypercalcemia associated with myeloma results from osteoclast activation, not secretion of parathyroid hormone–related protein (PTHrP). PTHrP is produced more commonly in solid tumors, such as squamous cell (head and neck, lung); renal cell; and bladder, breast, and ovarian carcinomas. Although the patient has an extensive smoking history, no findings on physical examination or chest radiograph suggest the presence of a solid tumor. Additionally, PTHrP-mediated hypercalcemia from an occult solid tumor would not explain this patient's proteinuria.

Question 49

A 48-year-old man is evaluated in the emergency department for fever and cough of 7 days' duration. Medical history is notable for an aortic valve replacement. His only regular medication is warfarin, although he reports taking acetaminophen every 2 to 3 hours to relieve his fever and chest pain as a result of coughing.

On physical examination, the patient appears ill and slightly jaundiced. Temperature is 38.9 °C (102.0 °F), blood pressure is 90/45 mm Hg, pulse rate is 120/min, and respiration rate is 24/min. Oxygen saturation is 91% breathing ambient air. Coarse breath sounds with rhonchi in the right lung base are heard on auscultation. Cardiac examination reveals regular tachycardia and a mechanical S_2 but no other findings. Right upper quadrant tenderness and multiple ecchymoses are noted.

Laboratory studies:

D-dimer	5800 µg/mL (5800 mg/L)
Leukocyte count	22,000/µL (22 × 10^9/L)
Platelet count	95,000/µL (95 × 10^9/L)
Prothrombin time	58 s
Fibrinogen	110 mg/dL (1.1 g/L)
INR	8.8 (6 weeks ago, 2.5)
Factor V	20% (normal, 50%-150%)
Factor VII	5% (normal, 50%-150%)
Factor VIII	200% (normal, 50%-150%)

Chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most likely cause of the patient's coagulation abnormality?

A
Disseminated intravascular coagulation

B
Liver failure

C
Vitamin K deficiency

D
Warfarin overdose

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose coagulopathy of liver disease.

Key Point

Coagulopathy of liver disease is characterized by prolonged prothrombin and activated partial thromboplastin times and increased factor VIII level.

The patient most likely has liver failure resulting from excessive acetaminophen use as the cause of his coagulopathy. He takes chronic warfarin therapy but presents with a significant coagulopathy of unclear cause. Specific factor level measurement is useful when it is clinically helpful to understand the basis of a coagulation disorder to guide therapy. A panel of factors, including factor V, factor VII, and factor VIII, may be checked when it is important to distinguish between liver failure, disseminated intravascular coagulation, or vitamin K deficiency/warfarin overdose. In liver failure, all clotting factor activity levels are low except for factor VIII, which is synthesized in all endothelial cells rather than only hepatic endothelial cells. Additionally, good hepatic function is required for factor VIII clearance, thus factor VIII levels increase in liver disease. Patients with severe liver failure (and on occasion those with acute liver failure) will have prolonged prothrombin and activated partial thromboplastin times because of decreased levels of coagulation factors. This is called the coagulopathy of liver disease. The elevated D-dimer level is also consistent with liver disease, because D-dimers are cleared by the liver; a high D-dimer level does not automatically indicate disseminated intravascular coagulation (DIC).

DIC begins with abnormal thrombin generation, rapid consumption of clotting factors and platelets, and accelerated fibrinolysis. Although hemorrhage may result from low levels of clotting factors and platelets, histopathologic examination of affected tissues shows a fibrin clot in the microvasculature. A thrombotic microangiopathy may ensue, and schistocytes develop in 30% of patients. An elevated factor VIII level, as seen in this patient, rules out DIC.

Factor V levels can be used to distinguish between liver disease and vitamin K deficiency, because factor V is synthesized in the liver but is not a vitamin K–dependent factor. Thus, someone with vitamin K deficiency will have normal levels of factor V, whereas a patient with liver failure will have low factor V levels. This patient's low factor V level rules out warfarin overdose as well as vitamin K deficiency, because normal levels would be expected in vitamin K deficiency.

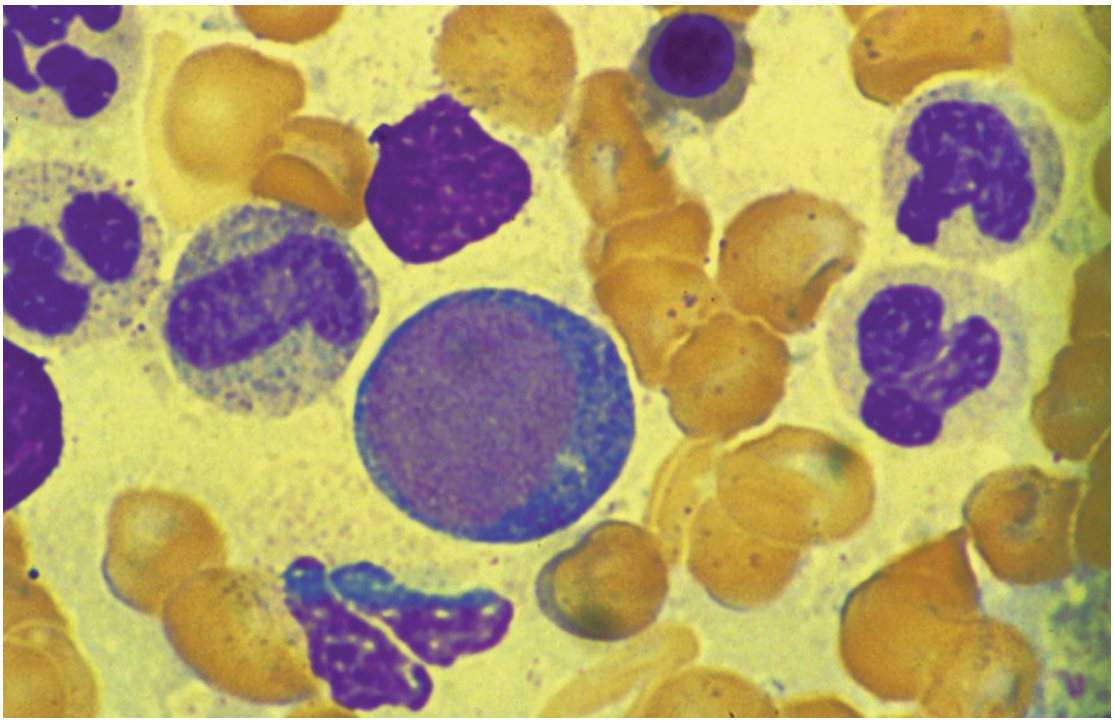
Question 50

A 34-year-old man is evaluated for a 3-month history of fatigue, early satiety, and a 10-kg (22 lb) weight loss. Medical history is notable for hypertension, which is well controlled with hydrochlorothiazide.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 135/81 mm Hg, pulse rate is 114/min, and respiration rate is 13/min. Cardiac and pulmonary examinations are normal, and no lymphadenopathy is noted. The spleen is palpable 10 cm below the costal margin.

Laboratory studies show a hemoglobin level of 8.4 g/dL (84 g/L), leukocyte count of 314,000/µL (314 × 109/L), and platelet count of 622,000/µL (622 × 109/L).

A peripheral blood smear is shown.



Which of the following is the most likely genetic mutation to explain this patient's findings?

A

BCR-ABL

B

IGH/CD1

C

JAK2 V617F

D

PML-RAR

Answer & Critique

Correct Answer: A

Educational Objective: Diagnose chronic myeloid leukemia.

Key Point

Patients with suspected chronic myeloid leukemia should be tested for an underlying *BCR-ABL* mutation.

This patient is most likely to have a *BCR-ABL* genetic mutation predisposing him to chronic myeloid leukemia (CML). He has the classic presentation for CML with the insidious onset of fatigue; early satiety and progressive weight loss associated with splenomegaly; and a peripheral blood smear demonstrating myelocytes, metamyelocytes, and basophils. The peripheral blood smear of CML is commonly described as mimicking a bone marrow aspirate. Basophilia is a general clue to the presence of a myeloproliferative neoplasm (MPN).

IGH/CD1 is the mutation associated with mantle cell lymphoma (MCL). MCL can present with hyperleukocytosis and massive splenomegaly, but myeloid precursors and basophilia would not be seen on peripheral blood smear.

The *JAK2* gene mutation is associated with polycythemia vera, essential thrombocytosis (ET), and primary myelofibrosis but not CML. Because CML is a more likely diagnosis, especially because of the prominence and degree of leukocytosis, *BCR-ABL* mutation should be excluded first in this patient.

PML-RAR protein mutation is associated with acute promyelocytic leukemia (APL). APL does not demonstrate basophilia or transitional myeloid precursors on the peripheral blood smear. Additionally, it is clinically associated with disseminated intravascular coagulation and thrombocytopenia rather than thrombocytosis, and splenomegaly is uncommon in APL.

Question 51

A 30-year-old man with acute lymphoblastic leukemia is evaluated for fever, chills, rigors, and dyspnea, which started toward the end of a platelet transfusion given for chemotherapy-induced thrombocytopenia.

On physical examination, the patient is lethargic, flushed, and clammy. Temperature is 39.4 °C (102.9 °F), blood pressure is 90/42 mm Hg, pulse rate is 150/min, and respiration rate is 24/min (before transfusion, temperature was 37.2 °C [99.0 °F], blood pressure was 140/76 mm Hg, and pulse rate was 90/min). Oxygen saturation is 94% breathing ambient air. Rigors are noted, and skin is warm to the touch without skin changes. Head, neck, and pulmonary examinations are unremarkable. Cardiac examination reveals tachycardia but no murmurs.

In addition to stopping the transfusion and administering intravenous fluids, which of the following is the most appropriate t reatment?

A
Diphenhydramine, acetaminophen, and meperidine

B
Epinephrine

C
Vancomycin and cefepime

D
No additional treatment

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient with transfusion-transmitted bacterial infection.

Key Point

Transfusion should be stopped immediately and intravenous fluids and antibiotics should be given to patients experiencing transfusion-transmitted bacterial infection.

In addition to stopping the transfusion and resuscitating the patient, broad-spectrum antibiotics such as vancomycin and cefepime should be started, and blood cultures should be drawn to determine the infecting organism. The patient is most likely experiencing sepsis as a result of transfusion-transmitted bacterial infection. Clinical criteria for a possible septic transfusion reaction include any of the following within 5 hours of completion of a transfusion: temperature greater than 39.0 °C (102.2 °F) or temperature two degrees higher than pretransfusion, rigors, pulse rate greater than 120/min or more than 40/min higher than pretransfusion, or a decrease or increase in blood pressure of greater than 30 mm Hg. Transfusion-transmitted bacterial infection remains an important cause of transfusion-related morbidity and mortality with rates of all septic reactions and fatal septic reactions reaching 1:74,807 and 1:498,711 per distributed platelet component. The majority of infections are due to staphylococcal species, although gram-negative organisms are also implicated. The blood product bag should be sealed and sent to the microbiology laboratory for culture.

Acetaminophen, diphenhydramine, and meperidine may be used as symptomatic treatment of a febrile nonhemolytic transfusion reaction. However, febrile nonhemolytic transfusion reactions are not typically associated with hypotension.

Epinephrine should only be used to treat anaphylaxis, which is less likely than sepsis in this patient. Anaphylaxis is associated with hypotension and respiratory distress, but this patient has no dermatologic (pruritus, urticaria, angioedema), pulmonary (wheezing, cough), or gastrointestinal (nausea, vomiting, abdominal cramping, diarrhea) manifestations suggesting anaphylaxis. Additionally, anaphylaxis is not associated with fever.

Considering the high morbidity and mortality associated with a septic transfusion reaction, stopping the transfusion and volume resuscitation alone are insufficient. This patient needs broad spectrum antibiotics to treat his transfusion-associated infection.

Question 52

A 61-year-old man is evaluated in the emergency department for diffuse, mild, left calf pain without swelling of 10 days' duration, which has worsened in the past 2 days. The patient reports no provoking injury or incident. He feels well otherwise. Medical and family histories are unremarkable. He takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 132/82 mm Hg, pulse rate is 75/min, and respiration rate is 16/min. BMI is 32. He is in no acute distress, but he scores his leg pain as 3/10 in intensity. Mild to moderately deep palpation of the calf muscles provokes diffuse discomfort. The left leg is not discolored, and no edema is present, but it feels slightly fuller than the right and is 1 cm in circumference larger than the right at the midcalf level.

Which of the following is the most appropriate management?

A
Anticoagulant therapy for 3 months

B
Blood D-dimer test

C
Duplex ultrasonography of the leg

D
Magnetic resonance venography of the leg

Answer & Critique

Correct Answer: B

Educational Objective: Choose the appropriate diagnostic test for a patient with a low pretest probability of deep venous thrombosis.

Key Point

A blood D-dimer test using a moderately or highly sensitive assay should be the first step in the diagnosis of deep venous thrombosis in a patient with low pretest probability.

A blood D-dimer test should be performed. American College of Chest Physicians guidelines suggest that a clinical pretest probability assessment of deep venous thrombosis (DVT) should be the first part of the diagnostic process for a first lower extremity DVT, rather than performing an imaging study in all patients. The pretest probability that this patient has a DVT is low. Applying the Wells criteria for DVT, this patient's score is 0, making DVT an unlikely diagnosis. The criteria include a medical history indicating increased risk for venous thromboembolism (VTE) (such as previously documented DVT; paralysis, paresis, recent cast immobilization of legs; recent bedridden state for ?3 days; major surgery) and leg symptoms highly suggestive of DVT (calf swelling ?3 cm; swelling of the entire leg; unilateral pitting edema; localized tenderness along the deep venous system). Because this patient has none of these factors and no alternative explanation for his leg symptoms, obtaining a D-dimer test is an appropriate next step. If the test is negative, no further testing is needed, because a VTE has been ruled out. However, if the D-dimer is positive, an imaging study is then indicated. The imaging test of choice is duplex ultrasonography of the leg. When using the D-dimer test for pretest probability assessments, a moderately or highly sensitive assay should be used. Physicians must be aware of the sensitivity of the test used in local laboratories. Lower sensitivity assays have not been validated as useful for predicting pretest probability.

Long-term anticoagulants should not be prescribed without a confirmed diagnosis of VTE. However, in a patient with high or intermediate clinical suspicion of DVT, beginning anticoagulation while awaiting diagnostic test results is appropriate. In a patient with low clinical suspicion of acute DVT, such as this patient, withholding anticoagulant therapy while awaiting the test result is suggested.

If a D-dimer test is not available or is positive, performing duplex ultrasonography would be the appropriate next step.

Magnetic resonance venography is a noninvasive diagnostic method that is as accurate as contrast venography for DVT diagnosis. However, it is not the study of choice for DVT diagnosis because of the complexities of performing the test and its high cost relative to duplex ultrasonography. Additionally, initial imaging is not indicated in this patient with a low risk of DVT before further assessment with D-dimer testing.

Question 53

A 23-year-old man is admitted to the hospital for severe right upper quadrant pain of 2 days' duration. Medical history is significant for homozygous sickle cell anemia (Hb SS). His only medication is folic acid.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 115/70 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Oxygen saturation is 98% breathing ambient air. Palpation confirms a tender right upper quadrant. The remainder of the examination is normal.

Laboratory studies reveal a hemoglobin level of 7.5 g/dL (75 g/L) and a platelet count of 415,000/µL (415 × 10^9/L).

Abdominal ultrasonography confirms a diagnosis of cholecystitis, and a laparoscopic cholecystectomy is planned before hospital discharge.

In addition to antibiotics, which of the following is the most appropriate preope rative management?

A
Erythrocyte exchange transfusion to a target hemoglobin S of less than 30%

B
Erythrocyte transfusion to a hemoglobin level of 10 g/dL (100 g/L)

C
Erythrocyte transfusion to a hemoglobin level of 12 g/dL (120 g/L)

D
Erythrocyte transfusion for symptomatic anemia

Answer & Critique

Correct Answer: B

Educational Objective: Manage transfusion in a patient with sickle cell disease who requires cholecystectomy.

Key Point

Patients with sickle cell disease undergoing low- to moderate-risk surgery should receive erythrocyte transfusion, which has been shown to be equivalent to exchange transfusion, targeting a hemoglobin level of 10 g/dL (100 g/L) before the procedure to avoid complications.

This patient should receive an erythrocyte transfusion to a target hemoglobin level of 10 g/dL (100 g/L). He has homozygous sickle cell anemia (Hb SS) and must undergo laparoscopic cholecystectomy, a surgical procedure of low to moderate risk. Patients requiring surgery should undergo transfusion before their procedure to avoid complications. Transfusion to a hemoglobin level of 10 g/dL (100 g/L) has been shown to be equivalent to exchange transfusion for low- to medium-risk surgeries. The recent TAPS study showed that, for this surgical risk group, significantly more clinically important complications occurred in the group that did not receive preoperative transfusion (39%) than the group that did receive transfusion (15%). Significantly more serious events were also recorded in the nontransfusion group (30%) than in the transfusion group (3%), most of which were acute chest syndrome (ACS). Erythrocyte transfusions must be given with care in patients with sickle cell disease, because these transfusions are associated with iron overload. In some patients, “hyperhemolysis” occurs because of alloimmune responses to erythrocyte antigens, which leads to a delayed transfusion reaction characterized by hyperbilirubinemia and anemia. Additionally, erythrocyte transfusions that result in hemoglobin levels greater than 10 g/dL (100 g/L) can increase blood viscosity and potentially cause thrombotic complications.

Several multicenter studies have documented the clinical efficacy of transfusion to 10 g/dL (100 g/dL) compared with the more aggressive strategy of exchange transfusion targeting a hemoglobin S level of 30%. Transfusion and exchange transfusion are associated with similar serious surgery-related complications and ACS, but transfusion is associated with fewer transfusion-related complications and exposure to less blood.

Question 54

A 65-year-old woman is evaluated in the emergency department for a 1-day history of pain and swelling in her left leg. Medical history is significant for coronary artery bypass graft surgery 8 days ago with vein harvesting from the right leg. She also has hypertension and hyperlipidemia. Medications are atorvastatin, atenolol, clopidogrel, and aspirin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 115/68 mm Hg, pulse rate is 65/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 96%. Her sternotomy incision is healing well. The cardiopulmonary examination is normal. The left leg is swollen to the mid-thigh.

Laboratory studies reveal a hematocrit of 33%, leukocyte count of 12,000/µL (12×10^9/L), and platelet count of 55,000/µL (55×10^9/L).

Duplex ultrasonography of the left leg shows acute thrombus in the common femoral vein.

Which of the following is the most appro priate next step in management?

2%

A
Await platelet factor 4 immunoassay before initiating anticoagulation

1%

B
Await serotonin release assay before initiating anticoagulation

55%

C
Initiate argatroban

39%

D
Initiate heparin

4%

E
Initiate warfarin

Answer & Critique

Correct Answer: C

Educational Objective: Manage heparin-induced thrombocytopenia.

Key Point

Heparin cessation and immediate treatment with a nonheparin alternative anticoagulant (lepirudin, argatroban, danaparoid) are mandatory when a high pretest probability of heparin-induced thrombocytopenia is present.

This patient most likely has heparin-induced thrombocytopenia (HIT) with thrombosis after being exposed to heparin during coronary artery bypass graft surgery, so the most appropriate next step is to initiate argatroban, a direct thrombin inhibitor used for anticoagulation in HIT. Patients who receive heparin during cardiothoracic surgery or after orthopedic surgery are more likely to develop HIT than are patients who receive heparin for dialysis or deep venous thrombosis prophylaxis. HIT develops 5 to 10 days after exposure to heparin, with a decrease in platelet counts of 50% or more and, in a subset of patients, paradoxical arterial or venous thrombotic events despite the presence of thrombocytopenia. The “4T score” has been devised to help clinicians decide the pretest probability for diagnosing HIT based on clinical factors, including degree of thrombocytopenia, timing of the decrease in platelet count, presence of potential sequelae of HIT (such as thrombosis), and whether another potential cause for thrombocytopenia exists. Possible point values range from 0 to 8; scores of 0 to 3 indicate low probability, 4 or 5 indicate intermediate probability, and 6 to 8 represent high probability. The patient's 4T score is 8 (2 points each for timing of platelet count decrease, presence of thrombosis, timing of thrombocytopenia, and no other cause of the thrombocytopenia), indicating a high pretest probability of HIT. In patients with a high pretest probability, immediate cessation of any heparin-containing products is indicated, with initiation of a nonheparin anticoagulant; the only anticoagulant approved for the treatment of HIT is argatroban.

Confirmatory testing for presumed HIT is performed by HIT antibody testing. Immunoassays detect the presence of a HIT antibody (such as those directed toward platelet factor 4) in a patient's serum. Functional assays measure the ability of a HIT antibody from a patient's serum to activate test platelets (such as by measuring the release of serotonin). Because of the high risk of

thrombosis associated with HIT and the possible delay associated with obtaining these studies, anticoagulation with a heparin alternative should be started before performing confirmatory testing.

Heparin cessation and treatment with a nonheparin anticoagulant are mandatory when a high pretest probability of HIT exists, because 30% to 50% of patients experience thromboses with heparin withdrawal alone. This patient already has evidence of thrombosis and must start treatment immediately to prevent extension and embolization.

Warfarin initiation alone is inadequate, because it may take 3 to 5 days to achieve a therapeutic anticoagulation effect. Additionally, starting warfarin before the platelet count has normalized in patients with HIT or starting warfarin without a bridging anticoagulant has been associated with development of warfarin skin necrosis and clot progression.

Question 55

A 32-year-old woman is evaluated for anticoagulation management after an uncomplicated vaginal delivery of a healthy newborn. She was diagnosed with a bilateral pulmonary embolism at 25 weeks' gestation and was treated with therapeutic low-molecular-weight heparin (LMWH). The LMWH was discontinued at the onset of labor and was restarted 6 hours after delivery. Medical history is otherwise unremarkable, and her only medication is full-dose LMWH.

Anticoagulation for 3 months is planned. The patient wishes to breastfeed her newborn.

Which of the following is the most appropriate anticoagulation option for this patient?

A
Apixaban

B
Dabigatran

C
Fondaparinux

D
Rivaroxaban

E
Warfarin

Answer & Critique

Correct Answer: E

Educational Objective: Treat a patient with venous thromboembolism who wishes to breastfeed.

Key Point

Warfarin and low-molecular-weight heparin are considered safe for use by women requiring anticoagulant therapy who wish to breastfeed.

Warfarin would be the most appropriate anticoagulation option for this patient. Warfarin is avoided during pregnancy because it crosses the placenta, causes fetal anticoagulation throughout the pregnancy, and is a teratogen. Because heparins do not cross the placenta and do not cause fetal anticoagulation, patients receiving chronic warfarin therapy are typically transitioned to either unfractionated or low-molecular-weight heparin (LMWH) during pregnancy. However, warfarin is not present in breast milk in any substantial amount and does not induce an anticoagulant effect in the breastfed infant. It is, therefore, a good option for anticoagulation in this patient. Similarly, heparins are minimally excreted in breast milk, and any drug ingested by an infant is unlikely to have any clinically relevant effect because of the very low bioavailability of oral heparins. Thus, LMWH and warfarin are both appropriate anticoagulant options for women who want to breastfeed.

It is unknown whether apixaban, dabigatran, or rivaroxaban are excreted in human milk. Therefore, known safe alternatives to these new oral anticoagulants should be used in women intending to breastfeed.

Fondaparinux has been demonstrated to be excreted in the milk of lactating rats. It is unknown whether it is excreted in human milk. Therefore, an alternative anticoagulant rather than fondaparinux is recommended for women who breastfeed.

Question 56

A 72-year-old woman is evaluated in follow-up for a recent diagnosis of multiple myeloma. She presented with an 8-month history of progressive fatigue and dyspnea with exertion, but has had no other symptoms. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 142/86 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. No focal neurologic deficits are observed. Cardiopulmonary examination is normal, and the remainder of the physical examination is unremarkable.

Initial laboratory studies showed a hemoglobin level of 9.2 g/dL (92 g/L), serum calcium level of 10.2 mg/dL (2.6 mmol/L), and serum creatinine level of 1.3 mg/dL (115 μmol/L).

A monoclonal IgG κ band of 4.2 g/dL was seen on serum protein electrophoresis and immunofixation, and myeloma was confirmed with a bone marrow aspirate and biopsy showing clonal plasma cells representing 70% of the overall cellularity.

A skeletal survey demonstrates diffuse osteopenia and a T12 compression fracture with 50% height loss. No lytic lesions are seen.

In addition to starting chemotherapy, which of the following is the most appropriate treatment?

A

Balloon kyphoplasty to the T12 vertebra

B

Radiation therapy to the thoracic spine

C

Zoledronic acid

D

No additional treatment

nswer & Critique

Correct Answer: C

Educational Objective: Treat multiple myeloma–related bone disease.

Key Point

The bisphosphonates pamidronate and zoledronic acid should be used for all patients with newly diagnosed multiple myeloma requiring therapy.

In addition to chemotherapy, this patient should be treated with a bisphosphonate such as zoledronic acid. She has multiple myeloma requiring therapy with anemia and myeloma-related bone disease manifested by osteopenia with a T12 compression fracture. Studies have shown that bisphosphonates inhibit osteoclast-mediated osteolysis, reduce the risk of skeletal-related events (pathologic fracture, need for radiation therapy or surgery to bone, spinal cord compression), decrease bone-related pain, and improve median overall survival. The risk of skeletal-related events was reduced in patients with or without evidence of lytic bone disease on plain radiographs. Bisphosphonates therefore represent a critical aspect of care for patients with myeloma requiring therapy, and guidelines call for the use of zoledronic acid or pamidronate in all patients with newly diagnosed multiple myeloma.

Although vertebroplasty has not been shown to be beneficial in the management of osteoporotic vertebral body compression fractures, a small randomized study comparing balloon kyphoplasty with nonsurgical management of painful vertebral body compression fractures in patients with multiple myeloma and solid tumors demonstrated improved short-term physical functioning, pain control, and quality of life for those undergoing kyphoplasty. However, data on long-term outcomes with kyphoplasty are lacking in patients with cancer, and no role has been established for the procedure in the absence of pain.

Radiation therapy is typically reserved for pain related to lytic bone disease, particularly in patients with increasingly chemotherapy-resistant disease, and would not be appropriate in this patient.

Because of the documented efficacy of bisphosphonate therapy in patients with multiple myeloma requiring therapy, it would be inappropriate not to provide further treatment for this patient.

Question 57

A 22-year-old woman is evaluated for a 2-month history of increasing fatigue and dyspnea, which is most noticeable with exercise. She otherwise feels well. She notes no gastrointestinal symptoms, although she believes that her urine sometimes appears darker than usual. She eats a normal diet, menstruation is of usual duration and flow, and she is physically active as a distance runner. Medical and family histories are otherwise unremarkable; her only medication is ibuprofen as needed.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 100/55 mm Hg, pulse rate is 65/min, and respiration rate is 16/min. She has no muscle tenderness or weakness. The remainder of the physical examination is normal. A stool sample is guaiac negative.

Laboratory studies:

Haptoglobin	Undetectable
Hematocrit	25%
Leukocyte count	5500/µL (5.5×10^9/L)
Mean corpuscular volume	72 fL
Platelet count	430,000/µL (430×10^9/L)
Reticulocyte count	1.2% of erythrocytes
Creatine kinase	165 U/L
Ferritin	3 ng/mL (3 µg/L)
Lactate dehydrogenase	1400 U/L
Urinalysis	Dipstick positive for 4+ blood; 0-1 leukocytes/hpf, and 0 erythrocytes/hpf

Peripheral blood smear shows hypochromic microcytic erythrocytes without schistocytes or spherocytes.

Which of the following is the most likely cause of this patient's anemia?

A

Exercise-induced hematuria

B

Exercise-induced hemolysis

C

Inflammatory myopathy

D

Rhabdomyolysis

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose exercise-induced hemolysis.

Key Point

Exercise-induced hemolysis (march hemoglobinuria or runner's hemolysis) is caused by erythrocyte damage through repetitive mechanical trauma such as running or marching, resulting in intravascular hemolysis with loss of iron in the urine

This patient likely has exercise-induced hemolysis, also known as march hemoglobinuria or runner's hemolysis. This is caused by erythrocyte damage through repetitive mechanical trauma such as running or marching, resulting in intravascular hemolysis. Hemolysis leads to increased levels of free hemoglobin in the plasma, which is filtered by the kidneys, resulting in hemoglobinuria. Urinalysis findings show evidence of blood in the urine by dipstick but no erythrocytes, as seen in this patient. With prolonged intravascular hemolysis, patients may become secondarily iron deficient through iron loss in the urine. Patients with this entity may show iron deficiency anemia with evidence of urine iron loss, indicated by the presence of hemosiderin in sloughed tubular cells by Prussian blue staining. Exercise-induced hemolysis is considered a benign condition and is treated by removal or reduction of the traumatic cause of erythrocyte injury.

Strenuous exercise is a well-described cause of either gross or microscopic hematuria. Although the mechanism for hematuria associated with exercise has not been fully elucidated, it is considered a benign condition and should resolve with termination of exercise. This patient has evidence of myoglobinuria but not of hematuria given the lack of erythrocytes in her urine, making this a less likely diagnosis.

An inflammatory myopathy, such as polymyositis, may cause muscle damage and the finding of positive blood on the urine dipstick without significant hematuria. However, inflammatory myopathies are usually associated with muscle weakness and tenderness and an elevated creatine kinase level, which are absent in this patient.

Rhabdomyolysis is caused by injury and necrosis of muscle with release of intracellular muscle contents into the circulation; myoglobin may be detected in the urine as hemoglobin in the

absence of erythrocytes. However, rhabdomyolysis is usually associated with muscle pain and significant elevations in circulating muscle enzyme levels, including creatine kinase. This patient has no muscle tenderness and her creatine kinase level is normal, making this diagnosis unlikely.

Question 58

A 27-year-old woman is evaluated during a follow-up visit. She was evaluated 3 months previously for symptoms of fatigue of 9 months' duration and a craving for ice. She experiences heavy, irregular menstrual cycles, but has no history of other bleeding. Medications are oral contraceptive pills and daily iron, which were initiated 3 months ago.

On physical examination, vital signs are normal; BMI is 31. No splenomegaly is noted.

Laboratory studies:

	3 Months Ago	2 Months Ago	Current
Ferritin	6 ng/mL (6 µg/L)	16 ng/mL (16 µg/L)	45 ng/mL (45 µg/L)
Hemoglobin	8.7 g/dL (87 g/L)	10.1 g/dL (101 g/L)	13 g/dL (130 g/L)
Mean corpuscular volume	71 fL	77 fL	88 fL
Platelet count	800,000/µL (800 × 10^9/L)	790,000/µL (790 × 10^9/L)	775,000/µL (775 × 10^9/L)

Which of the following is the most appropriate diagnostic test to perform next?

A

BCR-ABL genetic analysis

B

JAK2 V617F analysis

C

Prothrombin time and activated partial thromboplastin time

D

von Willebrand factor antigen

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose essential thrombocythemia.

Key Point

A patient with iron deficiency and isolated thrombocytosis that persists after correction of iron deficiency should undergo *JAK2 V617F* mutational analysis as part of the evaluation for essential thrombocythemia.

Mutational analysis for *JAK2 V617F* should be conducted. The patient presented with iron deficiency anemia and thrombocytosis. Thrombocytosis is often associated with iron deficiency anemia, particularly if bleeding is the cause of the anemia. However, when the patient's anemia was corrected with oral iron and oral contraceptive pills for better regulation of menstruation, thrombocytosis persisted, suggesting a disorder in platelet regulation. Iron deficiency is the most common cause of reactive thrombocytosis, which corrects within weeks of correcting the iron deficiency. Infection, inflammation, and malignancy are other causes. With iron deficiency ruled out as a cause and no other causes clinically apparent, essential thrombocythemia (ET) becomes more probable. Her lack of splenomegaly is fairly typical. The *JAK2* activating mutation is present in 50% of patients with ET, so a negative result would not exclude the diagnosis, but a positive result supports the diagnosis of a myeloproliferative neoplasm (polycythemia vera, ET, or primary myelofibrosis).

BCR-ABL testing, then bone marrow aspiration and biopsy, would be performed if the platelet count remained persistently elevated after correction of serum iron levels with a negative *JAK2* mutation status, because myeloproliferative neoplasms other than ET can less commonly elevate the platelet count. In ET, general hypercellularity and megakaryocyte hyperplasia would be seen on the bone marrow examination.

Testing the prothrombin and activated partial thromboplastin times would not be the most appropriate choice, because it focuses the diagnosis on a bleeding diathesis rather than thrombocytosis. Similarly, von Willebrand factor antigen testing does not address the patient's persistently elevated platelet count.

Question 59

An 18-year-old woman is evaluated in follow-up after routine evaluation 3 months ago revealed iron deficiency thought to be related to menorrhagia. She is African and emigrated from the Ivory Coast 6 months ago. Medical history is remarkable for a 2-year history of chronic dyspepsia treated occasionally with a liquid antacid. Her other medications are an oral contraceptive pill and oral ferrous sulfate three times daily.

On physical examination, vital signs are normal. She appears healthy.

Laboratory studies:

	3 Months Ago	**Current**
Hematocrit	30%	33%
Mean corpuscular volume	70 fL	70 fL
Platelet count	525,000/µL (525 × 10^9/L)	500,000/µL (500 × 10^9/L)
Reticulocyte count	—	0.4% of erythrocytes
Red cell distribution width	17.5% (normal, 14.6%-16.5%)	17%
Iron studies		
Ferritin	10 ng/mL (10 µg/L)	10 ng/mL (10 µg/L)
Iron	15 µg/dL (2.7 µmol/L)	15 µg/dL (2.7 µmol/L)
Total iron-binding capacity	425 µg/dL (76 µmol/L)	400 µg/dL (71.6 µmol/L)
Transferrin saturation	12%	13%

Which of the following is the most appropriate management?

A

Add ascorbic acid

B

Perform *Helicobacter pylori* stool antigen assay

C

Perform IgG antigliadin assay

D

Switch to ferrous gluconate

Answer & Critique

Correct Answer: B

Educational Objective: Manage refractory iron deficiency.

Key Point

Iron malabsorption is usually caused by generalized malabsorption conditions such as celiac disease, achlorhydria, or *Helicobacter pylori* infection.

The most appropriate management is to perform a stool antigen assay for *Helicobacter pylori* infection. This patient has iron deficiency anemia. Iron deficiency is a common problem because of the precarious balance between iron intake and use. Women of reproductive age may lose enough iron through normal menstrual blood loss to become iron deficient in the absence of uterine or gastrointestinal disease. Iron malabsorption is a relatively uncommon cause of iron deficiency but should be considered when no other cause of iron deficiency is apparent and particularly when the deficiency is refractory to adequate iron replacement therapy. It is usually caused by generalized malabsorption conditions such as celiac disease, achlorhydria secondary to atrophic gastritis or proton pump inhibitor therapy, or, occasionally, *H. pylori* infection. This patient's history of chronic dyspepsia and refractoriness to oral iron therapy suggest the possibility of *H. pylori* infection. *H. pylori* infection is endemic in many developing countries. Patients treated for underlying *H. pylori* infection may have improved iron absorption, making oral iron replacement an effective treatment.

Although ascorbic acid can facilitate iron absorption, no convincing data suggest the addition of this agent is worth the increase in cost or gastrointestinal toxicity.

Celiac disease is an immunologic response to dietary gliadins in patients genetically at risk as deemed by the presence of HLA-DQ2 or HLA-DQ8. The typical features of celiac disease are diarrhea, bloating, and weight loss; it is diagnosed mainly in whites of northern European ancestry and would be an unusual cause of refractory iron deficiency anemia in a woman of African descent with dyspepsia. Antigliadin assays have poor sensitivity and specificity and a high false-positive rate, so they are not recommended for diagnosing celiac disease.

Iron deficiency is most easily treated with oral iron salts. Oral ferrous sulfate is the least expensive preparation. Each 325-mg tablet of ferrous sulfate contains 66 mg of iron, 1% to 2% of which is absorbed. Although other oral iron salts such as ferrous gluconate or ferrous fumarate are available, none of these have proved superior to ferrous sulfate in tolerability or efficacy.

Question 60

A 63-year-old man is scheduled for recommended repeat colonoscopy in follow-up of adenomatous polyps detected on screening 3 years ago. Medical history is significant for an unprovoked pulmonary embolism 5 years ago. He was initially treated with warfarin but switched to rivaroxaban 1 year ago because of fluctuating INR values with warfarin. He is otherwise healthy and has had no bleeding.

Laboratory studies show a normal complete blood count and a serum creatinine level of 0.8 mg/dL (70.7 µmol/L).

Which of the following is the most appropriate management of this patient's anticoagulation for undergoing colonoscopy?

12%

A

Continue rivaroxaban without interruption

49%

B

Stop rivaroxaban 1 day before colonoscopy without bridging

9%

C

Stop rivaroxaban 1 day before colonoscopy and bridge with low-molecular-weight heparin

19%

D

Stop rivaroxaban 5 days before colonoscopy without bridging

10%

E

Stop rivaroxaban 5 days before colonoscopy and bridge with low-molecular-weight heparin

Answer & Critique

Correct Answer: B

Educational Objective: Manage a patient undergoing colonoscopy and taking a new oral anticoagulant.

Key Point

The new oral anticoagulants should be stopped 24 to 36 hours before surgeries with standard risk for bleeding and 2 to 4 days before surgeries with a high risk for bleeding in patients with normal kidney function.

The patient should stop rivaroxaban, a new oral anticoagulant (NOAC), the day before his scheduled colonoscopy. Because polypectomy or biopsy of lesions may become necessary during this patient's colonoscopy, interruption of anticoagulation is suggested in patients who are not at high risk for thromboembolic events, which includes this patient, because his thrombotic event occurred more than 3 months ago. Compared with warfarin, it is not yet known at what residual drug level procedures and surgeries can be safely performed without undue bleeding risk in patients taking an NOAC. In the absence of clinical data about when to stop these drugs before surgery, the half-life of the anticoagulant is the most frequently used parameter to decide when to stop the drug. Reported half-lives are 14 to 17 hours for dabigatran, 7 to 11 hours for rivaroxaban, 8 to 14 hours for apixaban, and 5 to 11 hours for edoxaban. For surgical procedures with standard risk for bleeding, the NOAC should be discontinued 2 to 3 half-lives beforehand, and in procedures with high bleeding risk, 4 to 5 half-lives beforehand. Close attention to kidney function is needed, because kidney impairment leads to prolonged half-lives of the NOACs. In this patient with normal kidney function, stopping rivaroxaban 24 to 36 hours before the procedure would be appropriate.

Bridging with low-molecular-weight heparin (LMWH) is not indicated, because LMWHs have half-lives of 4 to 7 hours, not much shorter than the NOACs. Additionally, this patient is not at high risk for thromboembolism and would not need preprocedural bridging even if he were taking warfarin.

Question 61

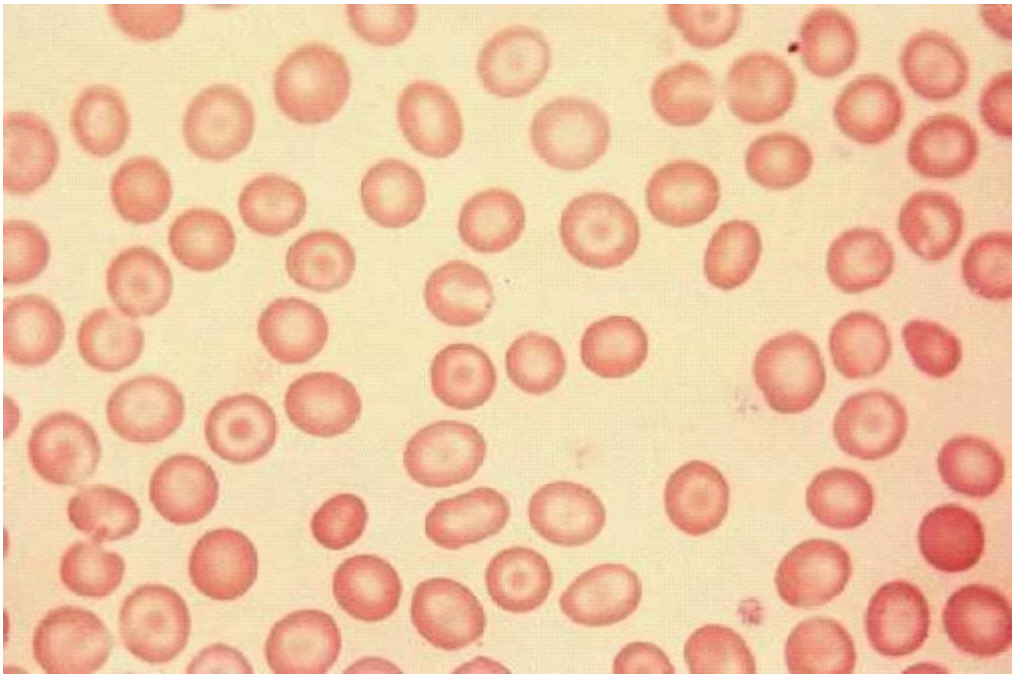
An 18-year-old woman is evaluated following the discovery of anemia on a precollege physical examination. She is asymptomatic. She has regular menstrual cycles every 28 days, which last 5 to 6 days with heavy bleeding on the first 2 days. Medical history is otherwise unremarkable; however, her mother has anemia that is refractory to oral iron therapy. Her only medication is oral iron, which she began taking independently after her anemia diagnosis.

The physical examination is unremarkable.

Laboratory studies:

Erythrocyte count	6.0×10^6/µL (6.0×10^{12}/L)
Hematocrit	33%
Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	6000/µL (6×10^9/L)
Mean corpuscular volume	70 fL
Platelet count	150,000/µL (150×10^9/L)
Reticulocyte count	2.3% of erythrocytes
Red cell distribution width	15 (normal range, 14.6-16.5)
Iron studies	
Ferritin	100 ng/mL (100 µg/L)
Iron	60 µg/dL (11 µmol/L)
Total iron-binding capacity	250 µg/dL (45 µmol/L)

A peripheral blood smear is shown.



Which of the following is the most appropriate management?

A

Discontinuation of oral iron supplementation

B

Fecal occult blood test

C

Oral contraceptive pill

D

Parenteral iron supplementation

Answer & Critique

Correct Answer: A

Educational Objective: Manage ?-thalassemia.

Key Point

?-Thalassemia trait (or ?-thalassemia minor), which is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results, requires no treatment.

This patient should discontinue her oral iron supplementation, because she does not have iron deficiency. She likely has ?-thalassemia trait presenting with a mild microcytic anemia. Microcytic hypochromic erythrocytes and target forms may be seen on the peripheral blood smear in ?- and ?-thalassemia, which can only be differentiated by hemoglobin electrophoresis, in which ?-thalassemia shows a normal pattern and ?-thalassemia typically has a slightly increased hemoglobin A_2 band. ?-Thalassemia trait (or ?-thalassemia minor, double gene deletion -?/-? or –/??) is associated with mild anemia, microcytosis, hypochromia, target cells on the peripheral blood smear, and, in adults, normal hemoglobin electrophoresis results. The (-?/-?) variant is often mistaken for iron deficiency. Microcytic anemia associated with a normal or slightly increased erythrocyte count is characteristic of thalassemia but not of iron deficiency. The red cell distribution width (RDW) is also useful in distinguishing between thalassemia and iron deficiency, because the RDW is often elevated in iron deficiency but normal in thalassemia. No treatment or monitoring is necessary for ?-thalassemia trait.

The mild anemia of ?-thalassemia is often confused with iron deficiency anemia, especially in a patient who could have a plausible cause for iron deficiency from menstrual blood loss. However, this patient's iron values are not consistent with iron deficiency, and the normal RDW argues against iron deficiency and the need for iron replacement therapy. This also rules out the need for evaluation for gastrointestinal blood loss with fecal occult blood testing.

Starting an oral contraceptive pill could potentially lessen the patient's menstrual bleeding, but because she is not iron deficient, oral contraceptives would not correct her mild anemia.

Question 62

A 19-year-old woman is seen for counseling regarding contraceptives. Medical history is unremarkable; she is nulliparous and has never taken prescription contraceptives. Her father had a pulmonary embolism at age 47 years, which was associated with arthroscopic knee surgery, and her 23-year-old sister experienced a deep venous thrombosis 3 weeks after delivering her first child. The patient does not smoke and takes no medications.

On physical examination, she appears well. Vital signs are normal; BMI is 31. The remainder of the examination is unremarkable.

She states that she does not want to use a copper intrauterine device (IUD).

Which of the following contraceptive methods would be most appropriate for this patient?

A

Estrogen-progestin vaginal ring

B

Low-dose combination estrogen-progestin pill

C

Progestin-releasing IUD

D

Transdermal estrogen-progestin patch

Choose an Answer

Answer & Critique

Correct Answer: C

Educational Objective: Determine the appropriate contraceptive choice for a woman at increased risk for venous thromboembolism.

Key Point

Progestin-releasing intrauterine devices are the most appropriate contraceptive option for women at increased risk for venous thromboembolism (VTE) because they are not associated with increasing the VTE risk further, whereas progestin-only pills, implants, and injections may slightly increase the risk for thrombosis.

A progestin-releasing intrauterine device (IUD) would be most appropriate for this patient. Other choices include the progestin-only pill, depot injection, or implanted rod. She is at increased risk for venous thromboembolism (VTE) because of her family history of VTE in two first-degree relatives and her obesity. Progestin-releasing IUDs do not appear to increase VTE risk, so they are a good contraceptive choice for women who are at increased risk for VTE. It is uncertain if oral progestin-only contraceptives (mini-pill) lead to an increased risk of VTE; however, the risk appears to be more clearly increased if additional VTE risk factors are present (obesity, immobility, surgery). Injectable progestins do appear to increase the risk of VTE.

Oral contraceptive pills (OCPs) include combination estrogen-progestin products and progestin-only pills. Combinations with lower estrogen doses are as effective with fewer side effects. Combined products are also available as a patch and a vaginal ring. Contraindications to combination products include history or increased risk of thrombosis, liver disease, breast cancer, migraine with aura, and uncontrolled hypertension. Women older than 35 years who smoke more than 15 cigarettes per day should not be prescribed estrogen-containing preparations because of an increased risk of stroke. Because this patient is at increased risk for thrombosis, she should not use any method of contraception containing estrogen.

Question 63

A 63-year-old man is evaluated in the emergency department for significant shortness of breath and pleuritic anterior chest pain of 48 hours' duration. Three days ago, he completed a 12-hour flight from Asia to the United States. Medical history is otherwise unremarkable and he takes no medications.

On physical examination, he is in mild respiratory distress. He is afebrile, blood pressure is 135/87 mm Hg, pulse rate is 108/min, and respiration rate is 18/min. Oxygen saturation breathing ambient air is 94%. The remainder of the physical examination is unremarkable.

Electrocardiography shows nonspecific ST- and T-wave changes. Echocardiography shows normal right ventricular function. CT angiography of the chest demonstrates multiple pulmonary artery filling defects in the distal branches of the right pulmonary artery consistent with pulmonary embolism.

Which of the following is the most appropriate next step in management?

A

Catheter-directed thrombolysis

B

Inpatient anticoagulation

C

Outpatient anticoagulation

D

Systemic thrombolysis

Answer & Critique

Correct Answer: C

Educational Objective: Manage pulmonary embolism with outpatient anticoagulation.

Key Point

Outpatient anticoagulation management is possible for patients with pulmonary embolism, unless they require supplemental oxygen, intravenous pain medications, or management of comorbid conditions that may contribute to rapid clinical deterioration or if home circumstances make outpatient therapy unfeasible.

This patient can receive anticoagulant therapy in the outpatient setting. When treating acute pulmonary embolism (PE), it is essential to initiate anticoagulation immediately and achieve therapeutic levels of anticoagulation within 24 hours; failure to do so correlates with an increased risk of clinical progression and recurrence. Anticoagulation can be achieved with unfractionated heparin (either intravenous or subcutaneous), subcutaneous low-molecular-weight heparin (LMWH), or the pentasaccharide fondaparinux. Outpatient management is safe for up to 50% of patients with PE, including some with mild right heart strain on cardiac echocardiography. However, hospital admission is appropriate for patients who are too ill to be managed at home (those needing supplemental oxygen or requiring intravenous pain medications) and those with comorbid conditions that may contribute to rapid clinical deterioration (for example, high bleeding risk).

A 2012 guideline from the American College of Chest Physicians (ACCP) recommends thrombolytic therapy for patients with PE and a systolic blood pressure less than 90 mm Hg and without contraindications (for example, high bleeding risk). Thrombolytic therapy does not appear to have therapeutic benefit in unselected patients with acute PE and is associated with an increased risk for major hemorrhage. No clear evidence indicates thrombolytic therapy should be used in patients with evidence of pulmonary hypertension or right ventricular dysfunction detected by echocardiography, positive cardiac enzymes, or both. This patient has no indications for thrombolytic therapy. If thrombolytic therapy were appropriate, the ACCP's guidelines recommend systemic administration rather than catheter-directed thrombolysis.

Question 64

A 67-year-old man is evaluated for progressive lower extremity swelling and dyspnea with exertion of 12 months' duration and orthopnea of 2 months' duration. He is black. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 118/64 mm Hg, pulse rate is 84/min, and respiration rate is 18/min. He has jugular venous distention, a summation gallop, and dullness to percussion and decreased breath sounds at the lung bases. Bilateral lower extremity pitting edema extends to the mid-calf level. The remainder of the physical examination is normal.

On laboratory testing, complete blood count is normal. Comprehensive metabolic profile reveals only an elevated total serum protein level. Serum protein electrophoresis and immunofixation reveal a monoclonal IgG κ band measuring 0.9 g/dL. A 24-hour urine protein electrophoresis and immunofixation reveal no monoclonal protein and no albuminuria.

Chest radiograph shows cardiomegaly and bilateral pleural effusions. Transthoracic echocardiography reveals severe symmetric left ventricular and septal thickening with a small ventricular cavity and reduced systolic function. Bone marrow aspirate and biopsy shows clonal plasma cells representing 8% of the total cellularity. Although a bone marrow biopsy is negative, a Congo red stain of a fat pad aspirate is positive for amyloid deposits.

Which of the following is the most appropriate management?

A

Amyloid typing

B

Autologous hematopoietic stem cell transplantation

C

Chemotherapy

D

Transmyocardial biopsy

Answer & Critique

Correct Answer: A

Educational Objective: Diagnose amyloidosis.

Key Point

Patients with amyloidosis should undergo amyloid typing of amyloid deposits to further classify the type of amyloidosis present.

This patient should undergo amyloid typing to classify his amyloidosis (for example, immunoglobulin light chain [AL], hereditary, or secondary [AA] amyloidosis). Amyloid typing can be accomplished by protein sequencing of the amyloid material from an involved biopsy specimen or by immunofluorescence or immunohistochemistry. He has an IgG ? monoclonal gammopathy, evidence of cardiac infiltration shown by diffuse myocardial thickening, and amyloid deposition seen on a fat pad aspirate; these findings suggest amyloid cardiomyopathy. The presence of an IgG ? monoclonal gammopathy suggests the possibility of AL amyloidosis. However, hereditary amyloidosis with incidental monoclonal gammopathy of undetermined significance (MGUS) must also be considered. The most common variant of hereditary cardiac amyloidosis is characterized by a Val122Ile mutation in transthyretin. It is present in 3.5% of black persons and is associated with late-onset cardiac involvement, typically after the age of 50 years, without evidence of other end-organ damage related to amyloidosis. Mass spectroscopy, which has 98% sensitivity and specificity, can be used to sequence and identify the composition of the amyloid deposits. Amyloid typing to establish the correct type of amyloidosis syndrome is absolutely critical, particularly in light of the high prevalence of MGUS, to avoid exposing a patient to inappropriate and potentially difficult therapy.

Chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) are appropriate therapies for a patient with an established diagnosis of AL amyloidosis but not hereditary amyloidosis. A diagnosis of AL amyloidosis requires initiation of chemotherapy or pursuit of autologous HSCT, whereas a diagnosis of Val122Ile transthyretin-mutated amyloidosis is treated supportively. Patients with earlier onset hereditary amyloidosis characterized by more extensive or severe organ involvement would be considered for liver transplantation.

Although a transmyocardial biopsy would show evidence of amyloid deposition in the heart, this invasive procedure is unnecessary in patients with a typical clinical presentation, consistent

noninvasive cardiac imaging findings, and documented amyloid deposition on biopsy from a noncardiac site, as seen in this patient.

Question 65

A 24-year-old woman with hemoglobin SS sickle cell disease is evaluated in the emergency department for extremity and chest pain of 24 hours' duration. She is 24 weeks pregnant. She reports the pain is similar to her usual vasoocclusive pain located in her legs and low back but is not sufficiently relieved by morphine taken at home. She experiences pain episodes approximately two to three times per year, which she often manages at home. Medical history is otherwise unremarkable. Her only other medication is a folic acid supplement.

On physical examination, the patient appears uncomfortable and pale, with slight scleral icterus. She is afebrile, blood pressure is 120/70 mm Hg, pulse rate is 110/min, and respiration rate is 24/min and unlabored. Oxygen saturation is 94% breathing ambient air. Cardiac examination reveals regular heart sounds with a grade 2/6 systolic murmur. The lungs are clear to auscultation.

Laboratory studies:

Hemoglobin	5.9 g/dL (59 g/L) (prepregnancy baseline: 7-8 g/dL [70-80 g/L]; during pregnancy: 6-7 g/dL [60-70 g/L])
Alanine aminotransferase	35 U/L
Aspartate aminotransferase	32 U/L
Creatinine	0.7 mg/dL (35.4 µmol/L)

Fetal examination reveals no fetal distress.

Which of the following is the most appropriate treatment?

A Erythrocyte transfusion

B Exchange transfusion

C Hydroxyurea

D Intravenous fluids and narcotic analgesics

Answer & Critique

Correct Answer: D

Educational Objective: Treat vaso-occlusive pain in a pregnant patient with sickle cell disease.

Key Point

Expert opinion recommends that pregnant patients should receive the same treatment for acute vaso-occlusive crisis as nonpregnant patients with sickle cell disease.

This patient should receive intravenous fluids and narcotic analgesics. She is experiencing a vaso-occlusive pain episode that does not differ greatly from those she typically experiences. Because no reliable physical findings or laboratory markers can objectively establish the vaso-occlusion, the diagnosis of vaso-occlusive pain is based on subjective reports by the patient. She has no signs of acute chest syndrome (ACS) (no fever or hypoxia [oxygen saturation >90% breathing room air]) or other end-organ damage (her creatinine and aminotransferase levels are normal). No randomized studies have been conducted on the effectiveness or harms of standard therapy for vaso-occlusive crisis during pregnancy. Expert opinion recommends this patient should receive the same treatment as nonpregnant patients with sickle cell disease, which includes rest, relaxation, warmth, NSAIDs (which are considered safe before 30 weeks' gestation), oral and intravenous hydration, and narcotic analgesia. Narcotics are safe to use during pregnancy, and she will benefit from hydration, which will theoretically correct any dehydration contributing to the vaso-occlusive episode.

Because neither the patient nor the fetus is displaying symptoms of anemia (significant shortness of breath, dizziness, and chest pain in the mother or fetal distress), transfusion is not indicated. The patient's hemoglobin level is slightly lower now than her prepregnancy baseline; however, neither transfusion nor exchange transfusion is indicated in asymptomatic patients without signs of end-organ damage. Neither has been shown to decrease maternal morbidity or mortality during pregnancy, but both would predispose the patient to iron overload and erythrocyte antibody production. Transfusion would be appropriate to treat symptomatic anemia or signs of end-organ involvement (stroke symptoms, kidney failure, ACS, hepatic involvement).

Hydroxyurea therapy results in decreased mortality in hemoglobin SS sickle cell anemia and is indicated in patients with recurrent painful episodes, ACS, and symptomatic anemia. However,

because of its potential teratogenicity, hydroxyurea should not be administered during pregnancy. Proper contraception before hydroxyurea initiation should be discussed with the nonpregnant patient.

Question 66

A 65-year-old man is evaluated in the emergency department for a 3-day history of abdominal pain. The pain began acutely and is constant. Medical history is remarkable only for a 4-month history of generalized progressive pruritus without a skin rash. He does not drink alcohol or smoke cigarettes and has no risk factors for chronic hepatitis. He takes no medications.

On physical examination, vital signs are normal. He has a plethoric complexion. Cardiopulmonary examination is normal. Tender hepatomegaly and splenomegaly are present.

Laboratory evaluation discloses erythrocytosis, leukocytosis, thrombocytosis, and markedly elevated serum aminotransferase levels.

Abdominal ultrasonography reveals hepatomegaly, splenomegaly, ascites, and a lack of blood flow in two of the hepatic veins, compatible with Budd-Chiari syndrome.

Which of the following is the most appropriate diagnostic test to perform next?

A

Bone marrow biopsy

B

Factor V Leiden genetic test

C

Flow cytometry for CD55 and CD59

D

JAK2 V617F mutation analysis

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose polycythemia vera as a cause of Budd-Chiari syndrome.

Key Point

Arterial or venous thrombosis is the initial symptom in 20% of patients with polycythemia vera (PV) and should prompt testing for the *JAK2 V617F* mutation, which is found in nearly 100% of patients with PV.

The appropriate next step would be to test for the*JAK2 V617F* mutation. This patient likely has polycythemia vera (PV), a myeloproliferative neoplasm (MPN). Symptoms include generalized pruritus that often worsens after bathing, erythromelalgia (a burning sensation in the palms and soles), and hypermetabolic symptoms such as fever, weight loss, and sweating. On physical examination, patients may have plethora and hepatosplenomegaly. Twenty percent of patients experience arterial or venous thrombosis as their initial symptom. PV and the other MPNs predispose to the development of the Budd-Chiari syndrome (BCS), which is characterized by hepatic venous outflow tract obstruction (including the suprahepatic inferior vena cava) and other intra-abdominal thromboses, such as thrombosis of the portal, superior mesenteric, or splenic vein. Abdominal pain, ascites, liver and spleen enlargement, and portal hypertension occur with symptomatic BCS. Ninety-five percent of patients with PV have the *JAK2*mutation, so it is an appropriate confirmatory test for suspected PV. Anticoagulant therapy is recommended for all patients with BCS regardless of whether an underlying prothrombotic disorder is discovered. Phlebotomy to normalize the hematocrit (goal <45% in men, <42% in women) is indicated, and adding the myelosuppressive agent hydroxyurea to phlebotomy decreases thrombotic events in patients with PV.

Bone marrow aspirate and biopsy findings are nonspecific in PV; they may show an increased number of megakaryocytes in a moderately to markedly hypercellular marrow and an increase in reticulin. Because they are not diagnostic and the procedure is invasive, bone marrow biopsy is typically unnecessary and is not an appropriate early diagnostic test.

Although factor V Leiden is a risk factor for venous thromboembolism, it would not explain the patient's erythrocytosis, leukocytosis, or thrombocytosis. Therefore, it is not a helpful test to perform in this patient.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder that should be considered in patients with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. Thrombotic complications of PNH may occur in atypical locations, such as the hepatic veins (BCS) or mesenteric or cerebral circulation, and develop more frequently in patients with large PNH clones. PNH is diagnosed by flow cytometry, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes. Erythrocytosis, leukocytosis, thrombocythemia, and generalized pruritus are not typical for PNH.

Question 67

A 58-year-old woman is diagnosed with acute deep venous thrombosis (DVT) of the proximal left leg. Low-molecular-weight heparin (LMWH) and warfarin are initiated. Medical history is otherwise nonsignificant, and she takes no other medications.

When should LMWH be discontinued?

A

In 3 days if the INR is therapeutic

B

In 3 days if the INR is therapeutic for 24 hours

C

In 5 days if the INR is therapeutic

D

In 5 days if the INR is therapeutic for 24 hours

Answer & Critique

Correct Answer: D

Educational Objective: Treat a patient with venous thromboembolism with an initial combination of a parenteral anticoagulant and warfarin.

Key Point

Parenteral anticoagulant administration must overlap with warfarin for at least 5 days and until the INR is greater than 2 for 24 hours.

Heparin should be given for no less than 5 days and only discontinued at that time if the INR is therapeutic for 24 hours. Warfarin may be initiated on the first or second day of heparin therapy. Because factor II and X levels require at least 5 days to decline sufficiently, parenteral anticoagulation should overlap with warfarin for at least 5 days and until an INR of 2 or more is achieved.

The initial warfarin dose may be based on a patient's predicted maintenance dose using available calculators, and a patient's nutritional status, comorbid diseases, and age must be considered. Excessively high initial doses should be avoided because they can lead to supratherapeutic INR values and premature discontinuation of parenteral therapy. Patients should be followed closely with frequent INR studies at the initiation of therapy to achieve values consistently within the desired range. After patients achieve consistently stable INR levels with an established dose, INR monitoring may eventually be extended to every 12 weeks for the duration of treatment, but testing frequency should be determined individually. The duration of warfarin therapy is determined by the type of thrombotic event and the presence or absence of situational triggers (provoked versus unprovoked), thrombophilic states, active cancer, and a history of thrombotic events.

Question 68

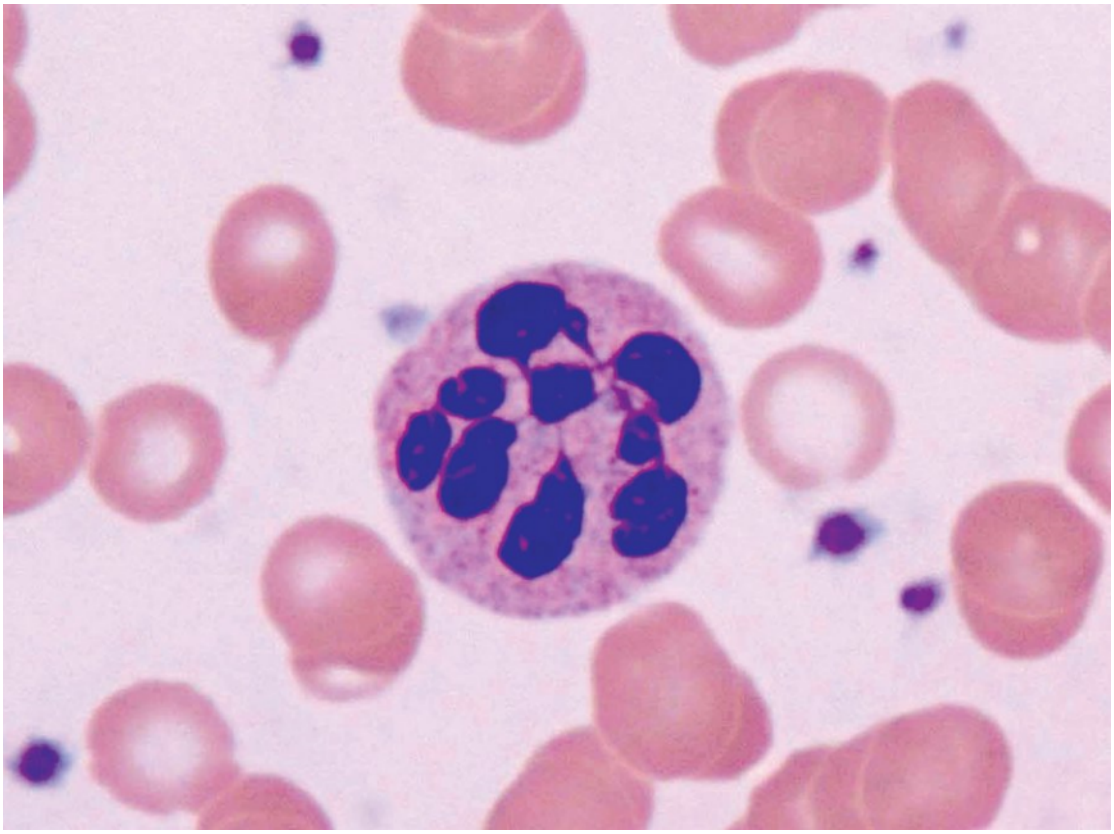
A 30-year-old woman is evaluated for progressive difficulty walking and numbness in both feet of 1 to 2 months' duration. She is otherwise healthy. She has followed a vegan diet for the past several years. Her only medication is an oral contraceptive pill.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 120/66 mm Hg, pulse rate is 76/min, and respiration rate is 12/min; BMI is 25. She has decreased sensation and vibratory sense in both legs below the knees. No other neurologic deficits are observed.

Laboratory studies:

Hemoglobin	10.4 g/dL (104 g/L)
Leukocyte count	2800/µL (2.8×10^9/L)
Mean corpuscular volume	105 fL
Vitamin B_{12}	210 pg/mL (155 pmol/L)

A peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test to perform next?

A

Bone marrow biopsy

B

Folate level measurement

C

Homocysteine level measurement

D

Methylmalonic acid level measurement

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose cobalamin (vitamin B_{12}) deficiency.

Key Point

The methylmalonic acid level is elevated in 98% of patients with cobalamin deficiency, making it a sensitive and specific laboratory test to use in determining deficiency.

The most appropriate diagnostic test is to measure the methylmalonic acid level. This patient likely has cobalamin (vitamin B_{12}) deficiency, which she is at risk for based on following a vegan diet for several years. Compared with folate deficiency, which develops within weeks, cobalamin deficiency develops over months to years. She also has neurologic findings typical of and concerning for cobalamin deficiency. If left untreated, neurologic function could continue to decrease. A macrocytic anemia is characteristic of cobalamin deficiency, and the peripheral blood smear shows a typical hypersegmented neutrophil, a result of ineffective myelopoiesis. In many patients with suspected cobalamin deficiency, vitamin B_{12} levels will be in the normal range, and further testing is indicated to obtain better sensitivity. Methylmalonic acid is elevated in 98% of people with cobalamin deficiency; therefore, this would be a sensitive and specific test to determine deficiency.

Cobalamin deficiency can occasionally present with pancytopenia, which could prompt a bone marrow examination; however, a bone marrow biopsy is not needed to diagnose suspected cobalamin deficiency. The patient's neutropenia will likely resolve as the cobalamin deficiency is corrected.

This patient is unlikely to have isolated folate deficiency considering her neurologic symptoms, which are commonly seen with cobalamin, but not folate, deficiency. Testing the methylmalonic acid level concomitantly rules out folate deficiency and diagnoses cobalamin deficiency, because methylmalonic acid levels will be normal in cases of folate deficiency.

Homocysteine levels are elevated in cobalamin deficiency, but they can also be elevated in folate deficiency, so checking the homocysteine level is not the best test to perform. Evaluating the methylmalonic acid level will more accurately provide a diagnosis.

Question 69

A 72-year-old man is evaluated for a 6-month history of progressive fatigue, dyspnea with exertion, intermittent drenching night sweats, and a 6.8-kg (15-lb) weight loss. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient appears fatigued. Temperature is 37.0 °C (98.6 °F), blood pressure is 148/86 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. BMI is 24. Neurologic and funduscopic examinations are normal. Lungs are clear to auscultation. Rubbery, 1.5- to 2.5-cm lymph nodes are palpable in the bilateral anterior cervical lymph node chains, right axilla, and bilateral inguinal regions. The spleen is palpable 2 cm below the mid left costal margin.

Laboratory studies:

Hemoglobin	9.4 g/dL (94 g/L)
Leukocyte count	5400/µL (5.4×10^9/L)
Platelet count	184,000/µL (184×10^9/L)
Reticulocyte count	1.5% of erythrocytes
Blood urea nitrogen	20 mg/dL (7.1 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Immunoglobulins	
IgG	540 mg/dL (5.4 g/L)
IgA	80 mg/dL (0.8 g/L)
IgM	3882 mg/dL (38.8 g/L)
Lactate dehydrogenase	120 U/L
Protein, total	9.3 g/dL (93 g/L)

A blood smear is unremarkable with the exception of a reduced number of erythrocytes. A direct antiglobulin (Coombs) test is negative. Serum protein electrophoresis and immunofixation reveal a monoclonal IgM κ band measuring 3.2 g/dL.

A bone marrow aspirate and biopsy reveals clonal plasma cells, plasmacytoid lymphocytes, and mature B cells, representing 50% of the overall marrow cellularity without erythroid hyperplasia. CT of the neck, chest, abdomen, and pelvis demonstrates splenomegaly and cervical, axillary, mesenteric, and inguinal lymphadenopathy with lymph nodes measuring up to 3 cm. The lung fields are clear.

Which of the following is the most appropriate management?

A

Cold agglutinin titer

B

Plasma exchange

C

Rituximab plus chemotherapy

D

Serum viscosity testing

Answer & Critique

Correct Answer: C

Educational Objective: Manage Waldenström macroglobulinemia.

Key Point

Initial therapy for Waldenström macroglobulinemia may consist of rituximab as monotherapy or combined with chemotherapy, which may include an alkylating agent or a purine analog.

This patient should begin combination rituximab plus chemotherapy. He has symptomatic Waldenström macroglobulinemia, demonstrated by a neoplastic infiltrate consisting of clonal lymphocytes, plasmacytoid lymphocytes, plasma cells, and immunoblasts comprising 10% or more of the bone marrow cellularity with disease-related manifestations, including night sweats, weight loss, anemia, lymphadenopathy, and splenomegaly. Management of this low-grade, mature B-cell, non-Hodgkin lymphoma consists of the anti-CD20 monoclonal antibody, rituximab, as single agent therapy or combined with chemotherapy. Considering this patient's degree of symptoms and tumor burden, along with his otherwise good health, combined rituximab and chemotherapy would be highly appropriate. The chemotherapy regimen may consist of an alkylating agent base (such as cyclophosphamide) or purine analog base (such as fludarabine).

Management of anemia should be directed at treating the underlying cause, in this case the Waldenström macroglobulinemia. Plasma exchange is essential for patients presenting with symptomatic hyperviscosity and is occasionally used as adjunctive therapy for cold agglutinin disease, an autoimmune hemolytic anemia that can be associated with Waldenström macroglobulinemia. However, it would not be appropriate in this patient, who does not have symptoms of hyperviscosity. Although the patient is anemic and has an elevated lactate dehydrogenase level, the reticulocyte count is low considering the degree of anemia, no erythrocyte clumps appear on the peripheral blood smear, and the direct antiglobulin (Coombs) test is negative, making a diagnosis of cold agglutinin disease highly unlikely. Furthermore, the patient does not have any clinical manifestations of this disorder (such as acrocyanosis), so a cold agglutinin titer would not be appropriate.

The patient has no symptoms of hyperviscosity (blurry vision, headache, hearing loss, tinnitus, vertigo, dizziness, altered mental status) or findings on physical examination to suggest hyperviscosity (dilated, tortuous retinal veins on funduscopic examination). In the absence of signs and symptoms of hyperviscosity and an M protein of less than 4 g/dL, serum viscosity testing is of no significant value.

Question 70

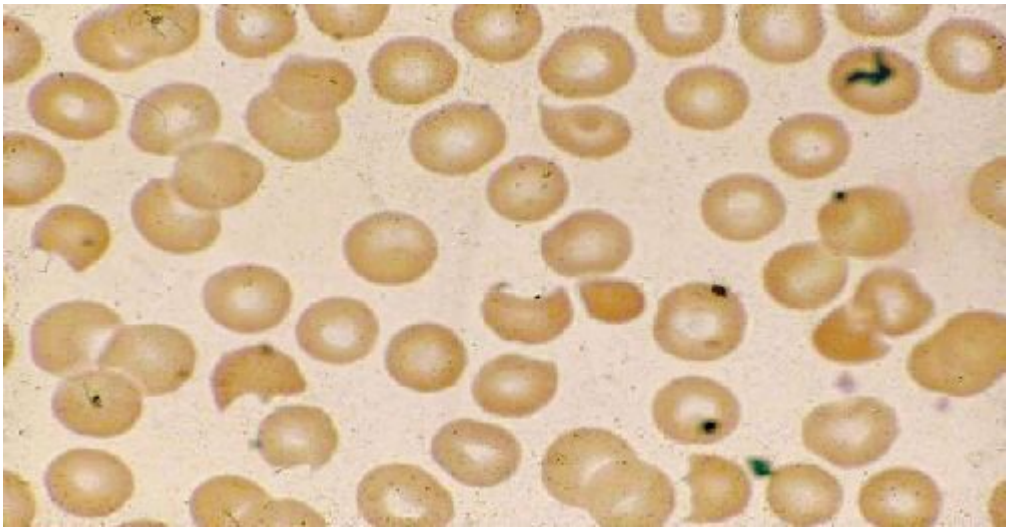
A 25-year-old man is evaluated in the emergency department for a 1-day history of brown urine, fatigue, and shortness of breath. He was diagnosed with a urinary tract infection 4 days ago, for which he was prescribed trimethoprim-sulfamethoxazole. Medical history is otherwise unremarkable. He is black.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/75 mm Hg, pulse rate is 90/min, and respiration rate is 24/min. BMI is 23. Scleral icterus is apparent. Abdominal examination is normal with no indication of hepatosplenomegaly.

Laboratory studies:

Hematocrit	21%
Platelet count	215,000/µL (215 × 10^9/L)
Reticulocytes	10% of erythrocytes
Bilirubin, total	5.0 mg/dL (85.5 µmol/L)
Lactate dehydrogenase	350 U/L

A peripheral blood smear is shown.



Trimethoprim-sulfamethoxazole is discontinued.

Which of the following is the most appropriate diagnostic test to perform next?

A
ADAMTS-13 activity assay

B
Direct antiglobulin (Coombs) test

C
Glucose-6-phosphate dehydrogenase activity

D
Osmotic fragility test

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose glucose-6-phosphate dehydrogenase deficiency.

Key Point

Glucose-6-phosphate dehydrogenase deficiency typically leads to episodic hemolysis in response to oxidant stressors (infections or drugs such as dapsone, trimethoprim-sulfamethoxazole, and nitrofurantoin).

This patient's glucose-6-phosphate dehydrogenase (G6PD) activity should be measured in 2 months. G6PD deficiency is an X-linked disease and occurs more commonly in men, often in blacks. This variant typically leads to episodic hemolysis in response to oxidant stressors (for example, infections or drugs such as dapsone, trimethoprim-sulfamethoxazole, and nitrofurantoin). Elevated levels of G6PD are found in normal young reticulocytes, and levels may appear falsely normal during an acute hemolytic episode, causing a missed diagnosis. Consequently, G6PD levels should be checked a few months after the occurrence of an acute event. During an acute hemolytic episode, bite cells may be seen on the peripheral blood smear, as are apparent in this patient's peripheral blood smear.

Thrombotic thrombocytopenic purpura (TTP) should be suspected in patients who have anemia, schistocytes on the peripheral blood smear, increased serum lactate dehydrogenase level, and thrombocytopenia. TTP can be triggered by drugs, especially quinine, ticlopidine, mitomycin C, cyclosporine, or gemcitabine. The mechanism of disease is thought to be antibodies directed against the protease ADAMTS-13 that is responsible for cleaving the high-molecular-weight multimers of von Willebrand factor. Assays for ADAMTS-13 activity are available but are not needed for a TTP diagnosis and are not indicated in patients who lack the essential diagnostic criteria for TTP.

Hereditary spherocytosis should be suspected in patients with a personal or family history of anemia, jaundice, splenomegaly, or gallstones. Spherocytes are present on the peripheral blood smear, and the direct antiglobulin (Coombs) test is negative. The osmotic fragility test with 24-hour incubation is a key diagnostic step, demonstrating increased erythrocyte fragility in hypotonic saline compared with control erythrocytes. This patient's ethnic background, absence of

splenomegaly, and presence of bite cells on the peripheral blood smear do not support a diagnosis of hereditary spherocytosis.

Bibliography

Question 71

A 35-year-old woman is evaluated in the emergency department for a 3-day history of worsening dyspnea on exertion. She reports no chest pain. Medical history is notable for systemic lupus erythematosus, which is well controlled with hydroxychloroquine. She takes no other medications.

On physical examination, the patient appears pale and fatigued. Temperature is 37.0 °C (98.6 °F), blood pressure is 110/72 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Oxygen saturation is 97% breathing ambient air. Neurologic examination is normal. Scleral icterus is noted. She has no lymphadenopathy. A grade 2/6 crescendo-decrescendo systolic murmur is auscultated at the upper right sternal border, and the lung fields are clear bilaterally. Abdominal examination reveals no hepatosplenomegaly or tenderness. Rectal examination shows no masses, and a stool sample is guaiac negative.

Laboratory studies:

Hemoglobin	6.2 g/dL (62 g/L)
Leukocyte count	15,000/µL (15 × 10^9/L)
Mean corpuscular volume	101 fL
Platelet count	280,000/µL (280 × 10^9/L)
Reticulocyte count	18% of erythrocytes
Bilirubin, total	2.3 mg/dL (39.3 µmol/L)
Creatinine	Normal
Lactate dehydrogenase	980 U/L
Direct antiglobulin (Coombs) test	Positive for C3 and IgG

Peripheral blood smear shows spherocytes and polychromatophilic erythrocytes but is otherwise normal.

Which of the following is the most appropriate management?

A Erythrocyte transfusion

B Prednisone

C Rituximab

D Splenectomy

E Vitamin B_{12}

Answer & Critique

Correct Answer: B

Educational Objective: Treat a patient with warm autoimmune hemolytic anemia.

Key Point

Treatment of warm autoimmune hemolytic anemia is based on initial immunosuppression with glucocorticoids to halt immune-mediated erythrocyte destruction and allow bone marrow to regenerate the erythrocytes.

The patient should be given prednisone. She has warm autoimmune hemolytic anemia (WAIHA), indicated by the high reticulocyte count, elevated bilirubin and lactate dehydrogenase (LDH) levels, the positive direct antiglobulin (Coombs) test, and spherocytes seen on peripheral blood smear. In WAIHA, IgG antibodies are directed against erythrocyte surface membrane molecules, which leads to phagocytosis by macrophages that cause erythrocytes to become progressively more spherocytic. These abnormal erythrocytes are then destroyed in the spleen. WAIHA can manifest as a primary disorder or as a complication of another disorder, including autoimmune conditions (systemic lupus erythematosus) or lymphoproliferative disorders (chronic lymphocytic leukemia). Treatment is immunosuppression to halt the immune-mediated erythrocyte destruction and allow the patient's own bone marrow to regenerate the erythrocytes, if possible. The best initial treatment for this condition is a glucocorticoid such as prednisone.

Transfusion in patients with WAIHA is a topic of debate. Although this patient has severe anemia, she has no organ dysfunction, is not hypoxic, and has no signs or symptoms of heart failure or angina. Additionally, her bone marrow is able to respond to her hemolysis, and her hemoglobin level would be expected to recover with treatment of her hemolytic condition. Additionally, erythrocyte transfusions are complicated in patients with WAIHA, because the antibodies causing hemolysis may crossreact with transfused erythrocytes, making crossmatch-compatible blood difficult to find. Therefore, transfusion in patients with WAIHA should be approached carefully, and if necessary, should be performed with type-specific, crossmatch-incompatible blood. Consultation with a hematologist and transfusion medicine specialist is recommended.

Rituximab and splenectomy are typically reserved to treat patients in whom first-line therapy for WAIHA has failed; they are not used in the acute setting. An inadequate response to glucocorticoids may indicate the need for splenectomy or alternative immunosuppression.

Although the mean corpuscular volume is elevated, this patient's clinical picture is inconsistent with vitamin B_{12} deficiency, which typically includes a low reticulocyte count (although the LDH and total bilirubin levels can be quite elevated because of intramedullary hemolysis). Additionally, no hypersegmented neutrophils are seen, and she has no abnormal neurologic findings.

Question 72

A 54-year-old man is evaluated during follow-up consultation regarding laboratory studies completed for a life insurance policy. He reports no symptoms.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 131/76 mm Hg, pulse rate is 88/min, and respiration rate is 15/min. No splenomegaly is noted.

Laboratory studies:

Hemoglobin	8.9 g/dL (89 g/L)
Leukocyte count	3000/µL (3.0×10^9/L) with 30% neutrophils, 10% monocytes, and 60% lymphocytes
Mean corpuscular volume	105 fL
Platelet count	75,000/µL (75×10^9/L)
Folate	Normal
Vitamin B_{12}	Normal

A bone marrow biopsy shows trilineage dysplasia with 1% blasts. Results of cytogenetic testing show loss of the Y chromosome (−Y).

These findings are compatible with low-risk disease by the International Prognostic Scoring System – Revised criteria.

Which of the following is the most appropriate management?

A

5-Azacytidine

B

Allogeneic hematopoietic stem cell transplantation

C

Erythropoietin

D

Observation

Answer & Critique

Correct Answer: D

Educational Objective: Manage low-risk myelodysplastic syndrome with observation.

Key Point

Myelodysplastic syndrome should be managed based on risk stratification, with patients with low-risk disease requiring no treatment.

Observation is appropriate for this patient with low-risk myelodysplastic syndrome (MDS), incidentally discovered by a complete blood count showing asymptomatic pancytopenia. The mild macrocytosis is typical. The bone marrow biopsy is appropriate to confirm a suspected diagnosis of myelodysplasia in the setting of the normal vitamin B_{12} and folate levels and to provide important prognostic information. This patient has low-risk disease by the revised International Prognostic Scoring System criteria despite two involved cell lines. The low-risk cytogenetics and low marrow blasts (<2%) indicate very low-risk MDS. Median survival is 8.8 years in a generally older adult population and the median time to 25% acute myeloid leukemia (AML) progression is more than 14 years. No therapy will improve prognosis in this situation.

5-Azacytidine is appropriate therapy for higher risk MDS for the purpose of improving blood counts, delaying AML progression, and extending survival. It would be indicated to lessen transfusion dependence or to improve prognosis for high-risk disease, but is inappropriate in this patient, whose disease is low risk.

Allogeneic hematopoietic stem cell transplantation is not justified, because this patient's disease is very low risk. In contrast, a patient with very high-risk disease has an expected median survival of less than 1 year, justifying the treatment-related morbidity associated with transplantation.

Erythropoietin is inappropriate because this patient is asymptomatic. Recombinant erythropoietin can be effective in approximately 25% of patients with MDS. However, the goal hemoglobin level is 10 g/dL (100 g/L), and targets to higher values have been associated with arterial and venous thrombosis.

Question 73

A 73-year-old man develops acute respiratory distress near the completion of a transfusion of 1 unit of erythrocytes following a total hip arthroplasty. Medical history is significant for hypertension, type 2 diabetes mellitus complicated by nephropathy, and hyperlipidemia. Medications are amlodipine, insulin, atorvastatin, and subcutaneous unfractionated heparin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 184/72 mm Hg, pulse rate is 114/min, and respiration rate is 24/min. Oxygen saturation is 86% breathing ambient air. Jugular venous pressure is 8 cm H_2O. Crackles are heard halfway up both lung fields. Cardiac examination reveals tachycardia but no murmurs. Trace bilateral pedal edema is noted.

Laboratory studies:

Hemoglobin	7.7 g/dL (77 g/L) (6.8 g/dL [68 g/L] before transfusion)
Bilirubin, total	1.2 mg/dL (20.5 µmol/L)
Creatinine	2.8 mg/dL (248 µmol/L) (2.7 mg/dL [239 µmol/L] before transfusion)
Lactate dehydrogenase	90 U/L
Urinalysis	Negative for protein or blood

Electrocardiography demonstrates sinus tachycardia but shows no evidence of ST-segment or T-wave abnormalities. A chest radiograph reveals bibasilar airspace opacities.

Which of the following is the most likely diagnosis?

A

Acute hemolytic transfusion reaction

B

Transfusion-associated circulatory overload

C

Transfusion-related acute lung injury

D

Transfusion-transmitted sepsis

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose transfusion-associated circulatory overload.

Key Point

Patients experiencing acute respiratory distress, elevated B-type natriuretic peptide level, elevated central venous pressure, evidence of left heart failure, evidence of positive fluid balance, or radiographic evidence of pulmonary edema within 6 hours of transfusion should be diagnosed with transfusion-associated circulatory overload.

The most likely diagnosis is transfusion-associated circulatory overload (TACO). TACO is an underdiagnosed condition that occurs in 0.3% to 8% of patients undergoing transfusion in the hospital and is associated with increased inpatient mortality and a longer length of hospital stay. TACO is defined as the new onset or exacerbation of at least three of the following findings within 6 hours of completing a transfusion: acute respiratory distress, elevated B-type natriuretic peptide (BNP) level, elevated central venous pressure (CVP), evidence of left heart failure, evidence of positive fluid balance, and radiographic evidence of pulmonary edema. Risk factors include age older than 60 years, chronic kidney disease, chronic heart failure, number of blood products transfused, and the volume transfused per hour. Preventive measures include a slower rate of infusion for those at risk (1 mL/kg/hour) and diuretic therapy to maintain euvolemia.

An acute hemolytic transfusion reaction (AHTR) is unlikely. The patient's hemoglobin level increased appropriately after the transfusion (1 g/dL/U [10 g/L/U]), and the lactate dehydrogenase and total bilirubin levels are not elevated. No protein was seen on urinalysis, kidney function is unchanged, and the patient is not hypotensive. Additionally, pulmonary opacities as seen on the radiograph would not be expected with AHTR.

Distinguishing TACO from transfusion-related acute lung injury (TRALI) can be challenging. Fever and hypotension occur in only one third of patients with TRALI. However, TRALI is not associated with signs of volume overload (increased jugular venous pressure, lower extremity edema, elevated CVP). BNP and N-terminal proBNP levels have not been studied in TRALI but are elevated with TACO.

Transfusion-associated sepsis is highly unlikely in the absence of fever and hypotension.

Question 74

A 47-year-old woman is evaluated for fatigue and easy bruising of 6 weeks' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 131/76 mm Hg, pulse rate is 95/min, and respiration rate is 15/min. Pallor and scattered lower extremity bruising are noted.

Laboratory studies:

Hemoglobin	7.6 g/dL (76 g/L)
Leukocyte count	2000/µL (2×10^9/L) with 30% neutrophils, 20% monocytes, and 50% lymphocytes
Mean corpuscular volume	103 fL
Platelet count	35,000/µL (35×10^9/L)
Folate	Normal
Vitamin B_{12}	Normal

A bone marrow aspirate and biopsy show trilineage dysplasia with 7% blasts. Cytogenetic testing results indicate a complex karyotype.

These findings define high-risk disease by the International Prognostic Scoring System – Revised criteria.

Which of the following is the most appropriate management?

A 5-Azacytidine

B Allogeneic hematopoietic stem cell transplantation

C Erythropoietin

D Observation

7 Answer & Critique

Correct Answer: B

Educational Objective: Treat high-risk myelodysplastic syndrome with hematopoietic stem cell transplantation.

Key Point

Younger, fit patients with high-risk myelodysplastic syndrome should receive allogeneic hematopoietic stem cell transplantation, which is the only curative therapy option.

This patient should undergo allogeneic hematopoietic stem cell transplantation (HSCT). She has myelodysplastic syndrome (MDS), diagnosed by complete blood count results from an investigation of symptomatic pancytopenia. The monocytosis and mild macrocytosis are typical. Bone marrow examination is required to confirm the diagnosis and to provide prognostic information that can inform therapeutic recommendations. The International Prognostic Scoring System – Revised criteria weigh cytogenetics most heavily when determining risk. A complex karyotype places this patient in a high-risk group. Involvement of three cell lines and more than 5% marrow blasts specifies the highest risk group. In very high-risk disease, median survival is expected to be less than 1 year. Such a prognosis in a younger patient justifies the recommendation for allogeneic HSCT at diagnosis. Although transplantation is associated with significant risks, it is also the only curative therapy for MDS.

5-Azacytidine is appropriate for higher risk MDS but does not have curative potential. In a younger, fit patient, HSCT is a better choice. For older patients (generally older than 60 years) or those with significant comorbidities, 5-azacytidine would be an appropriate option.

Erythropoietic agents, such as epoetin and darbepoetin alfa, may improve hemoglobin levels in patients with symptomatic anemia and lower risk MDS but are not appropriate as single therapy for high-risk disease. This patient is at high risk of transforming from MDS to acute myeloid leukemia (AML); HSCT will mitigate that risk, but treatment with erythropoietin will not.

Because of this patient's high-risk MDS, observation would be inappropriate. The natural history of high-risk MDS is progression to AML. Because secondary AML is much harder to cure, primary therapy before transformation improves prognosis.

Question 75

A 65-year-old man is evaluated for shortness of breath with light activity. Medical history is significant for type 2 diabetes mellitus with associated chronic kidney disease; progressive anemia has also been noted. He has no evidence of gastrointestinal bleeding. His only medication is glipizide.

On physical examination, temperature is 37.1 °C (98.7 °F), blood pressure is 140/80 mm Hg, pulse rate is 86/min, and respiration rate is 20/min; BMI is 30.

Laboratory studies:

Hemoglobin	8 g/dL (80 g/L)
Mean corpuscular volume	90 fL
Reticulocyte count	1% of erythrocytes
Creatinine	2.3 mg/dL (203 µmol/L)
Folate	Normal
Ferritin	550 ng/mL (550 µg/L)
Transferrin saturation	40%
Vitamin B_{12}	Normal
Glomerular filtration rate	25 mL/min/1.73 m^2

Which of the following is the most appropriate management?

A

Erythrocyte transfusion

B

Erythropoiesis-stimulating agent therapy

C

Erythropoietin level measurement

D Iron replacement

Answer & Critique

Correct Answer: B

Educational Objective: Treat anemia of chronic kidney disease.

Key Point

Erythropoiesis-stimulating agents should be considered for patients with chronic kidney disease and symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dL (100 g/L).

This patient should receive erythropoiesis-stimulating agent (ESA) therapy. He has anemia of chronic kidney disease (CKD), which affects 90% of patients with a glomerular filtration rate less than 25 to 30 mL/min/1.73 m^2. Erythropoietin is made by interstitial peritubular fibroblasts of the kidney, so patients with reduced kidney function may have low erythropoietin levels; however, erythropoietin resistance also occurs. When patients with reduced kidney function develop anemia, evaluation for other causes is appropriate; in particular, relative iron deficiency is common. If iron stores are adequate and other causes have also been eliminated (such as cobalamin and folate deficiency, gastrointestinal bleeding), the anemia can be attributed to CKD. The routine measurement of erythropoietin levels plays no role in CKD, because this expensive test does not aid in the diagnosis or guide treatment decisions. ESAs should be considered for patients with symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dL (100 g/L). Patients with CKD must be carefully counseled about the risks of ESAs, which include increased risk of thrombotic and cardiovascular events as well as increased blood pressure. Additionally, clinicians should explain that target hemoglobin values are lower than those used in the past, and that patients must be monitored regularly to titrate the dose to a target hemoglobin level of 10 to 11 g/dL (100-110 g/L).

Transfusions are avoided in patients with CKD unless a compelling reason exists, such as tissue ischemia. Transfusions sensitize patients to HLAs, which complicate kidney transplantation options.

Even though many patients benefit from iron replacement, this man has adequate iron stores, so replacement therapy is not indicated.

Question 76

A 23-year-old woman is evaluated in the emergency department for profound shortness of breath, which developed earlier in the day. She reports no chest pain but feels very weak. Medical history is significant for homozygous sickle cell anemia (Hb SS). She was evaluated in the emergency department 1 week ago for symptomatic anemia; she received a transfusion of 2 units of packed red blood cells, her hemoglobin level increased to 8.5 g/dL (85 g/L), and she was sent home. Her only medication is folic acid.

On physical examination, she appears pale and weak. Temperature is 37.1 °C (98.8 °F), blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 32/min. Oxygen saturation is 96% breathing ambient air. Scleral icterus is noted. Cardiac examination reveals a grade 3/6 early systolic murmur at the base of the heart. Lungs are clear. Abdominal palpation reveals no hepatosplenomegaly.

Laboratory studies:

Hemoglobin	3.5 g/dL (35 g/L)
Platelet count	415,000/µL (415 × 10^9/L)
Reticulocyte count	8% of erythrocytes
Bilirubin, total	7.7 mg/dL (132 µmol/L)
Lactate dehydrogenase	650 U/L

Which of the following is the most likely diagnosis?

A

Aplastic crisis

B

Delayed hyperhemolytic transfusion reaction

C

Hepatic sequestration crisis

D

Splenic sequestration crisis

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose delayed hyperhemolytic transfusion reaction.

Key Point

Delayed hyperhemolytic transfusion reaction can occur several days after transfusion and is diagnosed by a significant decrease in the hemoglobin level with reticulocytosis and concomitant increases in the bilirubin and lactate dehydrogenase levels.

This patient has delayed hyperhemolytic transfusion reaction (DHTR). Chronic transfusion in patients with sickle cell disease (SCD) can lead to iron overload, alloimmunization, and an increased risk for DHTR. DHTR is caused by an amnestic response of a preformed erythrocyte alloantibody after re-exposure to an erythrocyte antigen outside the ABO system. Additionally, an autoimmune component could be worsening the hemolysis. Following transfusion, a 1% to 1.6% chance exists of developing these antibodies. DHTR may then occur after re-exposure with subsequent transfusion. Clinical findings, which typically develop approximately 2 to 19 days after erythrocyte transfusion, include anemia, reticulocytosis, jaundice, a significant decrease in hemoglobin level, and increases in hemolytic markers such as lactate dehydrogenase and bilirubin levels, although many patients will be asymptomatic. Patients with SCD may present with a worsening pain crisis. Hemolysis is typically extravascular, and life-threatening complications are rare. Treatment is supportive. Subsequent transfusions should be minimized but not withheld when indicated, such as in situations of severely symptomatic anemia and multiorgan failure.

Transient aplastic crisis can occur when patients with chronic hemolytic anemia and shortened erythrocyte survival are infected with parvovirus B19, which leads to suppression of erythrocyte production identified by anemia and lack of reticulocytosis. Parvovirus B19 infection is a viral syndrome characterized by malaise, fever, and arthralgia; 25% of patients are asymptomatic.

A rare complication of SCD is hepatic sequestration crisis, characterized by large numbers of erythrocytes becoming trapped in the liver. Patients may develop acute anemia, reticulocytosis, hypovolemia, and distributive shock. Prominent symptoms include right upper quadrant pain, hepatomegaly, and anemia. The patient has none of these manifestations.

Splenic sequestration crisis occurs when splenic pooling of erythrocytes causes an acute anemia with reticulocytosis and a rapidly enlarging spleen. Patients may develop hypotension and shock. This condition is found primarily in children who have functional spleens that have not been subjected to multiple infarctions and subsequent development of fibrotic atrophy. This adult patient does not have splenomegaly. Splenic sequestration crisis is not the most likely diagnosis for anemia following a transfusion.

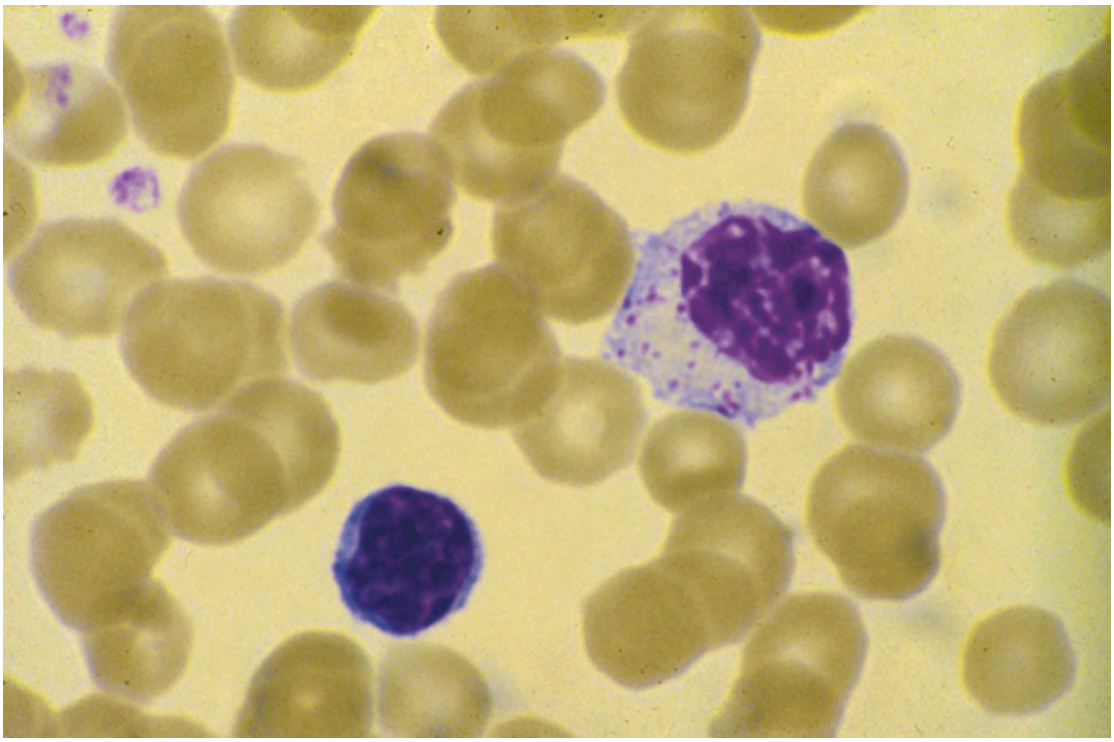
Question 77

A 46-year-old woman is evaluated for a 3-week history of increasing fatigue and new lymphadenopathy. Medical history is remarkable for a 3-year history of rheumatoid arthritis. Medications are methotrexate and ibuprofen as needed.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 128/78 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. Bilateral axillary lymph nodes are palpable. The spleen is palpable 1 cm below the left costal margin. Other than changes of rheumatoid arthritis apparent in the hands and feet, the remainder of the physical examination is normal.

Laboratory studies show a hemoglobin level of 12.5 g/dL (125 g/L); a leukocyte count of 2000/µL (2 × 109/L) with 70% lymphocytes, 10% monocytes, and 20% neutrophils; and a platelet count of 155,000/µL (155 × 109/L).

A peripheral blood smear is shown.



Which of the following is the most likely diagnosis?

A

Aplastic anemia

B

Autoimmune neutropenia

C

Felty syndrome

D

Paroxysmal nocturnal hemoglobinuria

Answer & Critique

Correct Answer: C

Educational Objective: Diagnose Felty syndrome.

Key Point

Felty syndrome is characterized by rheumatoid arthritis, splenomegaly, and neutropenia.

This patient has Felty syndrome, which is the clinical triad of rheumatoid arthritis (RA), splenomegaly, and neutropenia. Splenomegaly and lymphadenopathy may occur secondary to connective tissue disorders such as RA. The unusual cell seen on the peripheral blood smear is a large granular lymphocyte (LGL). LGLs may be seen in up to 40% of patients with Felty syndrome; they may also be associated with other collagen vascular diseases and autoimmune neutropenia. LGL leukemia may also occur in patients with rheumatoid arthritis. Because patients with Felty syndrome and LGL leukemia tend to share HLA-DR4 positivity, they are thought to be part of the same disease spectrum in which immune system dysfunction leads to expansion of this type of cell. The mechanism of neutropenia in Felty syndrome is considered partially autoimmune (likely related to the process leading to development of LGLs) and partially owing to sequestration associated with splenomegaly. Felty syndrome is the most appropriate diagnosis for this patient because the clinical triad is present. This is a useful syndrome to recognize clinically, because it may lead to an RA diagnosis when articular involvement is less prominent.

Aplastic anemia refers to conditions in which the bone marrow fails to produce blood cells, resulting in a hypocellular bone marrow and pancytopenia. It can be acquired or congenital and may be classified as moderate, severe, or very severe. This patient only has leukopenia, which is not consistent with aplastic anemia.

Autoimmune neutropenia is an acquired abnormality that may be associated with underlying disorders of immune regulation such as systemic lupus erythematosus or may exist in a more isolated form. The degree of neutropenia is generally not severe enough to be linked with frequent infections, and spontaneous remission may occur in patients with the primary form. Antineutrophil antibodies may be detected, although tests for them, which differ from the antineutrophil cytoplasmic antibody tests used to evaluate vasculitis, may not be widely available and have

variable sensitivity and specificity. In patients in whom antineutrophil antibodies are not detected, the diagnosis is established by excluding other causes.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal progenitor cell disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. PNH does not present with isolated leukopenia.

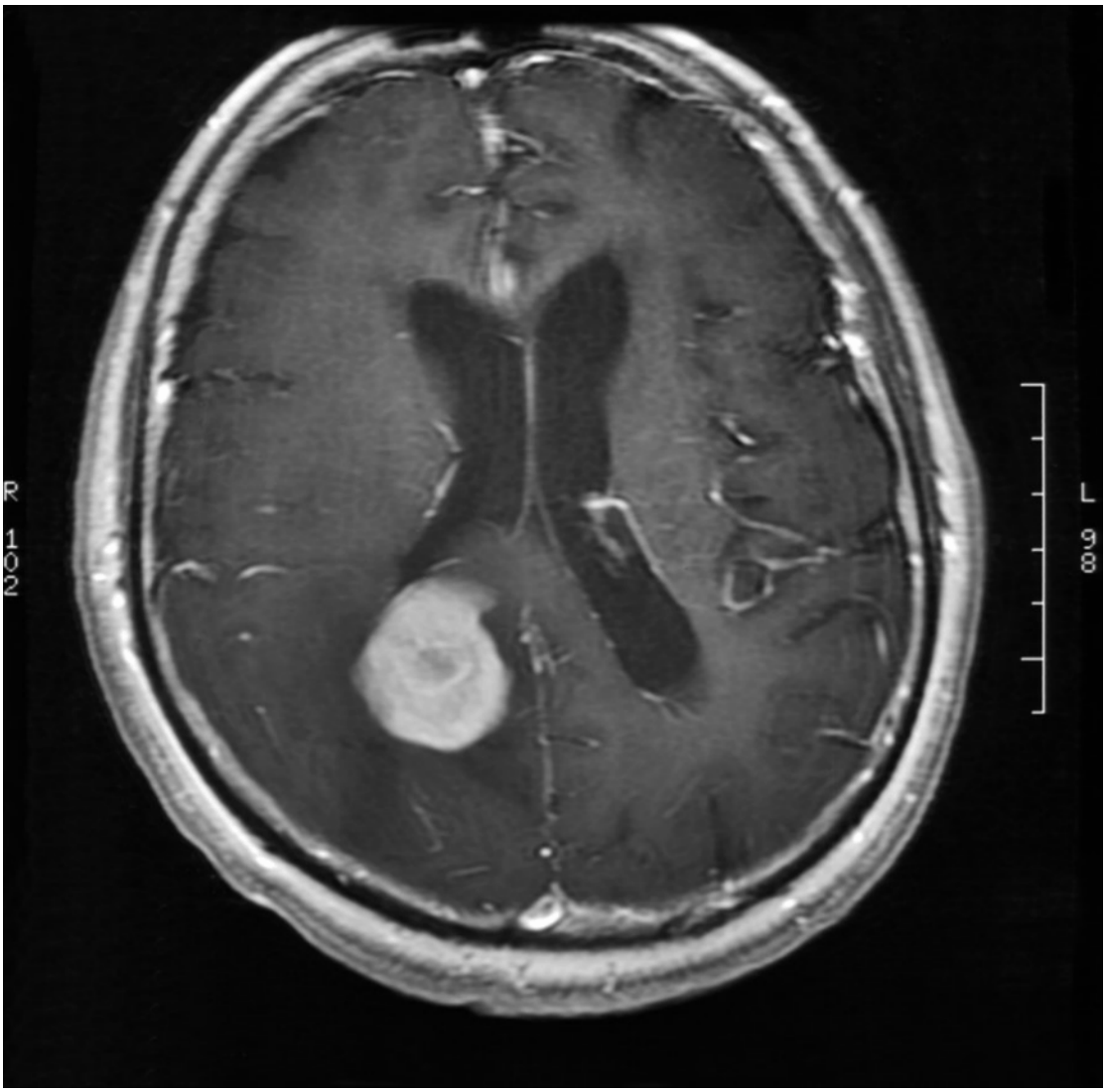
Question 78

A 28-year-old woman is evaluated in the emergency department for a 1-week history of progressive headache associated with nausea and vomiting. Medical history is significant for HIV infection. She is nonadherent to her antiretroviral therapy regimen and takes no other medications.

On physical examination, she is awake and oriented. The patient is afebrile, blood pressure is 130/80 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. No enlarged lymph nodes are palpated. The liver and spleen are not enlarged. The remainder of her physical examination is unremarkable, and her neurologic examination shows papilledema but no other focal findings.

Results of a complete blood count and serum chemistry panel, including toxoplasmosis titer measured at the time of HIV diagnosis, are normal.

CT scan of the head is shown.



Which of the following is the most appropriate next step in management?

A

Combination chemotherapy

B

High-dose intravenous glucocorticoids

C

Intracranial pressure monitoring

D

Stereotactic radiation therapy

Answer & Critique

Correct Answer: B

Educational Objective: Manage a patient with suspected central nervous system lymphoma.

Key Point

Patients who have increased intracranial pressure associated with suspected central nervous system lymphoma require immediate high-dose glucocorticoids to treat the mass effect and a brain biopsy to establish the tissue diagnosis.

In this patient who most likely has a primary central nervous system (CNS) lymphoma with evidence of mass effect, high-dose glucocorticoids should be administered immediately. Because the brain is enclosed in a fixed space, mass effect within the brain causes progressively increased intracranial pressure (ICP) that, if untreated, can lead to diffuse brain injury, permanent disability, and death. Headache is typically the first presenting symptom and is followed by nausea and vomiting; as ICP increases, more advanced findings include altered mental status, focal neurologic deficits (such as papilledema), and loss of consciousness. Because progression can be rapid, emergent CT or MRI imaging of the brain followed by immediate treatment are essential to avoid the late adverse consequences of increased ICP that lead to permanent neurologic dysfunction and death. Glucocorticoids remain the initial therapy of choice because of their rapid anti-inflammatory effect that decreases the edema associated with malignant mass lesions. Intravenous administration of dexamethasone is standard for later stages of increased ICP (impaired mentation, uncontrolled seizures) with a recommended dose of 8 to 10 mg every 6 hours. Higher-dose dexamethasone (100 mg/d) does not improve the response rate and is associated with more adverse effects.

Metastatic tumors originating from lung cancer and cutaneous melanoma are the most common malignancy-related causes of increased ICP. These tumors, particularly melanoma, are also associated with intracerebral hemorrhage. Other less common causes of increased ICP related to malignancy include lymphoma, primary brain tumors, and germ cell tumors. Because treatment of ICP varies markedly depending on the cause, a tissue diagnosis of the mass lesion is important in guiding subsequent therapy. A primary CNS lymphoma is the most likely diagnosis in this young patient with a brain mass and HIV infection that is not optimally treated. Because lymphomas are

extremely glucocorticoid sensitive, early administration may make obtaining a tissue sample difficult by distorting histologic findings; it is therefore preferable to obtain a biopsy in a stable patient with possible or likely CNS lymphoma prior to glucocorticoid therapy if there are minimal sequelae of increased ICP. However, in all patients with more advanced complications of increased ICP such as this patient, immediate glucocorticoid treatment is indicated.

Combination chemotherapy is appropriate only after initial steps are taken to lower the ICP and a tissue diagnosis is established, which has not yet been done in this patient.

Intracranial pressure monitoring is used to follow the effectiveness of therapies intended to decrease pressure in the cranial space and is most often used in association with severe traumatic brain injury. Although the benefit of pressure monitoring needs to be evaluated in an individual patient, it would not be appropriate to delay administration of glucocorticoids while assessing this patient for monitoring.

Either whole brain or stereotactic radiation therapy may be appropriate for some tumors causing increased ICP, but this therapy would be indicated only after the patient receives acute treatment and a tissue diagnosis is established.

Question 79

A 68-year-old woman is evaluated in the emergency department for a 1-week history of polyuria, polydipsia, and progressive confusion. She has a 2-year history of multiple myeloma that was treated 1 year ago with chemotherapy. Her medical history is otherwise noncontributory, and she takes no medications.

On physical examination, the patient is afebrile, blood pressure is 100/60 mm Hg, pulse rate is 100/min, and respiration rate is 14/min. The patient's skin and mucous membranes are dry. She appears confused, and her reflexes are hyporeactive. The remainder of her examination is unremarkable.

Laboratory studies:

Blood urea nitrogen	60 mg/dL (21.4 mmol/L)
Calcium	14.5 mg/dL (3.6 mmol/L)
Creatinine	3.5 mg/dL (309.4 µmol/L) (baseline 1.2 mg/dL [106.1 µmol/L])

Intravenous high-volume normal saline and high-dose glucocorticoids are started.

Which of the following is the most appropriate next step in treatment?

A

Cinacalcet

B

Hemodialysis

C

Intravenous bisphosphonate

D

Multiagent chemotherapy

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient with malignancy-associated hypercalcemia.

Key Point

Immediate hydration with large-volume normal saline infusion, forced diuresis with furosemide, glucocorticoid therapy for glucocorticoid-responsive malignancies such as multiple myeloma, and a bisphosphonate is appropriate treatment of malignancy-related hypercalcemia.

The most appropriate next step in treatment for this patient with malignancy-associated hypercalcemia is an intravenous bisphosphonate. Initial therapy for hypercalcemia is high-volume normal saline hydration, and in those with kidney failure, forced diuresis with a loop diuretic such as furosemide. This helps restore intravascular volume and decreases serum calcium levels acutely. For tumors that are glucocorticoid-sensitive, such as multiple myeloma and some types of lymphoma, glucocorticoids are indicated to decrease tumor-associated osteoclast activation. Bisphosphonates are powerful inhibitors of osteoclast-mediated bone resorption with an onset of effect occurring several days after administration and a duration of up to several weeks depending on the specific agent used, which allows longer-term control of calcium levels. Hypercalcemia is usually a manifestation of advanced disease, is associated with poor prognosis, and occurs in up to 10% of patients with cancer. Hypercalcemia is most common among patients with multiple myeloma and breast, renal, and lung cancer. Patients initially present with nausea, vomiting, constipation, and polyuria. Polydipsia, diffuse muscle weakness, and confusion follow.

Cinacalcet is a calcimimetic agent that is used to lower the calcium level in patients with primary and tertiary hyperparathyroidism associated with chronic kidney disease. It is not effective or approved for use in malignancy-associated hypercalcemia.

Dialysis is an effective method for lowering serum calcium levels, although it is generally reserved for patients with severe, symptomatic hypercalcemia who have not responded to acute treatment with hydration and other measures or patients in whom aggressive hydration is contraindicated. Dialysis would not be appropriate in this patient whose response to hydration and other initial therapies has not been assessed.

Treatment with chemotherapy or disease-specific targeted agents would be appropriate for long-term control of hypercalcemia but would not be effective for short-term therapy of hypercalcemia

Question 80

A 58-year-old man undergoes follow-up evaluation for cancer of the ascending colon diagnosed 3 weeks ago. Colonoscopy at that time revealed a fungating mass in the ascending colon. Biopsy revealed adenocarcinoma, and additional studies showed no evidence of metastatic disease. Right hemicolectomy was performed. The pathology report showed a 4-cm primary adenocarcinoma with clear margins at resection, full-thickness penetration through the colonic wall into pericolonic fat, and 4/21 lymph nodes involved (stage III). Medical history is otherwise unremarkable, and the patient takes no medications.

On physical examination, vital signs are normal. Examination of the abdomen shows well-healed surgical scars but is otherwise normal.

Which of the following is the most appropriate management at this time?

A

Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)

B

Radiation therapy

C

Radiation therapy and capecitabine followed by capecitabine plus oxaliplatin (CAPOX)

D

Observatio

Answer & Critique

Correct Answer: A

Educational Objective: Treat stage III colon cancer with adjuvant chemotherapy.

Key Point

Chemotherapy with capecitabine and oxaliplatin (CAPOX) or leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) is appropriate adjuvant therapy for patients with stage III colon cancer.

Chemotherapy with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) is most appropriate for this patient with stage III colon cancer. Stage III colon cancer is potentially curable, and the likelihood of cure is modestly but statistically significantly increased by the use of adjuvant chemotherapy. Administration of leucovorin plus 5-fluorouracil (5-FU) was established as an appropriate standard adjuvant treatment for stage III colon cancer in the 1990s. However, in 2004, a large randomized trial comparing adjuvant leucovorin and 5-FU with FOLFOX adjuvant chemotherapy showed that the FOLFOX regimen led to improved disease-free and overall survival. Capecitabine is an oral prodrug that is converted to 5-FU in the body. The combination of capecitabine plus intravenous oxaliplatin (CAPOX) is also an acceptable regimen for adjuvant treatment of patients with stage III colon cancer.

Because local recurrence of colon cancer rarely develops and because it can be difficult to isolate the small bowel from the radiation field, radiation therapy, either alone or in combination with chemotherapy, does not have a role in the routine management of patients with stage III colon cancer. In addition, radiation to the small bowel may cause substantial toxicity. However, because local recurrence is a greater problem in patients with rectal cancer and because it is far easier to isolate the small bowel from the radiation field when treating rectal cancer, the combination of radiation therapy and chemotherapy, preferably preoperatively, is routinely used for treating patients with stage II and III rectal cancer.

Stage III colon cancer is potentially curable with surgery and adjuvant chemotherapy. For patients with good performance status, adjuvant chemotherapy with its associated survival advantage is preferred to observation alone

Question 81

A 70-year-old man is hospitalized for new-onset abdominal pain and nausea. He has had little to eat or drink for the past 24 hours. The patient had a cerebrovascular accident 1 year ago and since then has resided in a nursing home. He has long-standing congestive cardiomyopathy, hypertension, type 1 diabetes mellitus with peripheral neuropathy, and chronic kidney disease. He is mostly bedbound but is able to sit in a chair with assistance for several hours each day. Medications are amlodipine, enalapril, furosemide, insulin, and metoprolol.

On physical examination, the patient appears chronically ill. Temperature is 37.7 °C (99.9 °F), blood pressure is 150/85 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. BMI is 21. The sclerae are icteric, and mucous membranes are dry. There are crackles at the bilateral lung bases. Heart examination is significant for an S_3 heart sound. The abdomen is moderately distended with diffuse mild tenderness but without rebound or guarding. The liver edge is palpable. There is bilateral pitting edema of the extremities.

The patient's Eastern Cooperative Oncology Group/World Health Organization performance status level is assessed to be 4 (completely disabled, totally confined to a bed or chair, and unable to do any self-care).

The serum albumin level is 2.8 g/dL (28 g/L), the serum total bilirubin level is 2.3 mg/dL (39.3 μmol/L), and the serum creatinine level is 2.6 mg/dL (229.8 μmol/L).

A CT scan of the abdomen without contrast shows hepatomegaly with multiple metastatic lesions, enlarged retroperitoneal lymph nodes, abdominal carcinomatosis, moderate ascites, and a nonobstructing mass lesion in the cecum. A diagnostic paracentesis is performed, and 2 liters of bloody ascitic fluid are removed; cytology samples are positive for adenocarcinoma.

Gentle intravenous hydration is begun, and the patient is given parenteral morphine, which provides adequate relief of pain.

Which of the following is the most appropriate management?

A

Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)

B

Single-agent, low-dose 5-fluorouracil

C

Surgical resection of the cecal mass

D

Supportive, comfort-oriented care

Answer & Critique

Correct Answer: D

Educational Objective: Manage a patient with metastatic cancer and poor performance status.

Key Point

Supportive, comfort-oriented care is appropriate for a frail patient with metastatic cancer, significant medical comorbidities, and a poor performance status.

Supportive, comfort-oriented care is most appropriate for this patient who has advanced metastatic adenocarcinoma in the setting of multiple severe chronic comorbidities and a debilitated medical condition resulting in a poor performance status. A key aspect of managing patients with cancer is an assessment of their performance status, define d as the specific level of well-being and ability to perform daily activities. Several formal measures of performance status are available, such as the Karnofsky score and the Zubrod score (also called the Eastern Cooperative Oncology Group/World Health Or ganization system). Scores on these measures correlate with the ability of an individual patient to tolerate potential therapeutic interventions. In patients with very low performance measure scores, a less aggressive and more supportive treatment approach is usually warranted based on likely outcomes of therapy. Virtually all oncology clinical trials showing efficacy of chemotherapy exclude patients with poor performance status because toxicity and harm occur more frequently and clinical benefit occurs less frequently in these patients. In addition, this patient has elevated serum bilirubin and creatinine levels. Because liver and kidney function affect metabolism of many oncology drugs, treatment of patients with chronic liver or kidney disease is challenging and is associated with a higher risk of complications. In some cases, poor performance has developed based on tumor-related symptoms and might be expected to improve with treatment of the cancer. However, this patient's poor performance status appears to be due to his chronic illnesses and is not likely to improve significantly following treatment of his cancer.

Combination chemotherapy is contraindicated in a debilitated patient and would likely cause severe and even life-threatening toxicity.

Single-agent, low-dose chemotherapy is highly unlikely to provide any benefit and is still associated with the risk of toxicity.

The patient is a poor candidate for surgery, has no evidence of colonic obstruction, and would likely have considerable postoperative and healing complications with little, if any, chance of benefit.

Bibliography

Question 82

A 55-year-old man is evaluated for a 3-month history of cough and unexplained weight loss and a 2-week history of shortness of breath. He has never smoked cigarettes.

On physical examination, vital signs are normal. Breath sounds are decreased, and there is dullness to percussion over the right lung field. Examination findings are otherwise unremarkable.

Chest radiograph shows a right pleural effusion and right hilar mass. CT scan of the chest reveals a large right pleural effusion, a right upper lobe mass with associated consolidation, hilar and mediastinal lymphadenopathy, and an irregular right adrenal mass. A CT-guided transthoracic biopsy of the right upper lobe mass shows adenocarcinoma.

Which of the following is the most appropriate management?

A

EGFR mutation testing

B

K-*ras* mutation testing

C

PET scanning

D

Surgical resection

Answer & Critique

Correct Answer: A

Educational Objective: Determine need for molecular testing in a patient with adenocarcinoma of the lung.

Key Point

Testing to identify an epidermal growth factor receptor (EGFR) mutation is a key component in the initial evaluation of metastatic nonsquamous non–small cell lung cancer due to improved survival in patients with EGFR mutations who are treated with EGFR tyrosine kinase inhibitors.

This patient with stage IV adenocarcinoma of the lung (based on the presence of a likely right adrenal metastasis) should undergo tumor testing for the presence of an epidermal growth factor receptor (EGFR) mutation. Because studies have documented improved survival in patients with EGFR mutations who are treated with an EGFR tyrosine kinase inhibitor (such as erlotinib, gefitinib, or afatinib), testing to identify this mutation is a key component of the initial evaluation of all patients diagnosed with metastatic nonsquamous non–small cell lung cancer (NSCLC). In patients with likely metastatic disease who might be candidates for therapy, ensuring that an adequate tissue sample is obtained (core needle biopsy at a minimum) is essential to allow for needed molecular testing.

Although K-*ras* testing can help determine the prognosis in patients with NSCLC, it is not currently considered a routine component of evaluation because existing renin-angiotensin system inhibitors used to treat patients with this mutation have not proven to be effective.

PET scanning has a role in evaluating patients who are believed to have potentially resectable disease. However, obtaining a PET scan in a patient who clearly has metastatic disease based on CT imaging is unnecessary.

Because this patient has both a pleural effusion and a likely adrenal metastasis that would classify his disease as stage IV, he is not considered a surgical candidate.

Question 83

A 68-year-old woman is evaluated for a 1-month history of a painful lump underneath the tongue. She has a 45-pack-year smoking history and continues to smoke.

On physical examination, vital signs are normal. An ulcerated lesion measuring approximately 1 cm is seen on the anterior floor of the mouth.

The lesion is resected. Pathology specimens identify poorly differentiated squamous cell carcinoma with negative margins.

The patient is encouraged to stop smoking. Following discussion of the benefits and risks, she is enrolled in a lung cancer screening program utilizing low-dose CT scanning.

Which of the following surveillance tests should also be recommended for this patient?

A

CT scans

B

PET/CT scan

C

Oral examinations and direct laryngoscopy

D

No additional follow-up

Answer & Critique

Correct Answer: C

Educational Objective: Manage posttreatment surveillance following therapy for head and neck cancer.

Key Point

Posttreatment surveillance of patients with head and neck cancer should be directed toward identifying development of both locally recurrent cancer and a second primary cancer at a more distant site.

Periodic oral examinations and direct laryngoscopy are indicated for this patient. Following successful treatment of localized squamous cell carcinoma of the head and neck, patients remain at risk for developing both local cancer recurrence and second primary cancers, especially cancers due to tobacco and alcohol use. Tobacco and alcohol act as chemical carcinogens and induce genetic changes in the squamous mucosa of the head and neck that are not limited to the site involved with the cancer. These genetic changes expose patients to ongoing risk for development of second primary cancers. Therefore, surveillance must be directed at identifying both locally recurrent cancer and second primary cancers elsewhere in the head and neck. This is accomplished by assessment of the primary site (for example, in this patient by direct oral examination) and periodic assessment of the remaining squamous mucosa of the head and neck via direct laryngoscopy. In addition, this patient population is at high risk for non–small cell lung cancer, which represents the most commonly diagnosed second cancer in patients with head and neck cancer. This patient also meets the general criteria for lung cancer screening with low-dose CT as she is between the ages of 55 to 74 years with a smoking history of at least 30 pack-years within 15 years of quitting. Inclusion of low-dose CT surveillance for lung cancer should therefore be discussed with any patient being treated for tobacco-related head and neck cancer.

Within the first 6 months following treatment, imaging of the primary tumor site and neck is performed to establish a baseline for future reference. Imaging techniques, including CT, MRI, PET, and ultrasonography, have been used in posttreatment surveillance for locoregional recurrence. Subsequent imaging is generally based on the presence of signs or symptoms. Biannual CT scans are not indicated, and the additional radiation poses an unnecessary danger to the patient.

Providing no posttreatment surveillance is not recommended, as this patient should be evaluated periodically for development of both locally recurrent cancer and a second primary cancer.

Question 84

A 55-year-old woman is evaluated in the emergency department for a 3-day history of diarrhea. She reports seven to eight stools daily without vomiting. She also notes abdominal cramping without vomiting and has been able to maintain adequate fluid intake. Medical history is significant for metastatic malignant melanoma, for which she recently completed the third of four planned doses of ipilimumab therapy. She has no history of inflammatory bowel disease, recent antibiotic use, recent travel, or consumption of uncooked foods. The remainder of the medical history is noncontributory, and she takes no other medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 125/85 mm Hg, pulse rate is 90/min without orthostatic changes, and respiration rate is 14/min. The abdomen is soft and nontender with increased bowel sounds. The remainder of the physical examination is normal.

Laboratory studies:

Hemoglobin	12.2 g/dL (122 g/L)
Leukocyte count	9300/μL (9.3×10^9/L) with normal differential
Alanine aminotransferase	120 U/L
Aspartate aminotransferase	160 U/L
Creatinine	1.2 mg/dL (106.1 μmol/L)
Fecal occult blood test	Negative

A chest radiograph is normal and abdominal films show nondilated bowel loops with no free air.

In addition to discontinuing the ipilimumab and providing supportive care, which of the following is the most appropriate next step in treatment?

A

Broad-spectrum intravenous antibiotics

B

Granulocyte-macrophage colony-stimulating factor

C

High-dose intravenous glucocorticoids

D

Observation

Answer & Critique

Correct Answer: C

Educational Objective: Manage ipilimumab-induced toxicity.

Key Point

Patients with acute ipilimumab toxicity should receive fluid replacement and immediate glucocorticoid therapy to reverse the damage this agent can cause; delay in treatment can be fatal.

Initiation of high-dose intravenous glucocorticoids and aggressive supportive care in addition to discontinuing the offending medication is the most appropriate treatment for this patient with ipilimumab toxicity with severe diarrhea and evidence of autoimmune hepatitis. Ipilimumab is a new class of antineoplastic therapy that inhibits the function of T-cell checkpoint receptors (ipilimumab or PD-1 and PD-L1 inhibitors), thereby enhancing the function of the immune system and inducing remissions in patients with various solid tumors, particularly metastatic melanoma. However, T-cell checkpoint inhibitors also can cause many potentially permanent and life-threatening organ toxicities that are autoimmune-mediated based on their enhancement of immune function. These include dermatologic (rash, mucositis), gastrointestinal (diarrhea, colitis), liver (autoimmune hepatitis), and endocrine (hypothalamic/pituitary, thyroid, and adrenal insufficiency). Other organ involvement (eye, kidney, hematologic, pulmonary, and neurologic) has also been reported. Because the toxicity results from triggering an exaggerated immune response, treatment of these toxicities involves removing the causative agent and providing immunosuppression, preferably with high-dose glucocorticoids due to their nonspecific immune-suppressing effects and rapid onset of action. Recognition of the autoimmune effect of the treatment is critical since the autoimmune-triggered toxicity from this class of medications can be fatal if immunosuppressive therapy is delayed.

Because the mechanism of toxicity is not directly related to leukopenia and this patient has a normal leukocyte count with no objective evidence of infection, broad-spectrum antibiotics are not indicated, and delayed recognition of the drug-related syndrome from treatment of possible bacterial infection could be detrimental.

Similarly, because the toxicity of T-cell checkpoint inhibitors is not due to leukopenia, treatment with growth factors, such as granulocyte-macrophage colony-stimulating factor, does not have a role in either the prevention or treatment of complications associated with this class of drugs.

Because rapid immunosuppression may reverse the severe autoimmune reactions triggered by ipilimumab, discontinuation of the medication and supportive care alone is inadequate therapy for this patient.

Question 85

A 33-year-old woman was diagnosed with *BRCA1* mutation 2 months ago. Her paternal aunt was diagnosed with breast cancer at age 45 years and was found to have a deleterious *BRCA1* mutation. She has no family history of ovarian cancer. She has one child and would like to have another child in the next year. She seeks advice on when to have prophylactic bilateral salpingo-oophorectomies (BSO). She is in good health and has no active medical problems.

Physical examination shows no worrisome breast masses. Pelvic examination is normal. The remainder of the physical examination is normal.

Laboratory studies are normal. Results of a mammogram 1 month ago, a transvaginal ultrasound 2 weeks ago, and a breast MRI 1 week ago are normal.

Which of the following is the most appropriate management?

A

Recommend immediate BSO

B

Recommend prophylactic BSO by age 35 years

C

Defer prophylactic BSO until age 40 years

D

Semi-annual pelvic ultrasound until age 50 years

Answer & Critique

Correct Answer: B

Educational Objective: Determine appropriate timing of prophylactic bilateral salpingo-oophorectomies for a *BRCA1* carrier.

Key Point

Risk-reducing bilateral salpingo-oophorectomies are recommended in women who carry deleterious *BRCA1* or *BRCA2*mutations between ages 35 and 40 years, once childbearing is complete.

Prophylactic bilateral salpingo-oophorectomies (BSO) by the age of 35 years is recommended for this patient. Patients with *BRCA1/2* mutations are at increased risk for ovarian cancer. The lifetime risk is 35% to 46% in *BRCA1* mutation carriers and 13% to 23% in *BRCA2* carriers. National guidelines recommend risk-reducing BSO in women who carry deleterious *BRCA1/2* mutations between ages 35 and 40 years, once childbearing is complete. A recent registry data analysis of almost 6000 women with *BRCA1* or *BRCA2* mutations proposed that risk-reducing BSO be done by age 35 years in women with *BRCA1* mutations due to a 4% risk of ovarian cancer between ages 35 and 40 years. Women with *BRCA2* mutations in this registry data did not develop ovarian cancers until after age 40 years and had an ovarian cancer risk under 1% if BSO was deferred to age 50 years.

Also shown was an 80% reduction in the risk of ovarian, tubal, or peritoneal cancer after prophylactic BSO and a 77% reduction in all-cause mortality. Previous studies have demonstrated a 48% reduction in breast cancer in *BRCA1/2* carriers who underwent prophylactic oophorectomy while premenopausal.

Hormone replacement can safely be given to healthy *BRCA1/2* carriers after BSO for relief of menopausal symptoms and preservation of bone health if nonhormonal options are not effective. Limited studies have not demonstrated an increased risk of breast cancer with hormone replacement therapy when stopped prior to the normal age of menopause.

At age 33 years, this patient will have two years to pursue further childbearing and still be able to have BSO by age 35 years. It is not necessary to recommend immediate BSO. In the study

mentioned above, there was a 0.5% risk of ovarian cancer between the ages of 30 and 34 years and only one occult ovarian cancer found at prophylactic BSO during these ages.

Semi-annual transvaginal ultrasound and serum CA-125 monitoring is recommended for *BRCA1/2*mutation carriers starting at age 30 years, but the evidence shows very limited effectiveness of such screening. Prophylactic BSO is the only method that has been shown to decrease ovarian cancer mortality in women at high risk for ovarian cancer.

Question 86

A 68-year-old man is evaluated for a 4-month history of fatigue, weight loss, and night sweats. He is a farmer and has been unable to work since his symptoms developed. Medical history is significant for hypertension, type 2 diabetes mellitus, and an anterior ST-elevation myocardial infarction. Medications are ramipril, glipizide, metoprolol, and low-dose aspirin.

On physical examination, the patient is afebrile, blood pressure is 140/88 mm Hg, pulse rate is 60/min, and respiration rate is 16/min. BMI is 30. Enlarged axillary lymph nodes are palpated.

Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Lactate dehydrogenase	Elevated
HIV	Negative
Epstein-Barr virus	Negative
Hepatitis B virus	Negative
Hepatitis C virus	Negative

CT scans show axillary, mediastinal, and pelvic lymphadenopathy. Echocardiogram shows a left ventricular ejection fraction of 30%.

Lymph node and bone marrow biopsies reveal diffuse large B-cell lymphoma.

Which of the following factors most strongly correlates with overall survival in this patient after treatment?

A

Revised International Prognostic Index score

B

Presence of anemia

C

Presence of B symptoms

D

Presence of type 2 diabetes mellitus

Answer & Critique

Correct Answer: A

Educational Objective: Determine the prognosis of a patient with newly diagnosed lymphoma.

Key Point

The revised International Prognostic Index (r-IPI) score has the greatest influence on the prognosis in patients with diffuse large B-cell lymphoma.

Although all of the options listed above affect the prognosis of this patient with an aggressive B-cell lymphoma, the revised International Prognostic Index score (r-IPI) correlates most strongly with his chance of overall survival after standard therapy.

Non-Hodgkin lymphoma (NHL) consists of over 20 subtypes defined by cell surface antigen expression and other morphologic features, including unique molecular profiles. The first major distinction divides NHL into three categories based on immunophenotyping to a B-cell, T-cell, or natural killer (NK) cell lineage. B-cell lymphomas account for 85% of all cases of NHL, T-cell lymphomas for 13%, and NK-cell lymphomas for 2%. A history of farming is not uncommon among newly diagnosed patients with B-cell lymphomas because components in some fertilizers are thought to be causative. Staging of lymphoma consists of structural disease assessment using physical examination findings, CT imaging, biopsy findings of potential disease sites, and disease activity assessment using PET scanning to quantify the standard uptake value. Age, concomitant infection or immunodeficiency, and expression of driver gene mutations can all influence prognoses. The Ann Arbor Staging System criteria can be used for most forms of lymphoma, however, the r-IPI score is most predictive of outcomes in patients with diffuse large B-cell lymphoma. The r-IPI incorporates multiple clinical factors, including the patient's age, performance status, disease stage, degree of extranodal involvement, and serum lactate dehydrogenase level to generate a score that correlates with progression-free and overall survival after standard therapy. This patient has a high r-IPI score due to stage IV disease (bone marrow involvement), a high serum lactate dehydrogenase level, and poor performance status.

The presence of anemia and B symptoms might be indicative of aggressive disease, but are not incorporated into the r-IPI score, which is the best predictor of clinical outcome.

The presence of diabetes appears to have a minimal effect on the outcome of lymphoma and is therefore not an independent predictive factor.

Question 87

A 42-year-old woman is evaluated for postcoital bleeding and intermittent pelvic pain. She otherwise feels well. The patient is premenopausal and has two children.

On physical examination, vital signs are normal. General examination is normal. An ulcerating 2-cm cervical mass is visible on speculum examination. Bimanual pelvic examination shows a bulky mass in the cervix that is fixed to the left pelvic side wall and is not mobile.

Results of complete blood count and serum chemistry panel are normal.

CT scan of the abdomen and pelvis shows a 4.5-cm mass involving the lower uterus and extending to the left pelvic side wall. Left hydronephrosis and hydroureter are present. No disease is detected outside the pelvis. Biopsy of the cervical mass shows poorly differentiated invasive squamous cell carcinoma. Chest CT is normal.

Which of the following is the most appropriate treatment?

A

Radiation therapy

B

Radiation therapy with concurrent chemotherapy

C

Radical hysterectomy

D

Radical hysterectomy followed by chemotherapy

E

Simple hysterectomy with ovarian preservation

Answer & Critique

Correct Answer: B

Educational Objective: Treat advanced cervical cancer with chemoradiation therapy.

Key Point

Patients with locally advanced cervical cancer should be treated with radiation therapy and concomitant chemotherapy, as use of chemoradiation is associated with a decrease in local and distant cancer recurrence compared with radiation therapy alone.

Radiation therapy and concurrent cisplatin-based chemotherapy is the most appropriate treatment for this patient who has bulky stage III cervical cancer (extending to the pelvic wall and/or involving the lower third of the vagina). Cervical cancer remains the second most common cancer in women worldwide. Early-stage cervical cancer without spread to the pelvic wall or to the lower third of the vagina can be treated successfully with surgery alone, but more locally advanced cancer requires radiation therapy instead of surgery. In 1999, based on five published randomized clinical trials, the National Cancer Institute issued a clinical alert recommending chemoradiation therapy for locally advanced cervical cancer. These initial studies used cisplatin-based chemotherapy during radiation; results showed a decrease in local and distant recurrence compared with radiation therapy alone.

Chemoradiation has since become the standard of care, and weekly cisplatin administration during radiation is the most frequently used regimen, although non–platinum-based chemotherapy regimens also have been shown to be effective. Radiation therapy alone can be used for patients with stage I (confined to the cervix) or nonbulky stage II cervical cancer (invading beyond the uterus but not to the pelvic wall or lower third of the vagina) as an alternative to hysterectomy but should be combined with chemotherapy for patients with bulky stage II, stage III, and stage IVA cervical cancers (spread to adjacent organs but no distant metastases).

Radical hysterectomy is appropriate for patients with stage I or nonbulky stage IIA cervical cancer, which includes invasion beyond the uterus but not extending to the pelvic wall or to the lower third of the vagina. However, radical hysterectomy is not an option for this patient who has bulky disease extending to the pelvic wall (stage III).

There is no benefit to using adjuvant chemotherapy after hysterectomy or to administering chemotherapy prior to surgery. The survival benefit of chemotherapy is proven only when given with concomitant radiation therapy for patients with intermediate- and high-risk cervical cancer.

Patients with stage I cervical cancer may have ovarian preservation if maintaining fertility is desired. For microscopic disease confined to the cervix (stage IA), simple hysterectomy, cone biopsy, or removal of the cervix alone are options, all of which include ovarian preservation.

Question 88

A 70-year-old man is evaluated for a 3-month history of fatigue, weight loss, fever, and night sweats. He has a longstanding history of Crohn disease treated with infliximab.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 110/60 mm Hg, pulse rate is 105/min, and respiration rate is 16/min. Fixed cervical, axillary, and inguinal lymphadenopathy is present on palpation. There is no splenomegaly. The remainder of the examination is unremarkable.

Chest radiograph is normal. CT scans show extensive cervical, axillary, abdominal, and pelvic lymphadenopathy; there is no mediastinal lymphadenopathy.

Which of the following is the most likely diagnosis?

A

Non-Hodgkin lymphoma

B

Sarcoidosis

C

Testicular cancer

D

Tuberculosis

Answer & Critique

Correct Answer: A

Educational Objective: Diagnose immunosuppression-induced non-Hodgkin lymphoma.

Key Point

Patients receiving long-term immunosuppressive therapy are at greater risk for developing non-Hodgkin lymphoma.

This patient, who presents with fixed, palpable lymphadenopathy in multiple sites and systemic B symptoms (night sweats, fever, and weight loss), most likely has non-Hodgkin lymphoma (NHL) associated with immunosuppression due to the long-term administration of infliximab. Viral infections including Epstein-Barr virus, HIV, human T-cell lymphotrophic virus type-1, and hepatitis B and C viruses are all capable of directly driving transformation of lymphoid tissue to lymphoma or contributing indirectly by causing immunodeficiency, a risk factor for lymphoma development. Specific examples include the development of posttransplant lymphoproliferative disorders presenting as high-grade B-cell NHL caused by ongoing immunosuppression with agents such as cyclosporine or tacrolimus to prevent rejection in solid organ transplantation or graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. Excisional biopsy of an adequate tissue sample that preserves the architecture of the lymph node is required for the diagnosis of lymphoma.

Sarcoidosis can present with or without symptoms that include fatigue, weight loss, joint pain, cough, and shortness of breath. Sarcoidosis is believed to be a consequence of an immune reaction to an unknown antigen, and not immunosuppression.

Testicular cancer can occur late in life but usually does not present with fever and night sweats and would not likely be associated with axillary and cervical lymphadenopathy without mediastinal lymphadenopathy.

Tuberculosis occurs more commonly in patients treated with infliximab. A nonreactive tuberculin skin test cannot be used to exclude tuberculosis because of this patient's immunosuppressed state. However, his extensive extra-abdominal lymphadenopathy without mediastinal lymphadenopathy makes tuberculosis unlikely.

Question 89

A 78-year-old man is hospitalized for a 1-week history of progressive and severe back pain and weakness in both legs. He describes a sense of “heaviness” in his legs and has had increasing difficulty climbing stairs and getting out of a chair. Medical history is significant for asymptomatic multiple myeloma that has been followed with periodic examinations and laboratory studies; his last assessment was 3 months ago and was stable.

On physical examination, vital signs are normal. He has point tenderness over the T10 and T11 vertebral bodies, decreased lower extremity muscle strength (3^{+}/5), increased reflexes isolated to both lower extremities, and bilateral extensor plantar responses. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a serum hemoglobin level of 6.5 g/dL (65 g/L) and a serum calcium level of 13 mg/dL (3.2 mmol/L).

MRI of the thoracic and lumbar spine shows a vertebral body mass with extension into the epidural space at T12 and compression of the spinal cord.

Which of the following is the most appropriate initial step in treatment?

A

Biopsy of the epidural mass

B

Decompressive surgery

C

Intravenous glucocorticoids

D

Multiagent chemotherapy

E

Radiation therapy

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient with spinal cord compression caused by multiple myeloma.

Key Point

Patients with cancer who develop symptoms of possible spinal cord compression require immediate administration of intravenous high-dose glucocorticoids to prevent permanent neurologic deficits.

This patient with spinal cord compression should receive immediate administration of intravenous high-dose glucocorticoids to prevent permanent neurologic deficits. This patient has MRI-confirmed spinal cord compression characterized by mid back pain and physical findings of lower extremity hyperreflexia and weakness. His known multiple myeloma with corresponding anemia and hypercalcemia suggest progression of his disease with a plasma cell tumor as the cause of his spinal cord compression. Glucocorticoid therapy is the initial treatment in most cases of malignant spinal cord compression as they decrease inflammation and reduce the mass effect due to edema associated with many tumors. In this case, glucocorticoid therapy has the added benefit of directly treating the hypercalcemia and plasma cell myeloma. Glucocorticoid treatment is then followed with more definitive therapy, often radiation and possible neurosurgical intervention in some cases.

Biopsy of the epidural mass is not necessary because of the patient's known likely causative disease and could delay initiation of glucocorticoids and radiation therapy and increase the risk of permanent nerve damage.

Although neurosurgical intervention consisting of decompressive surgery might be necessary in some patients with spinal cord compression, it would not be appropriate before administration of immediate glucocorticoids.

Definitive treatment with chemotherapy or an immunomodulator may be appropriate but would not have the required immediate effect of glucocorticoids in preventing progressive neurologic damage.

Radiation therapy alone would not address the swelling associated with spinal cord compression nor the hypercalcemia or underlying systemic plasma cell myeloma. However, radiation therapy is often a useful therapy for treating bulky disease.

Question 90

A 55-year-old woman is evaluated for a mass in her left breast. She otherwise feels well. She is postmenopausal. Medical and family histories are otherwise negative and she takes no medications.

On physical examination, vital signs are normal. A firm, mobile mass measuring 2.5 × 2.0 cm is palpated in the upper outer quadrant of the left breast, adjacent to the areola. There is no right breast mass. The remainder of the examination is unremarkable.

Mammogram of the left breast shows a 2.9-cm spiculated mass at the site of the palpable lesion. Ultrasound examination shows a 3.5-cm mass. Ultrasound-guided biopsy specimens reveal grade 3 invasive ductal carcinoma that is estrogen receptor negative, progesterone receptor negative, and*HER2* positive. No lymphovascular invasion is noted.

A preoperative echocardiogram is normal; the left ventricular ejection fraction is 65%.

The patient desires breast-conserving surgery, but the surgeon believes that the mass is too large to resect with a lumpectomy because of her small breast size, the moderately large size of the cancer, and its central location.

Which of the following is the most appropriate management?

A

Mastectomy with postoperative chemotherapy

B

Neoadjuvant anastrozole

C

Neoadjuvant trastuzumab-based chemotherapy

D

Staging CT and bone scans

Answer & Critique

Correct Answer: C

Educational Objective: Treat breast cancer with neoadjuvant chemotherapy in a patient who desires breast-conserving surgery.

Key Point

Neoadjuvant chemotherapy may be indicated for patients with *HER2*-amplified or triple-negative breast cancers and for patients with larger cancers who desire breast-conserving surgery.

This patient should receive neoadjuvant trastuzumab-based chemotherapy. Disease-free survival and overall survival are equivalent in patients treated with neoadjuvant and adjuvant chemotherapy. However, neoadjuvant chemotherapy may allow performance of more breast-conserving procedures by decreasing the size of the tumor. In addition, the response to neoadjuvant chemotherapy is predictive of long-term disease-free and overall survival. Cancers with the highest response rate to neoadjuvant chemotherapy are those that are either *HER2* positive or triple-negative tumors (tumors that are negative for estrogen receptor, progesterone receptor, and *HER2* amplification). Patients with these types of cancer can be offered neoadjuvant chemotherapy even if decreasing the tumor size in order to perform breast-conserving surgery is not needed. After neoadjuvant chemotherapy, pathologic complete response, defined as the absence of any residual invasive cancer in the breast or lymph nodes, occurs in up to 60% of patients with *HER2*-positive cancers and up to 40% of those with triple-negative cancers and correlates with an excellent long-term disease-free survival.

The regimens used for neoadjuvant chemotherapy are generally the same as those used for postoperative adjuvant chemotherapy. Patients are closely monitored with breast exams during neoadjuvant chemotherapy to make sure they are responding. Unless a patient has tumor progression or is on a clinical trial assessing the response of a new regimen, all of the chemotherapy is usually completed before surgery. A patient with a *HER2*-positive cancer would receive trastuzumab during the nonanthracycline part of adjuvant chemotherapy, receiving 1 year of trastuzumab in total. Trastuzumab-containing regimens without anthracyclines are an option, particularly for women with a higher risk of cardiomyopathy because of older age or pre-existing hypertension. Pertuzumab is a newly approved anti-*HER2* monoclonal antibody that may be used with trastuzumab and chemotherapy for neoadjuvant treatment of *HER2*-amplified breast cancers that measure 2 cm or more and/or are sentinel lymph node positive. The NeoSphere study

demonstrated improved pathologic complete response rates (46% vs 29%) when pertuzumab was added to trastuzumab and docetaxel for*HER2*-amplified breast cancers with these higher risk features.

Immediate mastectomy is not required for this patient, who desires breast conservation and is likely to achieve this goal with neoadjuvant chemotherapy.

Neoadjuvant antiestrogen therapy (for example, with anastrozole) is an option for postmenopausal women with large or locally advanced breast cancers that are hormone receptor positive, particularly patients who are not good candidates for adjuvant chemotherapy because of advanced age or medical comorbidities. However, this therapy is not effective in patients with estrogen receptor–negative cancers.

As this patient does not have any worrisome symptoms or signs suggestive of systemic metastases, she does not need CT or bone scans for staging. Current American Society of Clinical Oncology (ASCO) guidelines recommend against performing PET, CT, or radionuclide bone scans in patients with stages 0 to II breast cancer in the absence of findings that would suggest metastatic disease.

Question 91

An 80-year-old woman is hospitalized after a mechanical fall. She has a history of stage I estrogen receptor–positive and progesterone receptor–positive left breast cancer diagnosed 13 years ago; *HER2*testing was not done at that time. She was treated with breast-conserving surgery, primary breast radiation, and adjuvant tamoxifen for 5 years. She is not having any current bone pain or headaches.

On physical examination, vital signs are normal. A large palpable lesion is present over the left frontal skull. There is no lymphadenopathy. Examination of the left breast shows a healed incision with no masses. There are no right breast masses. The remainder of the examination is unremarkable.

Serum alkaline phosphatase level is elevated at 264 U/L (normal 36-92 U/L) and serum CA 15-3 level is 100.2 U/mL (normal <30 U/mL). Remaining laboratory studies, including serum calcium level, are normal.

CT scan of the head done in the emergency room shows a 3-cm lytic lesion in the left frontal skull. MRI of the brain confirms the presence of a large frontal skull lesion but shows no brain metastases. Bone and CT scans show lesions in the spine, skull, sternum, and bilateral ilium bones consistent with metastases. No visceral disease is present.

Biopsy of a lytic lesion in the right ilium shows metastatic adenocarcinoma consistent with primary breast cancer (estrogen receptor positive, progesterone receptor positive, and *HER2* negative).

Which of the following is the most appropriate treatment?

A

Anastrozole

B

Chemotherapy

C

Radiation to areas of bone involvement

D

Radium-223 isotope

Answer & Critique

Correct Answer: A

Educational Objective: Treat metastatic estrogen receptor–positive breast cancer that involves only bone.

Key Point

Patients with estrogen receptor–positive breast cancer who develop metastases limited to bone after a long disease-free interval should be treated initially with an aromatase inhibitor.

Because this patient's metastases involve only bone, her cancer is estrogen receptor positive, and she has had a long disease-free interval, she has a high likelihood of responding to primary antiestrogen therapy with anastrozole. Other aromatase inhibitors such as letrozole or exemestane would be equally effective. Aromatase inhibitors are superior to tamoxifen for first-line treatment of metastatic breast cancer because of improved response rates and disease-free survival. If she becomes resistant to aromatase inhibitor therapy, everolimus is a mammalian target of rapamycin (mTOR) inhibitor that is approved for treatment of metastatic breast cancer in combination with exemestane. If she responds to anastrozole and subsequently develops progressive disease, other antiestrogen agents, including tamoxifen and fulvestrant, could be used sequentially.

Chemotherapy with agents such as paclitaxel is used instead of antiestrogen therapy for treatment of metastatic breast cancer in patients with hormone receptor–negative disease, those with an impending visceral crisis due to extensive metastases, or those who do not respond to antiestrogen therapy.

Radiation to symptomatic areas of bone metastases is an important palliative treatment. However, patients with asymptomatic or minimally symptomatic bone lesions are not treated with radiation therapy unless bone stability is a concern.

Radium-223 is an alpha particle–emitting isotope that targets bone metastases. It is only used in bone metastases due to castrate-resistant prostate cancer.

Question 92

A 57-year-old woman undergoes follow-up evaluation. The patient underwent bilateral breast reduction surgery 3 months ago. The initial pathology report noted bilateral atypical ductal hyperplasia. Examination of additional pathology specimens showed no evidence of carcinoma. A mammogram obtained 2 months prior to the breast reduction surgery was normal.

The patient has been taking continuous conjugated estrogen and medroxyprogesterone hormone replacement therapy (HRT) since menopause at age 50 years. HRT has been tapered since the diagnosis of atypical ductal hyperplasia, and plans are to discontinue therapy in 1 month. There is no family history of breast or ovarian cancer.

On physical examination, vital signs are normal. Well-healed mastopexy incisions with mild induration are present. There are no breast masses. The remainder of the examination is unremarkable.

Which of the following is the most appropriate breast cancer prevention strategy?

A

Begin antiestrogen chemoprevention therapy

B

Begin vitamin D supplementation

C

Bilateral prophylactic mastectomy

D

Continue hormone replacement therapy

Answer & Critique

Correct Answer: A

Educational Objective: Prevent breast cancer in a patient with atypical ductal hyperplasia.

Key Point

Patients with newly diagnosed atypical ductal hyperplasia should be offered breast cancer chemoprophylaxis; exemestane is associated with the greatest reduction in breast cancer risk.

This patient with atypical ductal hyperplasia (ADH) should be offered breast cancer chemoprophylaxis, with exemestane being the most effective agent for postmenopausal women. ADH is a breast lesion associated with an increased risk of development of breast cancer. Studies have shown a three- to fivefold increased risk of breast cancer after a diagnosis of ADH, with a cumulative incidence at 30 years of 35%. Patients with ADH are candidates for breast cancer chemoprophylaxis. Among the available chemoprophylactic agents, exemestane is associated with the greatest reduction in breast cancer risk. Exemestane is an aromatase inhibitor that prevents conversion of androgens to estrogens and profoundly suppresses estrogen levels in postmenopausal women. The National Cancer Institute of Canada's Exemestane Prophylaxis Study compared administration of exemestane for 5 years with administration of placebo for the same period in patients with a 5-year risk of breast cancer of at least 1.67%. Patients with ADH were included in this study. At a median follow-up of 3 years, there was a 65% relative reduction in the annual incidence of invasive breast cancer in patients taking exemestane. Toxicities included a low incidence of grade 3 arthralgia and hot flushes. There was no difference in the incidence of skeletal fractures or development of osteoporosis, cardiovascular events, or other cancers in patients taking either exemestane or placebo.

Alternate chemoprophylaxis options include tamoxifen and raloxifene. Tamoxifen decreases the risk of breast cancer by 49% though it has a 0.1% risk per year of endometrial cancer and a 1% risk of vascular events including venous thrombosis and strokes. Raloxifene does not increase the risk of endometrial cancer and has a 25% lower risk of vascular events. It is less effective than tamoxifen, retaining 76% of the benefit of tamoxifen, but is an option in patients who want to decrease toxicities. All three chemoprophylaxis agents (tamoxifen, raloxifene, and exemestane) can be used in postmenopausal women but only tamoxifen is an option in premenopausal or perimenopausal women.

Vitamin D supplementation is being studied for breast cancer prevention, but any benefits are currently unclear. Some studies have shown a mild decrease in breast cancer risk in persons with normal serum vitamin D levels compared with those having low levels, whereas other studies have found no benefit.

Bilateral prophylactic mastectomy is an option for women with a high risk of breast cancer due to inherited syndromes, such as women with *BRCA1/2* mutations, but is not appropriate for women with atypical lesions such as atypical hyperplasia or lobular neoplasia.

Continuing hormone replacement therapy will increase the risk of breast cancer and prevent chemoprophylactic medications such as tamoxifen, raloxifene, and exemestane from decreasing this risk.

Question 93

A 70-year-old man undergoes follow-up evaluation for a recent diagnosis of colorectal cancer. He underwent left hemicolectomy and a bulky 8-cm tumor of the sigmoid colon was removed. Pathology reports revealed a poorly differentiated adenocarcinoma penetrating into pericolonic fat, with 1/22 resected lymph nodes involved with cancer (T3N1; stage III). The patient recovered well from surgery and completed 6 months of adjuvant chemotherapy.

Findings on physical examination today, including vital signs, are unremarkable.

The patient is scheduled to have physical examination and carcinoembryonic antigen monitoring every 3 to 6 months. Colonoscopy could not be performed preoperatively because of obstruction and is therefore scheduled to be done 6 months after surgery and repeated at 3- to 5-year intervals.

Which of the following surveillance imaging studies should also be done?

A

Chest/abdomen CT scans annually for 3 to 5 years

B

Chest/abdomen CT scans annually for 10 years

C

PET/CT scans annually for 5 years

D

No additional imaging studies

Answer & Critique

Correct Answer: A

Educational Objective: Manage postoperative surveillance for a patient with stage III colon cancer.

Key Point

Postoperative surveillance for patients with colorectal cancer includes physical examination and serum carcinoembryonic antigen measurement every 3 to 6 months, and CT scans of the chest and abdomen (and pelvis for patients with rectal cancer) annually for 3 to 5 years; colonoscopy, if done preoperatively, should be performed 1 year after resection and then repeated at 3- to 5-year intervals.

This patient has completed therapy for high-risk stage III colon cancer, and postoperative surveillance should include physical examination and serum carcinoembryonic antigen measurement every 3 to 6 months, as well as CT scans of the chest and abdomen (and pelvis for patients with rectal cancer) annually for 3 to 5 years. Colonoscopy, if done preoperatively, should be performed 1 year after resection and then repeated at 3 - to 5-year intervals. Because this patient was unable to undergo colonoscopy preoperatively, this procedure should be performed initially 6 months after surgery. Postoperative surveillance is done to identify patients with relapse of colorectal cancer that is pot entially curable by surgery. The risks of radiation exposure and false-positive findings leading to additional tests and possibly invasive procedures must be balanced against the benefits of surveillance studies.

Routine CT scans annually for 10 years is not indicated because most colorectal cancers recur within the first 3 years after surgery, and scanning beyond 3 to 5 years is therefore not warranted.

PET scans may be useful adjuncts to evaluate equivocal abnormalities seen on CT scans; however, they are not recommended for routine surveillance following resection of colorectal cancer and should not be used for this purpose.

A 2007 Cochrane review of follow-up strategies for patients treated for nonmetastatic colorectal cancer concluded that there is an overall survival benefit by intensifying the follow-up of patients after curative surgery, but because of the wide variations in follow-up programs included in the analysis, no conclusion could be drawn about the best combination and frequency of procedures and tests to maximize benefits and minimize

harms. However, the results of this review imply that some intensity of surveillance is more beneficial than observation alone.

Question 94

A 35-year-old man undergoes follow-up evaluation. The patient is asymptomatic. Testicular cancer was diagnosed recently and was treated with radical inguinal orchiectomy and adjuvant bleomycin/etoposide/cisplatin chemotherapy. Treatment was completed 3 months ago. Medical history is otherwise noncontributory, and the patient takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Which of the following treatment -related conditions is this patient most likely to develop?

A

Gastric ulcer

B

Metabolic syndrome

C

Obstructive uropathy

D

Soft-tissue sarcoma

Answer & Critique

Correct Answer: B

Educational Objective: Recognize the risk of treatment-related complications following therapy for testicular cancer.

Key Point

Treatment-related complications in men who had therapy for testicular cancer include cardiovascular disease (specifically metabolic syndrome), kidney disease, peripheral neuropathy, chronic pulmonary toxicity, secondary malignancy, and sexual dysfunction.

This patient is most likely to develop metabolic syndrome. Following treatment of testicular germ cell tumors, men remain at risk for both recurrent cancer and many other long-term medical complications. Although some complications occur during or soon after treatment, others develop years after initial therapy, particularly as many patients are relatively young at the time of diagnosis. The risks for an individual patient are associated with the type of treatment given. Both radiation therapy and chemotherapy are associated with specific risks. Among these is an increased risk for development of metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity). The risk is particularly increased in men treated with combination chemotherapy. Data indicate that the risk for cardiovascular diseases (such as ischemic coronary disease, heart failure, peripheral vascular disease) is also increased in this patient population. Additional risks associated with treatment of testicular cancer that would be relevant to this specific patient include kidney disease, peripheral neuropathy, chronic pulmonary toxicity, secondary malignancy, and sexual dysfunction. Most of these would be evident either during or soon after completion of treatment. Secondary malignancy typically develops years following treatment.

The risk of gastric and duodenal ulcer disease is increased slightly in men treated with radiation therapy, which this patient did not have.

Obstructive uropathy is only rarely associated with treatment of testicular cancer, and that association occurs only in men treated with radiation therapy.

The risk of secondary solid tumors is increased in patients treated for testicular cancer, with the most common sites of involvement being the lung, colon, bladder, pancreas, and stomach. Soft

tissue sarcomas are not commonly reported in these patients in the absence of radiotherapy, which is known to increase the risk of soft tissue sarcoma, typically diagnosed many years after treatment. As the patient in this case was not treated with radiation, he would not be expected to have an increased risk of soft tissue sarcoma.

Question 95

A 48-year-old woman is evaluated for a 6-week history of fatigue and an enlarged right cervical lymph node. She has no significant medical history and takes no medications.

On physical examination, vital signs are normal. A 4-cm firm, enlarged right cervical lymph node is palpated. There is no other lymphadenopathy and no splenomegaly. The remainder of the examination is unremarkable.

Laboratory studies, including complete blood count, erythrocyte sedimentation rate, serum lactate dehydrogenase level, and serum β_2-microglobulin level, are normal.

Lymph node biopsy reveals effacement of the normal architecture by sheets of atypical lymphoid cells. Flow cytometry results are positive for B antigens CD19, CD20, CD22, and CD79a, consistent with diffuse large B-cell lymphoma. CT scans of the chest, abdomen, and pelvis show an isolated enlarged right cervical lymph node but are otherwise normal.

Which of the following is the most appropriate treatment?

A

Allogeneic hematopoietic stem cell transplantation

B

Autologous hematopoietic stem cell transplantation

C

Involved-field radiation therapy

D Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)

Answer & Critique

Correct Answer: D

Educational Objective: Treat diffuse large B-cell lymphoma with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R -CHOP).

Key Point

Standard therapy for all patients with diffuse large B-cell lymphoma, regardless of disease stage or prognosis, is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Standard therapy for all patients with diffuse large B-cell lymphoma (DLBCL), regardless of disease stage or prognosis, includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Acceptable management includes chemotherapy alone or a shorter course of chemotherapy with involved-field radiation in early stage disease. The lymphomas are of B-cell or T-cell phenotype. DLBCL is the most common form of lymphoma and, together with the less common T-cell phenotype, represents 30% of all lymphomas. Most patients with DLBCL present with advanced (stage III and IV) disease and have symptoms including fever, night sweats, and weight loss (“B” symptoms). Disease progression is rapid without therapy. The revised International Prognostic Index (r-IPI) score was developed to assist in determining prognosis before therapy. The r-IPI score is based on the patient's age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status. Because this patient has limited disease and a low r-IPI score, standard R-CHOP chemotherapy should result in a durable complete remission. Expected cure rates range from less than 20% for patients with advanced disease and a high r-IPI score to greater than 80% for those with localized disease and a low r-IPI score. Studies are ongoing regarding the effectiveness of more aggressive initial therapy for patients with advanced disease associated with high r-IPI scores, such as using rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD) and adding novel agents, including immunomodulators such as lenalidomide. However, standard R-CHOP chemotherapy is appropriate for this patient at this time.

Allogeneic hematopoietic stem cell transplantation (HSCT) remains investigational as salvage therapy for patients with DLBCL due to the high risk of morbidity.

Autologous HSCT is reserved as salvage therapy for patients who have chemotherapy-sensitive relapsed disease associated with a greater than 1-year disease-free interval from the start of initial therapy. Early relapse patients have poor outcomes after autologous HSPCT and should be considered for clinical trials.

Involved-field radiation therapy is indicated for patients with bulky disease. This patient has no evidence of bulky disease at this time.

Question 96

A 62-year-old man is evaluated for a 1-month history of nausea, anorexia, right upper quadrant abdominal pain, and a 4.5-kg (10-lb) weight loss. A superficial spreading melanoma of the left thigh, 2.2 mm deep, with one positive sentinel lymph node was diagnosed 1 year ago. The patient declined adjuvant interferon alfa therapy.

On physical examination, vital signs are normal. There is a well-healed 4-cm incision on the upper left anterior thigh and a healed incision in the left inguinal area. Abdominal examination reveals mild right upper quadrant tenderness to palpation, and the liver is palpable 4 cm below the costochondral margin with a nodular, firm edge. The remainder of the examination is normal.

Laboratory studies are significant for alanine aminotransferase of 211 U/L, aspartate aminotransferase of 156 U/L, and serum bilirubin of 1.6 mg/dL (27.4 μmol/L).

CT scan of the abdomen and pelvis shows an enlarged liver with five hypodense lesions in both lobes measuring up to 2.5 cm that are consistent with metastases. There are no ascites, abdominal lymphadenopathy, or splenomegaly. Ultrasound-guided liver biopsy specimens show metastatic melanoma. CT scan of the chest is normal.

Which of the following is the most appropriate next step in management?

A

BRAF V600 mutation analysis

B

Dacarbazine-based chemotherapy

C

High-dose interferon alfa

D

Immunotherapy with ipilimumab

Answer & Critique

Correct Answer: A

Educational Objective: Manage metastatic melanoma with *BRAF* V600 mutation analysis.

Key Point

All patients with metastatic melanoma should have their tumor tested for the presence of a driver V600 *BRAF* mutation. If this mutation is present in patients with poor prognostic features, treatment with a *BRAF* inhibitor is recommended as initial therapy.

The most appropriate next step in management is*BRAF* V600 mutation analysis. Approximately 50% to 70% of cutaneous melanomas carry mutations in*BRAF*, a gene coding for a protein that leads to tumor activation though the mitogen-activated protein kinase (MAPK) pathway; 80% to 90% of these are the V600E mutation, with the remainder being other mutations at the V600 position. Inhibitors of *BRAF* are associated with response rates of over 50% and improved overall and progression-free survival in metastatic melanoma with a V600 mutation. Therefore, all patients with metastatic melanoma should have their tumor tested for the presence of driver V600 *BRAF* mutation to determine whether treatment with a *BRAF* inhibitor is a therapeutic option. Vemurafenib and dabrafenib are the available *BRAF* inhibitors. These agents have a rapid onset of action and are preferred over immunotherapy for initial treatment in patients with poor risk characteristics, including visceral metastases to sites other than the lung, an elevated serum lactate dehydrogenase, or a poor performance status. If a V600 mutation is present in this patient with liver metastases and an elevated serum lactate dehydrogenase, treatment with a *BRAF* inhibitor should be offered as a treatment option.

Chemotherapy with dacarbazine, the only chemotherapeutic agent approved for treatment of metastatic melanoma, has a response rate of only 7% to 12% and has not been shown to improve overall survival. It is usually reserved for patients who are not candidates for high-dose interleukin-2 (IL-2), ipilimumab, or *BRAF* inhibitor therapy.

High-dose interferon alfa is used as adjuvant therapy for patients with nonmetastatic melanoma who are at high risk for recurrence but is inferior to other immunotherapy options, including ipilimumab and high-dose IL-2, for patients with metastatic melanoma.

Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4), which is a normal immune checkpoint molecule that down-regulates pathways of T-cell activation. CTLA-4 inhibition unleashes an immune response against the tumor. In patients with metastatic melanoma, treatment with ipilimumab improves overall survival. However, the response to ipilimumab can be delayed and there can be transient worsening of disease initially. In patients with poor prognostic features and a *BRAF* V600 mutation, the more rapid response of a *BRAF* inhibitor is preferred. If this patient's melanoma does not have a driver *BRAF* mutation, then treatment with ipilimumab would be offered.

Question 97

A 61-year-old woman undergoes routine follow-up evaluation. Stage II colon cancer was diagnosed 3 years ago and was treated with surgical resection. The patient now feels well. She works full time and exercises regularly. Medical history is otherwise unremarkable, and she takes no medications.

Findings on physical examination, including vital signs, are normal.

Routine surveillance CT scans of the chest and abdomen show three new hypodense lesions in the right lobe of the liver, ranging in size from 1 to 3 cm. No other abnormalities are seen.

Which of the following is the most appropriate management?

A

CT-guided needle biopsy of a liver lesion

B

Hepatic artery embolization

C

Palliative systemic chemotherapy

D

Radiation therapy to the liver

E

Right hepatectomy

Answer & Critique

Correct Answer: E

Educational Objective: Treat oligometastatic colorectal cancer by surgical resection.

Key Point

The development of oligometastatic disease (usually to the liver or lung) in a patient who previously was treated for colorectal cancer is potentially curable by surgical resection.

Right hepatectomy is most appropriate for this patient who underwent primary resection for stage II colon cancer 3 years ago and now has three new liver lesions in a surgically resectable pattern. The role of monitoring patients after initial resection is to detect recurrent, surgically curable tumors, such as oligometastatic liver or lung metastases, and monitor for the development of new primary cancer. Monitoring typically includes a physical examination and measurement of serum carcinoembryonic antigen levels every 3 to 6 months for the first 3 years and every 6 months during years 4 and 5. Surveillance CT scans of the chest and abdomen are recommended annually for at least the first 3 years postoperatively. This patient has oligometastatic disease that is potentially curable by surgical resection and should undergo right hepatectomy.

A needle biopsy is not indicated. The clinical presentation is so strongly indicative of metastatic colorectal cancer that a negative needle biopsy would not exclude the diagnosis of cancer and would therefore not alter management. Surgical resection would be warranted regardless of the biopsy results.

Hepatic artery embolization is a palliative technique used to treat patients with more vascular tumors, such as hepatocellular carcinoma and neuroendocrine tumors. It is not routinely used for treatment of metastatic colorectal cancer and would not be an appropriate consideration when a potentially curative alternative such as surgery is available.

Given that this patient's liver metastases are potentially curable, palliative chemotherapy is not indicated.

Radiation therapy is not routinely used to treat liver metastases and would also not be an appropriate consideration for a patient who is a candidate for potentially curative surgery.

Question 98

A 62-year-old man is evaluated for a 4- to 6-week history of passing bright red blood stool. He has no other symptoms. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Abdominal examination is normal; the liver and spleen are not enlarged. Digital rectal examination reveals brown stool that is positive for occult blood.

Colonoscopy reveals a nonobstructing polypoid mass in the sigmoid colon. The remainder of the colon, from the ileocecal valve to the anus, is normal. Biopsy of the mass shows adenocarcinoma.

Which of the following diagnostic studies should be performed next?

A

Bone scan

B

CT colonography

C

CT of the chest, abdomen, and pelvis

D

PET/CT

Answer & Critique

Correct Answer: C

Educational Objective: Determine preoperative staging for a patient with newly diagnosed colorectal cancer.

Key Point

Contrast-enhanced CT scanning of the chest, abdomen, and pelvis is the preferred study for preoperative staging of patients with newly diagnosed colorectal cancer.

Contrast-enhanced CT scanning of the chest, abdomen, and pelvis is the preferred study for preoperative staging of patients with newly diagnosed colorectal cancer. This provides the most reliable means of detecting the presence of metastatic disease to the lungs, liver, intra-abdominal lymph nodes, and peritoneum, which are the most common sites of metastatic spread, and is useful in planning appropriate therapy.

A bone scan is not indicated at this time. Although bone metastases may be present in patients with several other types of cancer at presentation, this finding is extremely rare in patients with newly diagnosed colorectal cancer. Up to 10% of patients with colorectal cancer may develop bone metastases as a late complication of advanced metastatic disease, but evaluation at the time of diagnosis in the absence of specific and compelling symptoms is not warranted.

CT colonography appears to be an acceptable alternative to colonoscopy for screening of otherwise low-risk healthy individuals; however, this study is not part of the staging work-up for a patient with a known cancer diagnosis.

PET/CT scans have not been shown to improve the accuracy of preoperative staging for patients with colorectal cancer and are not recommended for either preoperative staging or postoperative surveillance.

Question 99

A 27-year-old man is evaluated in the emergency department for a 1-week history of bruising and gingival bleeding with flossing. He has no significant medical history and takes no medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 110/80 mm Hg, pulse rate is 80/min, and respiration rate is 14/min. Scattered ecchymoses and cutaneous petechiae are present. There is no lymphadenopathy or splenomegaly.

Laboratory studies:

Leukocyte count	150,000/µL (150 × 10^9/L)
Platelet count	20,000/µL (20 × 10^9/L)
Creatinine	4 mg/dL (353.6 µmol/L)
Fibrinogen	Normal
Phosphorus	8 mg/dL (2.58 mmol/L)
Urate	12 mg/dL (0.71 mmol/L)

Peripheral blood smear shows 70% circulating myeloblasts.

Which of the following is the most appropriate treatment?

A

Fresh frozen plasma

B

High-volume normal saline hydration and rasburicase

C

Multiagent chemotherapy

D

Platelet transfusion

Answer & Critique

Correct Answer: B

Educational Objective: Treat acute tumor lysis syndrome with high-volume normal saline hydration and rasburicase.

Key Point

Patients with spontaneous tumor lysis syndrome in the setting of newly diagnosed leukemia or lymphoma should be emergently treated with high-volume normal saline prior to initiation of chemotherapy; rasburicase should also be administered in the case of kidney failure.

This patient requires treatment with high-volume normal saline and rasburicase because he has spontaneous tumor lysis syndrome triggered by rapid cell turnover from his acute myelogenous leukemia. Malignancies associated with rapid cell turnover can release large quantities of electrolytes and procoagulants into the circulation, causing the potentially life-threatening complication of tumor lysis syndrome. Tumor lysis syndrome may occur spontaneously with some cancers, but most often occurs after the initiation of cytotoxic therapy for tumors with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic agents. Therefore, treatment aimed at preventing tumor lysis syndrome should be considered prior to starting chemotherapy in patients at high risk. In tumor lysis syndrome, rapid cell breakdown results in hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and disseminated intravascular coagulation (DIC). Hyperuricemia can lead to urate nephropathy and acute kidney injury. Prevention or treatment involves aggressive hydration with normal saline to maintain renal perfusion and minimize uric acid or calcium phosphate deposition in the renal tubules. Because this patient already has evidence of kidney failure, hydration must be undertaken carefully to prevent significant volume overload. Hypouricemic agents are also indicated. Allopurinol is a competitive inhibitor of xanthine oxidase, which decreases the formation of new uric acid. Rasburicase is a urate oxidase (uricase) that catalyzes the breakdown of existing uric acid. Allopurinol is typically used in patients for prophylaxis for tumor lysis syndrome and in those without existing significant (>8 mg/dL [0.47 mmol/L]) elevations of serum urate. The more expensive rasburicase is usually used in patients with significantly elevated serum urate levels or in those with baseline kidney failure or in those with evidence of kidney injury related to tumor lysis, in order to rapidly decrease the serum urate level.

Fresh frozen plasma may be indicated if the patient develops DIC after initiating chemotherapy with resultant depletion of procoagulant. However, fresh frozen plasma would not treat tumor lysis syndrome and is only indicated when DIC is present. Based on this patient's normal serum fibrinogen level, this patient does not have DIC.

The initiation of multiagent chemotherapy prior to aggressive hydration and treatment with rasburicase is contraindicated in this patient who has acute kidney failure, likely due to tumor lysis syndrome, to prevent life threatening electrolyte abnormalities (such as hyperkalemia) associated with chemotherapy.

Platelet transfusions are indicated only for patients whose platelet count is less than 10,000/?L (10×10^9/L) or who develop spontaneous bleeding.

Question 100

A 32-year-old woman undergoes postoperative follow-up evaluation. The patient was diagnosed with a 1.9-cm, stage II, estrogen receptor–positive, progesterone receptor–positive, *HER2*-positive grade 3 invasive ductal carcinoma of the left breast, with 2/6 positive lymph nodes. She underwent breast excision 2 weeks ago. Medical history is otherwise noncontributory. She and her husband have one child and wish to have additional children.

On physical examination, vital signs are normal. There is a healing left breast incision. There is no lymphadenopathy. The remainder of the examination is unremarkable.

Laboratory studies are normal.

Which of the following is the most appropriate next step in the management of this patient?

A

Begin adjuvant chemotherapy without trastuzumab

B

Delay chemotherapy until after further childbearing

C

Recommend embryo cryopreservation before chemotherapy

D

Advise against further pregnancies

Answer & Critique

Correct Answer: C

Educational Objective: Manage preservation of fertility in a patient about to start chemotherapy for stage II breast cancer.

Key Point

Women being treated for breast cancer who wish to preserve fertility should be referred to a fertility specialist to discuss embryo cryopreservation or other fertility preservation methods before adjuvant chemotherapy is initiated.

Embryo cryopreservation or other fertility preservation methods before chemotherapy should be recommended to this patient who wishes to have additional children. She has stage II breast cancer that is hormone receptor positive and *HER2*positive. Adjuvant chemotherapy with trastuzumab should be started within 4 to 6 weeks of surgery. Although infertility effects of chemotherapy are age-, dose-, and drug-dependent, with younger women being affected less often than older women, patients of any age can become infertile, particularly after taking cyclophosphamide. Starting adjuvant chemotherapy and trastuzumab now will result in infertility in a significant percentage of women and is not the best option for this patient who desires continued fertility.

Fertility preservation is almost always done with the assistance of a fertility specialist with expertise in fertility preservation procedures and can usually be completed within a few weeks. An established fertility preservation option for a woman with a partner is in vitro fertilization with embryo freezing. Newer options, often done as part of clinical trials, include freezing of unfertilized eggs and ovarian cryopreservation with future reimplantation.

Trastuzumab does not cause infertility. It is the chemotherapy itself that can result in premature menopause and infertility. Adding trastuzumab to chemotherapy as adjuvant treatment for *HER2*-positive breast cancer decreases the risk of recurrence by 50% and should be included in this patient's adjuvant regimen.

Delaying chemotherapy until after the patient completes further childbearing will result in a higher risk of distant recurrence and is not a safe option. Studies evaluating the ideal sequence of adjuvant chemotherapy and primary breast radiation showed that giving chemotherapy after

radiation was associated with a higher risk of systemic recurrence. Based on these studies, a delay of more than 12 weeks in starting adjuvant chemotherapy may be detrimental and should be avoided.

There is no reason to recommend against future pregnancies in this patient. Several large retrospective studies have shown that breast cancer recurrence is not increased and survival is not decreased in breast cancer survivors who become pregnant, including patients with hormone receptor–positive cancers.

Question 101

A 64-year-old man is evaluated for a 2-month history of increasing abdominal discomfort, right upper quadrant abdominal pain, and decreased appetite. He has lost 2.5 kg (5.5 lb) during this time. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 29. A 3-cm left supraclavicular lymph node is palpated. The abdomen is moderately distended, soft, and nontender. The liver is enlarged on palpation. Testicular examination is unremarkable. A digital rectal examination shows a normal rectum and moderately enlarged prostate without nodularity. A stool sample is negative for occult blood.

Laboratory studies are significant for a serum alkaline phosphatase level of 340 U/L, serum total bilirubin level of 1.3 mg/dL (22.2 μmol/L), and serum creatinine level of 0.7 mg/dL (61.9 μmol/L).

CT scans of the chest, abdomen, and pelvis show extensive metastases scattered throughout the liver, with enlarged periportal and retroperitoneal lymph nodes measuring up to 4 cm in diameter and no bony metastases. CT-guided needle biopsy of the liver shows moderately differentiated adenocarcinoma. Upper endoscopy and colonoscopy are normal.

Treatment for which of the following malignancies would be most appropriate?

A

Gastrointestinal

B

Germ cell (testicular)

C

Lung

D

Neuroendocrine

E

Prostate

Answer & Critique

Correct Answer: A

Educational Objective: Treat adenocarcinoma of unknown primary site predominantly below the diaphragm in the same manner as a gastrointestinal malignancy.

Key Point

When adenocarcinoma of unknown primary site presents in a pattern predominantly below the diaphragm, even when upper endoscopy and colonoscopy findings are normal, empiric treatment for a gastrointestinal malignancy is appropriate.

This patient should be treated for a gastrointestinal malignancy. He has a moderately differentiated adenocarcinoma of unknown primary site, with most of the disease occurring below the diaphragm. When adenocarcinoma of unknown primary site presents in a pattern predominantly below the diaphragm, even when upper endoscopy and colonoscopy findings are normal, empiric treatment for a gastrointestinal malignancy is appropriate.

Platinum-based chemotherapy regimens such as carboplatin plus paclitaxel or cisplatin plus etoposide would be reasonable for treating patients with a poorly differentiated cancer of unknown primary site (CUP), such as a germ cell (testicular) tumor. This patient's biopsy findings, which show adenocarcinoma with moderately differentiated histology, do not support empiric treatment for germ cell cancer.

Empiric lung cancer regimens may be used to treat patients with CUP occurring above the diaphragm. Because this patient has no evidence of involvement of the lungs, treatment using a lung cancer paradigm is not indicated.

Platinum-based chemotherapy regimens such as carboplatin plus paclitaxel or cisplatin plus etoposide would be reasonable for treating patients with a poorly differentiated neuroendocrine CUP. However, this patient's biopsy findings do not support a diagnosis of neuroendocrine cancer.

Antiandrogen therapy, which may have potential activity against prostate cancer, may be considered in male patients with extensive bone metastases, but that is not the case in this patient.

Question 102

A 60-year-old woman is evaluated for a 5-year history of asymptomatic, intermittently enlarged lymph nodes. She has no other significant medical history and takes no medications.

On physical examination, the patient is afebrile, blood pressure is 140/85 mm Hg, pulse rate is 76/min, and respiration rate is 12/min. Enlarged cervical, axillary, and epitrochlear lymph nodes are palpated. There is no splenomegaly. The remainder of the examination is unremarkable.

Complete blood count and peripheral blood smear are normal. Chest radiograph is normal. CT scans show no evidence of mediastinal, abdominal, or pelvic lymphadenopathy.

A lymph node biopsy reveals a CD20-positive grade II follicular lymphoma, and a bone marrow biopsy shows infiltration with small CD20-positive lymphocytes representing 20% of the cellular elements. Fluorescence in situ hybridization analysis shows the presence of the *BCL2* oncogene.

Which of the following is the most appropriate treatment?

A

Lenalidomide

B

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)

C

Rituximab

D

Rituximab plus involved-field radiation therapy

E

Observation

Answer & Critique

Correct Answer: E

Educational Objective: Treat a patient with asymptomatic, nonbulky follicular lymphoma.

Key Point

Early treatment does not improve survival in patients with grade 1 and 2 follicular lymphoma.

Observation is most appropriate for this 60-year-old asymptomatic patient with follicular lymphoma who has nonbulky disease, no vital organ involvement or impingement, and a normal complete blood count. Follicular lymphoma accounts for 20% of all cases of non-Hodgkin lymphoma (NHL) in the United States and Europe and 70% of all indolent NHL, ranking second in incidence to diffuse large-cell lymphoma (30%). It is characterized by surface B-cell markers (CD10, 19, 20, and 22) and small cells on morphologic analysis. The incidence increases with age, and the median age at presentation is 60 years. There is no sex predilection. Diagnosis is confirmed by biopsy of palpable lymph nodes and cytogenetic studies showing a translocation [t(11:18)] that causes overexpression of the *BCL2* oncogene. Therapy is not curative, and early initiation of treatment does not improve survival in patients with grade 1 and 2 follicular lymphoma. Treatment is therefore withheld until patients become symptomatic. Some patients do not require therapy for several decades after the initial diagnosis.

Lenalidomide, used in combination with rituximab, is a new therapy that may be effective for patients with advanced symptomatic disease, which this patient does not have.

Systemic disease–causing symptoms require multiagent therapy that traditionally includes one of three combinations: (1) rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (2) rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or (3) rituximab plus bendamustine. Radioimmunoconjugates (tositumomab and ibritumomab) have been used effectively to induce long-term remissions. Any of these approaches are suitable for patients requiring treatment.

Lymphoma causing localized symptoms can be treated effectively with involved-field radiation therapy in combination with rituximab, but such treatment is not yet needed for this patient.

Question 103

A 44-year-old woman is evaluated for a 2-month history of a painless right neck mass. Medical history is unremarkable, and she takes no medications. She is a lifelong nonsmoker.

On physical examination, vital signs are normal. A 5-cm right anterior neck mass is palpated. The remainder of the examination is unremarkable.

An initial CT scan of the neck shows a 4.5-cm, partially necrotic, right-sided lymph node. Asymmetric thickening of the right base of the tongue is also seen. Subsequent laryngoscopy shows an ulcerated mass involving the right base of the tongue. Biopsy of the tongue mass identifies poorly differentiated invasive squamous cell carcinoma. PET/CT scans show no evidence of distant metastases.

Which of the following studies should be performed next?

A

Bone scan

B

Human papillomavirus immunohistochemistry testing

C

MRI of the brain

D

Right cervical lymph node biopsy

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose human papillomavirus infection in a patient with head and neck cancer.

Key Point

p16 immunohistochemistry testing to detect human papillomavirus is now a widely accepted standard-of-care intervention to help determine prognosis in patients with squamous cell carcinoma of the head and neck, particularly those with oropharyngeal primary tumors.

The most appropriate study to perform next in this patient is p16 immunohistochemistry testing. Although most squamous cell carcinomas of the head and neck were previously thought to be related primarily to tobacco and alcohol exposure, very recently, the important causative role played by human papillomavirus (HPV) has been widely recognized. HPV infection has definitively been associated with squamous cell carcinoma of the cervix for some time, and currently, it is estimated that most oropharyngeal cancers in North America and Europe are also linked to this infection. Evidence of underlying HPV infection is identified by testing for p16, which is a viral protein found in cancers that arise as a result of HPV infection. Although identifying evidence of HPV infection does not yet influence treatment decision-making, it does provide very important information regarding prognosis. The cure rate for locally advanced cancers that are linked with HPV is markedly higher than for those not linked with this virus. Because of this difference, testing for HPV is now a widely accepted intervention for any patient diagnosed with squamous cell carcinoma of the head and neck, particularly for patients with an oropharyngeal primary tumor.

A bone scan has no role in the management of this patient, as PET/CT scans have already been done. In addition, she has no indications for underlying bone metastasis based on her history.

MRI of the brain is not indicated because occult central nervous system metastases are very rare in patients with head and neck cancer, and this patient has no clinical indication of underlying brain metastasis.

Biopsy of the enlarged right cervical lymph node would provide no additional information, as the diagnosis has already been established based on biopsy of the lesion at the base of the tongue. Furthermore, because the cervical lymph node is so markedly enlarged, biopsy is not needed to establish involvement.

Question 104

A 72-year-old man is evaluated in the emergency department for a 3-week history of headache and facial swelling and a 2-week history of shortness of breath.

On physical examination, the patient is afebrile, blood pressure is normal, pulse rate is 104/min, and respiration rate is 22/min. Oxygen saturation is 90% on ambient air. Diffuse facial erythema is present, and neck veins are dilated bilaterally.

CT scan of the chest shows a 7-cm medial left lung mass and bulky mediastinal lymphadenopathy. Superior vena cava compression with associated collateral vessels is also identified. MRI of the brain is negative.

Which of the following is the most appropriate management?

A

Biopsy of the lung mass

B

Immediate radiation therapy

C

Placement of a superior vena cava stent

D

Venography

Answer & Critique

Correct Answer: A

Educational Objective: Manage a patient with lung cancer and superior vena cava syndrome.

Key Point

In patients with apparent malignant superior vena cava syndrome, a histologic diagnosis should be established, whenever possible, before treatment is begun.

Biopsy of the lung mass to obtain a histologic diagnosis is indicated. This patient has superior vena cava (SVC) syndrome, which is caused by inhibition of blood flow through the SVC or one of its major tributaries. The syndrome may occur in patients with both malignant and nonmalignant conditions. Cancers more commonly associated with SVC syndrome include lung cancer (both small cell and non–small cell lung cancer accounting for 65% of cases), aggressive lymphoma, thymoma, and primary mediastinal germ cell tumors. Nonmalignant causes include thrombosis and fibrosing mediastinitis. Presenting symptoms typically develop over weeks and include dyspnea, facial swelling, headache, and in more severe cases, stridor or mental status changes. The most common radiographic findings include mediastinal widening and pleural effusion; however, 16% of patients have a normal chest radiograph. Although in the past emphasis was placed on immediate treatment, current management emphasizes the importance of obtaining a histologic diagnosis, whenever possible, in patients with apparent malignant SVC syndrome. This allows for accurate decision-making regarding treatment of the underlying malignancy. Mediastinoscopy is routinely used to obtain tissue biopsy samples for histologic diagnosis. The complication rate from this procedure is only 5% in patients with SVC syndrome. Percutaneous transthoracic CT-guided needle biopsy appears to be a safe alternative to mediastinoscopy and has a sensitivity of 75%.

Although the patient clearly has SVC syndrome, he does not have stridor, laryngeal edema, or mental status decline. Immediate radiation therapy or stent placement is therefore not indicated.

Venography to identify a possible thrombosis is not indicated because the SVC syndrome in this patient is caused by external compression from a mediastinal mass and lymphadenopathy rather than by a thrombotic disorder.

Question 105

A 65-year-old woman is evaluated for aching pain in the bilateral hips, knees, and ankles.

Two years ago she was diagnosed with estrogen and progesterone receptor–positive, *HER2*-negative, stage IIIA cancer of the left breast, with 4 positive lymph nodes. She received adjuvant chemotherapy, breast radiation, and anastrozole. After eight months of anastrozole, she experienced severe arthralgia in her knees, hips, and ankles, worse in the morning and after sitting. Anastrozole was stopped for 3 weeks, and her symptoms markedly improved. Letrozole was then started. Now 4 months after beginning letrozole, her joint pains have recurred and are again debilitating. NSAIDs do not provide relief.

On physical examination, vital signs are normal. Well-healed bilateral mastectomy incisions are present without nodularity. There is no lymphadenopathy. The remainder of the physical examination is unremarkable.

In addition to discontinuing the letrozole, which of the following is the most appropriate management?

A

Obtain PET scan

B

Prednisone

C

Restart anastrozole

D

Start tamoxifen

Answer & Critique

Correct Answer: D

Educational Objective: Manage aromatase inhibitor arthralgia in a patient with aggressive breast cancer who requires antiestrogen therapy.

Key Point

In patients with aggressive breast cancer who develop severe arthralgia while on antiestrogen therapy due to an aromatase inhibitor, a second aromatase inhibitor should be tried; if the arthralgia fails to resolve, tamoxifen should be started.

This patient should be started on tamoxifen. She has aggressive stage IIIA breast cancer with four positive axillary lymph nodes. With adjuvant chemotherapy alone, she remains at high risk for recurrence and should receive at least 5 years of antiestrogen therapy, ideally with at least 2 years of an aromatase inhibitor, if tolerated. As aromatase inhibitors may be associated with debilitating musculoskeletal symptoms, such as arthralgia in this patient, these agents should be discontinued if patients cannot tolerate them and tamoxifen should be started as an alternative antiestrogen therapy.

Approximately one third of patients taking aromatase inhibitors develop intolerable adverse effects that lead to discontinuation of these agents. In one study, 22% of all patients stopped taking these drugs following development of the aromatase inhibitor–induced arthralgia syndrome (AIIAS). Predictors of AIIAS include younger age, prior taxane chemotherapy, and a history of pre-existing joint pain. The cause of the musculoskeletal symptoms, which can occur in the upper or lower extremities, is unknown. This patient's symptoms of joint pain that are symmetric, bilateral, and worse when lying down or sitting are very typical of AIIAS.

Her symptoms are not concerning for metastases, especially because the arthralgia resolved when aromatase inhibitors were discontinued. Therefore, a PET scan is not indicated at this time.

For patients whose aromatase inhibitor–induced arthralgia does not respond to NSAIDs, treatment with duloxetine has been of benefit in clinical trials and is under further study. There is no known benefit to using prednisone for AIIAS. The Hormones and Physical Exercise (HOPE) trial showed that a regular exercise program can ameliorate arthralgia caused by aromatase inhibitors.

Restarting anastrozole will almost certainly cause the same intolerable arthralgia and is therefore not indicated. In one prospective trial of patients with AIIAS, stopping the initial aromatase inhibitor for 2 to 8 weeks and then switching to an alternate aromatase inhibitor resulted in 40% of patients being able to continue with the alternate agent. No studies to date support recommending a third attempt at use of aromatase inhibitor therapy.

Question 106

A 76-year-old woman is evaluated for a 3-month history of abdominal pain and weight loss. She has also had a nonproductive cough for several weeks. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 22. A firm 3-cm left supraclavicular lymph node is palpated. Abdominal examination reveals a liver edge that is palpable 3 cm below the right costal margin. On digital rectal examination, a stool sample is positive for trace occult blood.

Contrast-enhanced CT scans of the chest and abdomen show multiple lung and liver metastases and a mass in the transverse colon. Biopsy of the mass obtained during colonoscopy reveals adenocarcinoma.

Which of the following diagnostic studies should be performed next?

A

K-*ras* and N-*ras* genotyping of the tumor

B

Measurement of serum dihydropyrimidine dehydrogenase (DPD) level

C

Measurement of serum *UGT1A1* level

D

Multigene array analysis of the tumor for prognostic markers

Answer & Critique

Correct Answer: A

Educational Objective: Manage metastatic colorectal cancer with K-*ras* and N-*ras* genotyping of the tumor.

Key Point

Mutations in the K-*ras* or N-*ras* genes, present in approximately 50% of colorectal cancers, are associated with resistance to epidermal growth factor receptor–targeted agents (cetuximab, panitumumab).

This patient has metastatic colorectal cancer, and K-*ras* and N-*ras* genotyping of the tumor biopsy sample is necessary for treatment planning. The presence of multiple lung and liver metastases is not amenable to surgical resection and, as such, is incurable. In these cases, the goal of treatment is to extend survival and palliate symptoms. The increased number of chemotherapy options that are effective against metastatic colorectal cancer has prolonged median survival for patients with incurable disease from a median survival of 6 months without chemotherapy, to 12 months with 5-fluorouracil alone, to approximately 2 years with multiagent chemotherapy. This patient will likely benefit from systemic chemotherapy; the use of multiple chemotherapy agents can be anticipated, and all agents with demonstrated activity in colorectal cancer need to be considered. One consideration in planning treatment is determining whether the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab can be included in the treatment plan. Approximately 50% of colorectal cancers have a mutation in the K-*ras*or N-*ras* genes. Tumors that carry these mutations will not respond to anti-EGFR agents, and patients with these tumors are therefore not candidates for treatment with these drugs.

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the catabolism of 5-fluorouracil. Although assays are commercially available to measure DPD levels, these assays do not inform management and have no role in the routine treatment of patients with colorectal cancer at this time.

Patients with specific *UGT1A1* polymorphisms are more prone to irinotecan toxicity. Although commercial assays are also available to detect this polymorphism, they also do not inform management and are not indicated when treating patients with colorectal cancer at this time.

Multigene array prognostic assays are commercially available but also do not guide clinical decision making and therefore are not currently part of the routine management of patients with colorectal cancer.

Question 107

A 68-year-old man requests evaluation for prostate cancer. He is asymptomatic. Following a discussion of the risks and benefits of prostate cancer screening, the patient decides to be screened.

Physical examination findings are normal. Digital rectal examination is normal.

Serum prostate-specific antigen level is 5.8 ng/mL (5.8 µg/L).

Transrectal ultrasound–guided prostate biopsy is done and shows adenocarcinoma in 2/12 cores, confined to the right lobe (Gleason score: 3 + 3 = 6).

Which of the following diagnostic imaging studies should be done next?

A

Bone scan

B

CT of the chest, abdomen, and pelvis

C

Immunoscintigraphy

D

PET/CT

E

No imaging studies are needed

Answer & Critique

Correct Answer: E

Educational Objective: Determine need for diagnostic imaging studies in a patient with low-risk prostate cancer.

Key Point

Imaging studies are not indicated for men with newly diagnosed early-stage prostate cancer in the absence of symptoms or other high-risk features.

No imaging studies are indicated at this time. The United States Preventive Services Task Force has concluded that the harms of screening for prostate cancer outweigh the benefits in men of any age regardless of risk factors. In contrast, the American Cancer Society and American Urological Association recommend offering both serum prostate-specific antigen (PSA) measurement and digital rectal examination to men annually beginning at the age of 50 years. The American College of Physicians and American Academy of Family Physicians both recommend that clinicians have individualized discussions with their patients regarding obtaining PSA measurements and support measuring PSA levels after such discussions in patients 50 years and older who have life expectancies of at least 10 years. This patient has low-risk prostate cancer based on the presence of a TNM stage T1c tumor (identified after an elevated screening serum PSA level is found in the absence of symptoms), a serum PSA level less than 10 ng/mL (10 µg/L), and a Gleason score less than 8. Imaging studies are currently not recommended for men with low-risk disease, as there is no evidence that such studies reliably alter management decisions.

Prostate cancer is among the most commonly diagnosed cancers in men in the United States. Most men are diagnosed with clinically occult cancer, which is identified on the basis of an abnormal serum PSA value. Most often, there are no symptoms or indicative physical findings as in the patient described here. Once the diagnosis of prostate cancer is made, the focus moves to assessment and treatment decision making. The role of imaging studies in men diagnosed with prostate cancer is to assess disease status, particularly the presence of metastatic disease. Imaging studies are indicated to evaluate symptoms suggestive of metastatic disease and also to evaluate patients at high risk for occult metastatic disease. Currently accepted parameters for imaging studies include a serum PSA level of 20 ng/mL (20 µg/L) or higher, a PSA level of 10 ng/mL (10 µg/L) or higher associated with a T2 tumor, a Gleason score of 8 or higher, or a T3 or T4 tumor.

Question 108

A 38-year-old man is evaluated for a pigmented lesion on his upper left back. The lesion has been increasing in size over the past 2 months. He is otherwise asymptomatic. Medical history is unremarkable.

On physical examination, vital signs are normal. A 1.8-cm, irregular, dark, pigmented, slightly raised papule with irregular borders is present on his upper back. There are no adjacent lesions and no associated lymphadenopathy. The remainder of the examination is unremarkable.

Skin biopsy shows malignant melanoma, superficial spreading type, and measuring 1.4 mm in thickness, with invasion into the reticular dermis but not into the subcutaneous tissue. Dermal mitotic figures are not identified, and there is no lymphovascular invasion. Tumor extends to the lateral and deep margins of the excision. There is evidence of a vertical growth phase.

In addition to complete excision with a 2 -cm margin, which of the following is the most appropriate treatment?

A

Adjuvant chemotherapy

B

Adjuvant interferon alfa

C

Sentinel lymph node biopsy

D

No further therapy

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient with a newly diagnosed intermediate-thickness melanoma.

Key Point

Sentinel lymph node biopsy is recommended for patients with melanomas of 1- to 4-mm thickness to provide accurate staging, as metastasis to regional lymph nodes is the most important prognostic factor in patients with early-stage melanoma.

Sentinel lymph node biopsy is recommended for patients with melanomas of 1- to 4-mm thickness to provide accurate staging. It is also recommended for lesions less than 1 mm with certain high-risk features, such as ulceration, more than 1 mitosis/mm^2, or lymphovascular invasion. A 2-cm excision margin is appropriate for melanomas that are 1 mm thick or deeper. Metastasis to regional lymph nodes is the most important prognostic factor in early-stage melanoma and is found in 20% of patients with intermediate-thickness melanomas. Patients with intermediate-thickness melanomas have an average 5-year survival of 70% if lymph nodes are negative but only 45% if positive lymph nodes are present. If a positive sentinel lymph node is found, complete lymphadenectomy is recommended, which improves regional disease control. However, it is not known whether this procedure improves overall survival.

Adjuvant chemotherapy is not of benefit in treating melanomas. Palliative chemotherapy can be used for metastatic melanomas, although immunotherapy or targeted treatments offer improved efficacy and are usually recommended instead for advanced disease.

Whether to recommend adjuvant interferon alfa is guided by lymph node status. Adjuvant interferon alfa is an option for patients with positive lymph nodes and/or melanomas that are 4 mm or more thick. In these high-risk patients who have a 25% to 75% risk of dying of metastatic melanoma, adjuvant interferon alfa improves relapse-free survival, with less clear benefit for overall survival. Adjuvant interferon alfa would only be recommended for this patient if lymph node involvement is present.

A meta-analysis showed an improvement in disease-free and overall survival with adjuvant interferon alfa. However, in one of the largest trials, the improvement in overall survival was lost

with more prolonged follow-up. Given the toxicities of interferon alfa, including fatigue, myalgia, fever, depression, and autoimmune disease, participation in clinical trials of newer agents is encouraged as an alternative option. Observation alone is also reasonable.

Because of important staging and prognostic information, as well as guidance for potential additional treatment options obtained from a sentinel lymph node biopsy in patients with intermediate-thickness melanoma, performing no further testing would be inappropriate.

Question 109

A 69-year-old man undergoes follow-up evaluation. He was diagnosed with stage II colon cancer 3 years ago, and surgical resection was performed. The patient has been followed since then without additional treatment. He has no other medical problems and takes no medications.

Physical examination findings, including vital signs, are normal.

Follow-up contrast-enhanced CT scans of the chest and abdomen show two new hypodense lesions (6 cm and 4 cm) confined to the right lobe of the liver, with the larger lesion located close to hilum but without evidence of vascular invasion. No other metastases or additional abnormalities are identified.

The patient is evaluated by an experienced liver surgeon who believes that the larger lesion is unresectable due to its close proximity to the middle hepatic vein.

Laboratory studies, including measures of liver and kidney function, are normal.

Which of the following is the most appropriate approach to providing chemotherapy in this patient?

A

Adjuvant chemotherapy

B

Conversion chemotherapy

C

Neoadjuvant chemotherapy

D

Palliative chemotherapy

E

No chemotherapy

Answer & Critique

Correct Answer: B

Educational Objective: Understand chemotherapy terminology.

Key Point

Conversion chemotherapy is given to patients with unresectable tumors in an attempt to shrink the tumor to a resectable size. Neoadjuvant and adjuvant chemotherapies are given before or after curative-intent surgery, respectively, for tumors that are resectable at presentation.

This patient should receive conversion chemotherapy for his currently unresectable tumor. Conversion chemotherapy is given for the purpose of shrinking a tumor that is unresectable usually due to its location, often because of proximity to significant vascular structures as in this patient. Through shrinkage of the tumor with conversion chemotherapy, an adequate plane of resection between the tumor and the middle hepatic vein may become available, allowing complete removal of the tumor. This is particularly important in this patient with localized metastatic colon cancer. Although metastatic colorectal cancer is generally considered treatable but not curable, some patients with metastatic disease confined to a single organ (usually the liver or lung) may be amenable to surgical resection, and complete removal of all gross disease may be curative. Patients with a limited number of liver-only lesions, such as this patient, have been reported to have long-term disease-free survival rates of 25% to 50%.

Adjuvant chemotherapy is the term used for treatment given *after* resection of a tumor is performed with curative intent. The purpose of adjuvant chemotherapy is to eradicate any residual microscopic metastatic disease that might still be present outside of the surgical field. Adjuvant chemotherapy would not be possible in this patient with currently unresectable disease.

Neoadjuvant chemotherapy is similar to adjuvant chemotherapy in that it is given in the setting of curative-intent surgery; however, neoadjuvant therapy is given *before* surgery in an attempt to eradicate any unseen micrometastases that might be present outside of the surgical field. Although neoadjuvant chemotherapy may have the effect of tumor shrinkage, it differs from conversion chemotherapy in that it is given in patients who have resectable disease preoperatively.

Palliative chemotherapy is given to a patient with incurable, unresectable cancer and is given without realistic curative intent. Palliative chemotherapy may be administered for the purposes of possibly prolonging survival and/or controlling tumor-related symptoms.

Because chemotherapy may increase the opportunity for cure in this clinical setting, it would be inappropriate to not offer this treatment option.

Question 110

A 49-year-old woman is evaluated for a 3-month history of abdominal discomfort and fatigue. She has recently noted increasing abdominal girth despite a decreased appetite. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 29. Cardiopulmonary examination is normal. The abdomen is moderately distended, soft, and nontender with shifting dullness consistent with ascites.

CT scans of the chest, abdomen, and pelvis are consistent with abdominal carcinomatosis with omental masses and ascites. No adnexal masses are seen.

Which of the following is the most appropriate management?

A

Cytoreductive surgery followed by systemic chemotherapy

B

Intraperitoneal chemotherapy

C

Omental mass biopsy followed by pelvic radiation therapy and chemotherapy

D

Ovarian biopsy followed by systemic chemotherapy

E

Supportive comfort-oriented care

Answer & Critique

Correct Answer: A

Educational Objective: Treat women with abdominal carcinomatosis of unknown primary site in the same manner as ovarian cancer.

Key Point

Women with cancer of unknown primary site presenting as abdominal carcinomatosis and ascites are classified as a favorable prognostic subgroup and should be treated as if they have ovarian cancer.

Cytoreductive surgery followed by systemic chemotherapy is most appropriate in this patient with abdominal carcinomatosis due to cancer of unknown primary site (CUP). When evaluating a patient with CUP, it is important to identify whether the CUP is of a favorable or unfavorable prognostic subgroup to help guide management. Women with CUP presenting as abdominal carcinomatosis and ascites are classified as a favorable prognostic subgroup and should be assumed to have ovarian cancer until proved otherwise. Treatment is the same as for primary ovarian cancer and includes cytoreductive surgery (tumor debulking along with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, selective lymphadenectomy, and appendectomy, as well as administration of a platinum/taxane-containing chemotherapy regimen).

Ovarian cancer is unique in that its spread is mostly confined to the peritoneal cavity. The use of adjuvant intraperitoneal chemotherapy plus intravenous chemotherapy offers a survival advantage to intravenous chemotherapy alone. However, this survival advantage is associated with substantially increased toxicity. Combined intraperitoneal and intravenous chemotherapy without cytoreduction surgery is not adequate therapy for patients with CUP presenting as ovarian cancer–like disease.

Radiation therapy and concurrent chemotherapy are recommended for patients with stage IB through stage IV cervical cancer, as large randomized clinical trials have confirmed a survival advantage with this combined approach. This approach is not effective for patients with peritoneal carcinomatosis and ascites.

Systemic chemotherapy without cytoreductive surgery would be inadequate as the initial treatment of a patient with an ovarian cancer–like presentation.

Because this patient has a significant chance of meaningful benefit from treatment and has no comorbidities, providing only supportive care would be inappropriate.

Question 111

A 70-year-old man undergoes follow-up evaluation to determine treatment options following a third occurrence of bladder cancer. High-grade transitional cell carcinoma of the bladder was initially diagnosed 7 months ago following cystoscopy to evaluate painless hematuria. Transurethral resection of the bladder tumor (TURBT) was performed followed by administration of intravesical bacillus Calmette-Guérin (BCG). Three months later, surveillance cystoscopy identified recurrent superficial high-grade transitional cell carcinoma in the same location that was again treated with TURBT and BCG. Now, 4 months following the second episode, high-grade transitional cell carcinoma is again diagnosed. This time, the cancer is in the same location with an additional focus near the trigone. No evidence of invasion into the muscle layer of the bladder has ever been identified.

Physical examination findings, including vital signs, are normal.

CT scans of the abdomen and pelvis (done at the time of the second recurrence) identified no evidence of significant bladder wall thickening, regional lymphadenopathy, or evidence of metastatic disease.

Which of the following is the most appropriate treatment at this time?

A

Chemotherapy

B

Cystectomy

C

External-beam radiation therapy

D

TURBT followed by intravesical BCG

Answer & Critique

Correct Answer: B

Educational Objective: Treat recurrent superficial bladder cancer with cystectomy.

Key Point

Cystectomy is indicated for patients who develop recurrence of superficial bladder cancer within 6 to12 months of undergoing initial transurethral resection of bladder tumor or after receiving one to two courses of intravesical bacillus Calmette-Guérin.

Cystectomy without prior chemotherapy is most appropriate for this patient who has superficial bladder cancer. Superficial bladder cancer is the most common form of bladder cancer and is characterized by cancer cells confined to the mucosa, with no evidence of invasion into the muscle layer of the bladder. It is best managed by transurethral resection of the bladder tumor (TURBT), followed in most patients by either bacillus Calmette-Guérin (BCG) or mitomycin infused directly into the bladder. Although this treatment is effective in eradicating superficial bladder cancer, recurrences are common. Careful observation with serial cystoscopy is therefore essential. Many patients with recurrent superficial bladder cancer can be managed with repeat TURBT and additional intravesical infusion. However, patients who develop recurrence within 6 to 12 months of initial TURBT, or after one to two courses of BCG infusion (such as the patient described here), should undergo cystectomy. Cystectomy in this setting is associated with improved disease-specific survival. This procedure is not indicated in the initial management of superficial bladder cancer unless patients have ongoing tumor-related symptoms that cannot be managed with TURBT alone or if they are subsequently found to have muscle-invasive disease.

Systemic chemotherapy, although used prior to cystectomy for patients with muscle-invasive disease, has no role in the treatment of patients with superficial bladder cancer who are to undergo cystectomy.

External-beam radiation therapy has no established role in the treatment of superficial bladder cancer.

Repeat TURBT and BCG infusion is not indicated because this treatment has already been ineffective on two occasions.

Question 112

A 48-year-old man is evaluated for a 3-month history of dyspepsia, increasing episodes of nausea, and fatigue. He is maintaining adequate caloric intake and is continuing to work and participate in all routine daily activities, albeit with some increased fatigue.

On physical examination, the patient is afebrile, blood pressure is 115/70 mm Hg, pulse rate is 72/min, and respiration rate is 10/min. BMI is 26. A firm liver edge is palpated 5 cm below the right costal margin. The remainder of the examination is unremarkable.

Upper endoscopy reveals a mass arising in the wall of the proximal stomach just below the gastroesophageal junction. Biopsy of the mass reveals adenocarcinoma. CT scans of the chest and abdomen show multiple liver metastases and evidence of peritoneal carcinomatosis.

Before selecting a systemic chemotherapy regimen, which of the following information about the tumor biops y specimen would be most helpful?

A

BRAF mutational status

B

Estrogen and progesterone receptor status

C

HER2 expression status

D

K-*ras* mutational status

Answer & Critique

Correct Answer: C

Educational Objective: Evaluate *HER2* expression status in a patient with metastatic gastric cancer.

Key Point

Determination of *HER2* tumor status is indicated for patients with newly diagnosed metastatic gastric cancer, as the anti-*HER2*monoclonal antibody trastuzumab, when added to a systemic chemotherapy regimen, is beneficial in treating patients whose tumors overexpress *HER2*.

HER2 expression status should be determined in this patient with metastatic gastric cancer. This patient continues to have adequate caloric intake and good performance status. As such, he is an appropriate candidate for systemic chemotherapy. Approximately 20% of gastric cancers and 30% of gastroesophageal junction tumors overexpress*HER2* growth factor receptor. The anti-*HER2*monoclonal antibody trastuzumab, when added to a systemic chemotherapy regimen, is beneficial in treating patients with these tumor types. For example, an early trial of patients with gastric and gastroesophageal junction adenocarcinomas expressing *HER2* found that the median survival was statistically significantly improved by adding trastuzumab to cisplatin plus 5-fluorouracil or capecitabine (13.5 months versus 11.1 months). Use of trastuzumab is limited to those patients whose tumors overexpress *HER2*.

BRAF mutations are present in 40% of melanomas, and patients with these tumors are treated with selective *BRAF* inhibitors. However, these agents are not part of gastric cancer therapy, and knowledge of the *BRAF* mutation status of a gastric tumor would not alter treatment.

Determining the estrogen and progesterone receptor status of a tumor is important when planning treatment of patients with breast cancer but is not relevant when selecting therapy for patients with gastric cancer.

K-*ras* genotyping is needed for all patients with newly diagnosed metastatic colorectal cancer, as K-*ras*mutations inhibit activity of the anti–epidermal growth factor receptor agents cetuximab and panitumumab that are used to treat many of these tumors. However, because these agents are not active in treating upper gastrointestinal malignancies, determining K-*ras* mutation status is not indicated for this patient.

Question 113

A 34-year-old woman is evaluated for a 4-week history of tenderness in her left lower breast. Her paternal grandmother died of ovarian cancer at age 54 years. There is no family history of breast cancer. She has a 2-cm palpable left lower outer breast mass on exam. The remainder of the examination is unremarkable.

Results of complete blood count and serum chemistry panel are normal. A mammogram shows increased density and calcifications at the site of the palpable mass. Ultrasound examination reveals a 1.9-cm hypoechoic mass. Ultrasound-guided needle biopsy specimens show a high-grade invasive ductal carcinoma, estrogen receptor–negative, progesterone receptor–negative, and negative for *HER2*amplification.

Which of the following is the most appropriate initial management?

A

Bilateral mastectomy

B

BRCA1/2 testing

C

Left mastectomy

D

Lumpectomy with sentinel lymph node biopsy

Answer & Critique

Correct Answer: B

Educational Objective: Determine indications for *BRCA1/2* testing in a woman with newly diagnosed breast cancer.

Key Point

Offering *BRCA1/2* testing prior to surgery is recommended for patients diagnosed with breast cancer before age 45 years, patients with breast cancer at any age and a family history of breast and/or ovarian cancer, and patients with triple-negative breast cancers diagnosed before age 60 years.

This patient should be offered *BRCA1/2* testing before surgical treatment is recommended. Offering*BRCA1/2* testing prior to surgery is recommended for patients younger than 45 years with either newly diagnosed breast cancer or a family history of breast or ovarian cancer. *BRCA1/2* testing is also recommended for patients with breast cancer diagnosed at any age if one or more first-, second- or third-degree relatives have been diagnosed with ovarian cancer and is recommended for women with “triple negative breast cancer” (estrogen receptor–negative, progesterone receptor–negative, and negative for *HER2* amplification) diagnosed before age 60 years. Because this patient was diagnosed with breast cancer at age 34 years and has a family history of ovarian cancer in a paternal grandmother, she has an 18% risk of having a *BRCA1/2*mutation. Offering *BRCA1/2* testing prior to breast surgery is therefore recommended, particularly if the result will influence the patient's choice of surgery. If she tests positive for a *BRCA1* or *BRCA2*mutation, bilateral mastectomy should be considered because of the high risk for subsequent contralateral and ipsilateral breast cancers. The lifetime risk of contralateral breast cancer in women with breast cancer and a *BRCA1/2* mutation is 40% to 60%. The risk is highest in women younger than 40 years of age at diagnosis. In the United States, 50% to 70% of women with breast cancer who have a*BRCA1/2* mutation elect bilateral mastectomy, and studies suggest a survival benefit of prophylactic contralateral mastectomy in this situation.

If the patient were to test negative for a *BRCA1/2* mutation, bilateral mastectomy would not be recommended.

Left mastectomy is not usually required for a 2-cm breast cancer amenable to breast-conserving treatment, although it is an option if patients want to avoid radiation or have contraindications to

radiation therapy. In addition, left mastectomy would not decrease the high risk of contralateral breast cancer for patients with a *BRCA1/2* mutation.

Lumpectomy with sentinel lymph node biopsy, followed by breast radiation therapy, is a reasonable option in patients with tumors measuring less than 5 cm that can be resected with clear margins. Survival following breast conservation therapy is equal to mastectomy in patients without *BRCA1/2*mutations.

Question 114

A 54-year-old woman undergoes an examination. She feels well and is asymptomatic. The patient asks to be screened for ovarian cancer. She is postmenopausal and has two children. She used oral contraceptives from age 20 to 35 years. There is no family history of breast, ovarian, colon, endometrial, or gastric cancer.

On physical examination, vital signs are normal. Other findings on physical examination, including pelvic and rectal examinations, are normal.

Which of the following is the most app ropriate ovarian cancer screening option for this patient?

A

Serum CA-125 testing

B

Transvaginal ultrasound

C

Transvaginal ultrasound and serum CA-125 testing

D

No screening studies are indicated

Answer & Critique

Correct Answer: D

Educational Objective: Determine need for screening a patient at average risk for ovarian cancer.

Key Point

Screening is not recommended for asymptomatic women at average risk of developing ovarian cancer.

Ovarian cancer screening is not indicated for this patient. The lifetime risk of developing ovarian cancer is 1.4%, and this patient is of average risk. She does not have a family history suggestive of a hereditary ovarian cancer syndrome, such as family members with ovarian cancer; premenopausal breast cancer; bilateral breast cancer; the presence of both ovarian and breast cancer on the same side of the family; or the presence of Lynch syndrome cancers such as colon, endometrial, or gastric cancers. She is multiparous, has no symptoms suggestive of ovarian cancer, and has a normal pelvic examination. In addition, she used oral contraceptives for 15 years, which lowers the risk of ovarian cancer by 50%, with the protective effect lasting 30 years.

Neither serum CA-125 testing nor transvaginal ultrasound is indicated for asymptomatic women at average risk for ovarian cancer. Serum CA-125 levels are elevated in approximately 50% of women with early-stage ovarian cancer and in 80% of those with advanced ovarian cancer, but this finding is not very specific. Levels are also elevated in approximately 1% of healthy women and fluctuate during the menstrual cycle. Elevated serum CA-125 values also occur in several benign conditions, such as endometriosis, uterine fibroids, hepatitis, and peritonitis, as well as in endometrial, breast, lung, and pancreatic cancers.

The largest randomized controlled trial evaluating ovarian cancer screening in women at average risk was the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial, in which 78,216 women were assigned to either usual care or annual serum CA-125 testing for 6 years plus annual transvaginal ultrasound for the first 4 years. After a median follow-up of 12 years, ovarian cancer was diagnosed in 5.7% of women in the screening group and 4.7% of women in the usual care group, but there was no difference between the two groups in the number of deaths due to ovarian cancer. In addition, 3285 women had false-positive results, 1080 of whom underwent surgery; 163

of the women who underwent surgery experienced at least one serious complication (15% of surgical procedures).

Patients who have a high risk of ovarian cancer, such as women with *BRCA1/2* mutations, are recommended to have semi-annual screening with pelvic examinations, serum CA-125 testing, and transvaginal ultrasound beginning at age 30 years. However, even in this high-risk group, there is no evidence that screening decreases ovarian cancer mortality. For these women, prophylactic bilateral salpingo-oophorectomy once childbearing is completed, ideally by age 35 to 40 years, is recommended.

Question 115

A 60-year-old woman is evaluated for right-sided flank pain. Medical history is unremarkable.

Findings on physical examination, including vital signs, are normal.

CT scan of the abdomen and pelvis identifies a 6-cm right upper pole kidney mass. The lesion is resected with negative margins. Pathology specimens show clear cell carcinoma with evidence of renal vein involvement.

Which of the following is the most appropriate managemen t after surgery?

A Adjuvant sunitinib

B Adjuvant temsirolimus

C Radiation therapy

D Observation

Answer & Critique

Correct Answer: D

Educational Objective: Treat a patient with localized renal cell carcinoma after surgical resection.

Key Point

Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma, as no studies to date have identified an adjuvant therapy that improves survival in these patients.

Close observation is the standard of care for patients following surgical resection for nonmetastatic renal cell carcinoma. The primary treatment of suspected renal cell carcinoma is surgery. Staging is predicated on tumor size as well as extension into the renal vein and into or through the Gerota fascia. Although this patient presented with symptoms suggesting an underlying process, more early-stage renal cell carcinomas are currently being identified incidentally because of the development and more frequent use of sensitive imaging techniques. Various treatment options are available for patients with advanced disease, including immunotherapy and many small-molecule tyrosine kinase inhibitors. However, at present, there is no evidence that any of these approaches is clearly associated with improved survival following resection of nonmetastatic disease, and they are therefore not used as adjuvant therapy.

The tyrosine inhibitors sunitinib and temsirolimus have shown significant activity against renal cell carcinoma and are used in patients with metastatic disease. However, they have no established role as adjuvant therapies following surgical resection. Although studies are ongoing, particularly trials of some of the tyrosine kinase inhibitors, the current standard of care following surgical resection is close observation.

Radiation therapy has no role in the management of patients following resection for localized renal cell carcinoma, even when surgical margins are positive.

Bibliography

Question 116

A 52-year-old woman is evaluated for a 3-month history of enlarged bilateral axillary lymph nodes. She has also recently developed fever, weight loss, and night sweats. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 100/60 mm Hg, pulse rate is 90/min, and respiration rate is 14/min. Firm bilateral axillary lymph nodes are palpated. Splenomegaly is present. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	9.0 g/dL (90 g/L)
Leukocyte count	18,000/μL (18×10^9/L)
Platelet count	70,000/μL (70×10^9/L)
Lactate dehydrogenase	Elevated
β_2-microglobulin	Elevated

CT scans of the chest, abdomen, and pelvis show bilateral enlarged axillary and intra-abdominal lymph nodes and an enlarged spleen. Axillary lymph node excisional biopsy reveals diffuse infiltration with small monoclonal lymphoid cells with CD20+ and cyclin D1 overexpression. Subsequent colonoscopy is performed, and biopsy indicates mucosal infiltration with lymphoid cells expressing B-cell markers.

Which of the following is the most likely diagnosis?

A

Diffuse large B-cell lymphoma

B

Follicular lymphoma

C

Hodgkin lymphoma

D

Mantle cell lymphoma

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose mantle cell lymphoma.

Key Point

Mantle cell lymphoma is a rare form of non-Hodgkin lymphoma characterized by extranodal involvement and overexpression of cyclin D1, and it is associated with a poor prognosis.

The most likely diagnosis of this patient with diffuse lymphadenopathy, B symptoms, extranodal involvement, and cyclin D1 overexpression is mantle cell lymphoma. Overexpression of cyclin D1, a cell cycle gene regulator, is associated with a chromosomal translocation [t(11:14)] that is diagnostic of mantle cell lymphoma. Mantle cell lymphoma is a rare form of non-Hodgkin lymphoma that has a varied clinical course depending on the extent of disease at presentation. Patients usually have advanced disease at presentation, including lymphadenopathy, weight loss, and sometimes fever, and are found to have diffuse sites of involvement, including the gastrointestinal tract, bone marrow, and blood stream.

Diffuse large B-cell lymphoma can also involve multiple organs, including the bowel; however, the cells in diffuse large B-cell lymphoma are large and do not overexpress cyclin D1.

Similarly, follicular lymphoma does not usually involve the bowel and is not characterized by overexpression of cyclin D1.

Common findings in patients with Hodgkin lymphoma include palpable lymphadenopathy or a mediastinal mass. Hodgkin lymphoma is not associated with cyclin D1 overexpression or bowel involvement and is associated with a much better prognosis than mantle cell lymphoma, regardless of stage.

Question 117

A 62-year-old woman undergoes follow-up evaluation. Stage II ovarian cancer was diagnosed 5 months ago. No residual cancer was identified after debulking surgery. Postoperative chemotherapy was given and resulted in complete remission. The patient currently reports feeling well.

Medical history includes stage I endometrial cancer diagnosed at age 42 years for which the patient underwent hysterectomy without bilateral salpingo-oophorectomy. Family history is significant for endometrial cancer in her maternal grandmother and colon cancer in her mother and maternal uncle.

On physical examination, vital signs are normal. A well-healed abdominal midline incision is present. Remaining examination findings are unremarkable.

Results of complete blood count, serum chemistry panel, and serum CA-125 level are normal.

Which of the following studies should be done next?

A

BRCA1/2 testing

B

Serial CT scans of abdomen and pelvis

C

Serum CA-125 monitoring

D

Testing for Lynch syndrome

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose a hereditary ovarian cancer syndrome.

Key Point

Women with a personal and family history of ovarian, endometrial, and colon cancer should undergo testing for genetic mutations caused by Lynch syndrome (also known as hereditary nonpolyposis colon cancer).

This patient should undergo testing for Lynch syndrome (also known as hereditary nonpolyposis colon cancer). Because she has a personal history of both ovarian and endometrial cancer, as well as a family history of colon and endometrial cancer, her ovarian cancer is likely related to inheriting one of the genetic mutations present in patients with Lynch syndrome. This is an autosomal dominant cancer susceptibility syndrome caused by a germline mutation in one of the DNA-mismatch repair genes (*MLH1, MSH2,* and *MSH6* being the most common). Patients have an increased risk for several types of cancer, usually with early onset. The most common are a 70% risk for colon cancer, 27% to 71% risk for endometrial cancer, and 3% to 14% risk for ovarian cancer. Less common cancers include tumors of the upper urinary tract, bladder, stomach, small bowel, gallbladder, pancreas, brain, and sebaceous glands. Endometrial or, less often, ovarian cancer, can be the sentinel cancer in a patient with Lynch syndrome. Although identification of a Lynch syndrome mutation will not change the management of this patient's ovarian cancer, it will change screening for other cancers, including the need for colonoscopy every 1 to 2 years, annual skin examinations, and consideration of screening upper endoscopy. In addition, if she has Lynch syndrome, genetic testing should be offered to her first-degree relatives, with testing offered in addition to more distant relatives if first-degree relatives are unavailable or unwilling to be tested.

Based on National Comprehensive Cancer Network guidelines, all patients with ovarian cancer are eligible for *BRCA1/2* testing. Patients with *BRCA1/2* mutations are at risk for other cancers, particularly breast cancer, and additional screening and prophylaxis options should be discussed. In addition, patients with *BRCA1* mutations are eligible for clinical trials of agents that are particularly effective in*BRCA1*-related recurrent ovarian cancers, such as PARP inhibitors. If this patient does not have a Lynch syndrome–related mutation, testing for a *BRCA1/2* mutation would be recommended. However, because of her family and personal history of colon and endometrial cancers, testing for Lynch syndrome mutations is recommended first.

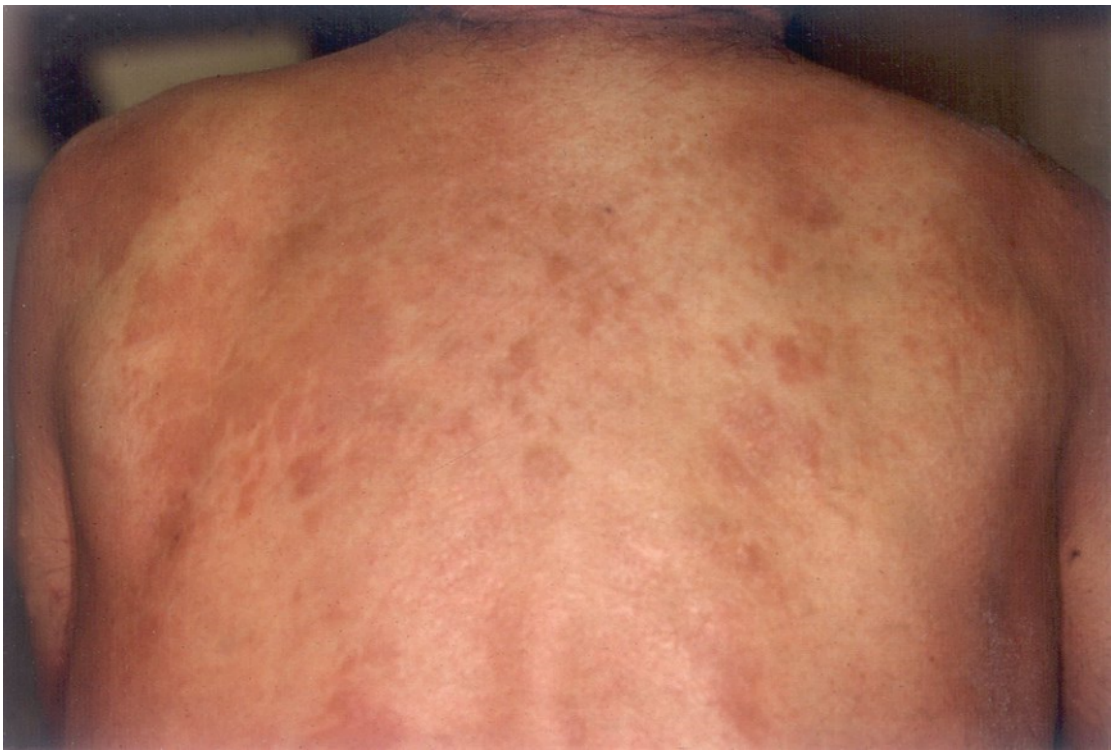
Serial abdominal/pelvic CT scans are not recommended to monitor patients with ovarian cancer. CT scans should be reserved for patients with symptoms or with recurrence of cancer based on clinical examination or elevated serum CA-125 levels.

Guidelines differ as to whether to monitor serum CA-125 levels in patients after treatment for ovarian cancer, and this should be discussed with individual patients. In one trial, patients with ovarian cancer treated with first-line platinum-based chemotherapy were randomized to receiving early treatment for ovarian cancer recurrence based on an increasing serum CA-125 level alone versus delaying treatment until clinical symptoms developed. Although patients in the early treatment arm started chemotherapy an average of 4.8 months earlier, there was no difference in overall survival

Question 118

A 48-year-old man is evaluated for a 7-year history of spreading plaques associated with dry, itchy skin. He has no other significant medical history and takes no medications.

On physical examination, vital signs are normal. Skin lesions are present on the arms, back, and legs. Representative skin findings on the back are shown.



here is no lymphadenopathy or hepatosplenomegaly. The remainder of the examination is unremarkable. Results of complete blood count and serum chemistry panel are normal.

Chest radiograph is normal. Skin biopsy reveals infiltration with CD4-positive T cells with cerebriform-appearing nuclei consistent with mycosis fungoides.

Which of the following is the most appropriate management?

A Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy
B Psoralen plus ultraviolet A (PUVA) therapy
C Topical glucocorticoids
D Rituximab

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient with stage I mycosis fungoides.

Key Point

Patients with early-stage mycosis fungoides are treated initially with topical glucocorticoids; if glucocorticoids are ineffective, adding retinoids and psoralen and ultraviolet light therapy, sometimes combined with interferon alfa, may be effective.

Topical glucocorticoids are most appropriate for this patient with mycosis fungoides, which is one form of cutaneous T-cell non-Hodgkin lymphoma. Lymphomas expressing T-cell surface antigens (CD4) are among the more common forms of cutaneous T-cell lymphomas. These antigens infiltrate skin and initially cause rash (mycosis fungoides) and, occasionally, also circulate in the blood (Sézary syndrome). The CD4-expressing malignant T cells are large and have classic "cerebriform"-appearing nuclei and clonal T-cell receptor gene rearrangements. Patients usually present with dry, pruritic, erythematous skin patches; mycosis fungoides confined to the skin can mimic these benign dermatologic conditions, and be undiagnosed for many years. Patients with progressive disease develop raised plaques, diffuse skin erythema, and cutaneous ulcers. In the final stages of progression, organ infiltration and evolving immunodeficiency cause recurrent bacterial infections, sepsis, and death.

Therapy is guided by disease stage. Early-stage disease (stages I and II) is limited to the skin, and patients have a median survival of over 20 years. Patients with early-stage disease are treated effectively with topical glucocorticoids. If there is no response to glucocorticoids, adding retinoids (such as bexarotene) and psoralen plus ultraviolet light (PUVA) therapy, at times combined with interferon alfa, may be effective. Patients with advanced disease (stages III and IV) have extensive skin and organ involvement and a median survival of 4 years. These patients require more aggressive therapy, including electron-beam radiation therapy; photopheresis; systemic therapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; histone deacetylase inhibitors (such as romidepsin and vorinostat); and monoclonal antibodies (such as alemtuzumab). Allogeneic hematopoietic stem cell transplantation may be curative in young patients who have advanced disease and an appropriate donor.

CHOP chemotherapy is indicated for patients with advanced disease, which this patient does not have due to absence of lymphadenopathy or organ involvement.

PUVA therapy may be effective for patients with early-stage disease who do not respond to topical glucocorticoids.

Monoclonal antibody therapy may be used in advanced stage mycosis fungoides using agents such as alemtuzumab, which is directed toward T cell surface proteins. Rituximab is a monoclonal antibody directed toward surface proteins typically found on immune system B cells and is not used in treatment of mycosis fungoides.

Question 119

A 69-year-old woman is evaluated for a 3-month history of intermittent rectal bleeding and increasing fatigue. Medical history is unremarkable, and she takes no medications. Her father died of metastatic colon cancer at age 78 years.

On physical examination, vital signs are normal. The abdomen is soft and nontender. Bowel sounds are normal, and the liver and spleen are not enlarged. Digital rectal examination discloses blood-streaked stool.

Colonoscopy reveals a nonobstructing 4-cm mass in the mid rectum, approximately 8 cm from the anal verge. Biopsy findings show adenocarcinoma. Pelvic MRI shows tumor penetration into, but not through, the rectal wall (TNM stage T2); no abnormal lymph nodes are seen (TNM stage N0). Contrast-enhanced CT scans of the chest and abdomen are normal.

Which of the following is the most appropriate treatment at this time?

A

Chemotherapy

B

Radiation plus chemotherapy

C

Radiation plus chemotherapy followed by surgical resection

D

Surgical resection

Answer & Critique

Correct Answer: D

Educational Objective: Treat stage I rectal cancer with surgical resection.

Key Point

Surgical resection is the initial treatment for patients with stage I rectal cancer (defined as a tumor that invades into, but not fully through, the rectal wall, with no evidence of lymph node metastases).

Surgical resection is indicated as the initial treatment for this patient who has stage I rectal cancer, which is defined as a tumor that invades into, but not fully through, the rectal wall, with no evidence of lymph node metastases (T2N0M0, stage I). The procedure for a tumor of the mid rectum, such as that in this patient, is a low anterior resection using the technique of total mesorectal excision to accomplish an en-bloc removal of the rectum with a fully intact mesorectum. The mesorectum is the fatty sheath that surrounds the rectum and contains the locoregional lymph nodes. Careful pathologic examination of the primary tumor and lymph nodes is necessary to confirm the disease stage. If pathology findings indicate that the tumor is a higher T stage than expected (T3 or T4) or if any of the locoregional lymph nodes in the mesorectum are found to contain cancer (N1 or N2), postoperative chemoradiation and chemotherapy would be indicated. However, if the final pathology report confirms stage I rectal cancer, the probability of cure with surgery alone is high, and no additional treatment is indicated.

Neither chemotherapy, radiation therapy, nor combined chemotherapy plus radiation has been demonstrated to improve outcomes in patients with stage I rectal cancer, and all of them would expose these patients to unnecessary risk and toxicity.

Question 120

A 58-year-old woman is undergoes a routine cervical cancer screening examination. She is asymptomatic. The patient is postmenopausal and has two children. Medical history is unremarkable. Her mother was diagnosed with breast cancer at age 72 years.

On physical examination, vital signs are normal. An ovarian mass, measuring approximately 8 cm, is palpated on pelvic examination. Remaining examination findings are unremarkable.

Laboratory studies show a normal complete blood count, chemistry panel, and serum CA-125 level.

Transvaginal ultrasound shows a 12.8-cm complex mass in the cul de sac extending to both adnexa. No ascites are present. CT scan of the pelvis shows a 13.4-cm complex left pelvic mass and a 5.8-cm right pelvic mass but no liver lesions, ascites, peritoneal masses, or pleural effusions. Chest radiograph and chest CT scans are normal.

Which of the following is the most appropriate management?

A

CT-guided biopsy of the mass

B

Exploratory surgery

C

MRI of the abdomen and pelvis

D

BRCA1/2 testing

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose early-stage ovarian cancer through exploratory surgery.

Key Point

The diagnosis of ovarian cancer is usually made by surgical exploration, as there is survival benefit following intact removal of an adnexal mass in patients with early-stage disease.

This patient, who has early-stage ovarian cancer (clinical stage II, with spread beyond the ovaries but confined to the pelvis), should undergo exploratory surgery. The diagnosis of ovarian cancer is usually made by surgical exploration, as there is survival benefit following intact removal of an adnexal mass in patients with early-stage disease. Survival is also improved when surgery is performed by a specialized gynecologic oncologic surgeon. If ovarian cancer is confirmed at surgery, appropriate procedures include peritoneal washings for cytology, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, full abdominal and pelvic exploration with biopsy of any masses suspicious for cancer, lymph node evaluation, and, for patients with advanced ovarian cancer, debulking of the tumor by removing as much of the cancer as possible. Optimal tumor debulking (leaving residual masses that are each less than 1 cm) improves survival.

CT-guided or ultrasound-guided biopsy of a suspected ovarian mass is contraindicated, as this may cause rupture and dissemination of cancer cells. Rupture of an ovarian mass increases the risk of peritoneal recurrence; when such rupture occurs during surgery, it is an indication for adjuvant chemotherapy, even in early stage disease.

MRI of the abdomen and pelvis is sometimes used in the preoperative staging of ovarian cancer as an alternative to CT but is unlikely to yield additional information after CT scans and ultrasound examinations are done.

Based on National Comprehensive Cancer Network guidelines, all women with ovarian cancer are eligible for *BRCA1/2* testing. Ten percent to 15% of ovarian cancers are hereditary, with *BRCA1/2*mutations being the most common. Although the initial surgical and standard adjuvant chemotherapy treatments for ovarian cancer are the same regardless of the presence of

a hereditary mutation, patients with *BRCA1/2* mutations are at risk for other cancers, particularly breast cancer, and additional screening and prophylaxis options would be discussed once treatment for ovarian cancer is complete. In addition, patients with *BRCA1* mutations are eligible for clinical trials of agents that are particularly effective in *BRCA1*-related recurrent ovarian cancers, such as PARP inhibitors. However, it is not yet known whether this patient has ovarian cancer, and testing before this diagnosis is established is inappropriate.

Question 121

A 54-year-old man is evaluated for a 3-month history of worsening dyspepsia, gastric bloating, and abdominal discomfort. His dyspepsia has so far been treated with ranitidine. The patient is allergic to penicillin.

On physical examination, the patient is afebrile, blood pressure is 112/70 mm Hg, pulse rate is 83/min, and respiration rate is 14/min. BMI is 25. No palpable lymphadenopathy is present. Abdominal examination reveals mild epigastric tenderness. The remainder of the examination is unremarkable.

The hemoglobin level is 11.5 g/dL (115 g/L). Complete blood count and differential are otherwise normal. Results of fecal occult blood testing are positive.

Upper endoscopy shows several small gastric ulcers. Histopathologic studies reveal evidence of*Helicobacter pylori* infection and small clonal mucosa-associated B cells expressing the CD20 antigen consistent with mucosa-associated lymphoid tissue lymphoma. A CT scan of the abdomen shows no evidence of lymphadenopathy.

Ranitidine is discontinued.

Which of the following is the most appropriate management?

A

Begin omeprazole, metronidazole, and clarithromycin

B

Begin rituximab

C

Obtain bone marrow biopsy

D

Obtain PET/CT scan

Answer & Critique

Correct Answer: A

Educational Objective: Manage a patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection.

Key Point

The initial treatment of a patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection is antimicrobial therapy plus a proton pump inhibitor.

In this patient with a gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection, ranitidine should be discontinued and omeprazole, metronidazole, and clarithromycin begun. MALT lines the entire gastrointestinal tract, providing immune surveillance and initiating immunologic responses to pathogens. Chronic antigen stimulation can lead to clonal expansion of MALT. Malignant transformation of MALT to lymphoma can occur, originating in the B cells of the marginal zone of MALT and expressing the CD20 surface antigen. Gastric MALT lymphoma associated with *H. pylori* infection usually presents as local disease in patients with gastric ulcers. A complete response is generally obtained following administration of combination antimicrobial therapy and a proton pump inhibitor (PPI) to treat the *H. pylori* infection. Usually, amoxicillin is combined with omeprazole and clarithromycin, but because of this patient's penicillin allergy, metronidazole is substituted for amoxicillin. A complete remission rate of nearly 80% can be expected after a full course of therapy. The duration of therapy lasts from 6 to 8 weeks to several months and is guided by treatment response as assessed by repeat upper endoscopy.

Rituximab has no role in the initial treatment of a patient with a gastric MALT lymphoma. This agent is indicated for disease that does not resolve after a complete course of combination antimicrobial therapy plus a PPI and may be combined with chemotherapy, radiation therapy, or surgery when additional treatment is required.

Bone marrow biopsy is not indicated because of the extremely low likelihood of bone marrow involvement in this setting.

A PET/CT scan is not needed because gastric MALT lymphoma usually presents as local disease, and this patient's abdominal CT scan revealed no lymphadenopathy.

Question 122

A 61-year-old man is evaluated in follow-up after surgical resection of a tongue base tumor.

A neck CT showed asymmetric thickening of the left tongue base and a 2-cm lymph node on the left. Biopsy identified moderately differentiated invasive squamous cell carcinoma. Preoperative PET/CT showed no distant metastatic disease. At surgery, the mass was resected with one positive margin; left modified radical neck dissection identified 3/31 positive lymph nodes, with one lymph node with extracapsular extension.

On physical examination, vital signs are normal. The tongue base resection is well healed and the oral cavity is otherwise normal. The neck incisions are clean and dry, and no lymphadenopathy is detected.

Which of the following is the most appropriate postsurgical management?

A

Cetuximab alone

B

Chemotherapy alone

C

Chemotherapy and radiation therapy

D

Radiation therapy followed by chemotherapy

E

Observation

Answer & Critique

Correct Answer: C

Educational Objective: Treat squamous cell carcinoma of the neck with chemoradiation therapy following surgical resection.

Key Point

Adjuvant combined-modality chemotherapy and radiation has been shown to improve survival in patients with resected squamous cell carcinoma of the head and neck associated with either positive surgical margins or lymph node metastases with extracapsular extension.

Adjuvant combined-modality treatment with chemotherapy and radiation is most appropriate for this patient with locally advanced squamous cell carcinoma. Most patients with resected squamous cell carcinoma of the head and neck will require some form of adjuvant therapy. Combined-modality chemotherapy and radiation has been shown to improve survival in patients with either positive surgical margins or lymph node metastases associated with extracapsular extension. Although several earlier studies showed a survival benefit when combined-modality therapy was used for patients with multiple positive lymph nodes without extracapsular extension, more recent studies have failed to confirm a survival benefit in that setting. Therefore, currently, either the presence of positive surgical margins at the primary resection site or of extracapsular lymph node extension is the only standard indication for combined-modality adjuvant therapy. The patient described here clearly meets these criteria.

Although cetuximab alone can be used for patients with advanced disease, it has not been associated with improved survival in the adjuvant setting.

Neither adjuvant chemotherapy alone nor adjuvant radiation therapy followed by chemotherapy has a role in the care of patients with resected squamous cell carcinoma of the head and neck.

Although not listed as an option, adjuvant radiation therapy alone is most often used for patients with earlier-stage disease and is associated with significantly decreased recurrence rates. However, it is not appropriate for patients with either positive resection margins or those with metastatic lymph nodes associated with extracapsular extension. In both of those circumstances, recurrence rates following treatment with radiation alone are clearly higher than those associated with combined chemotherapy and radiation treatment.

Question 123

A 24-year-old man is evaluated after he felt a mass in his right testicle. The patient is asymptomatic and is otherwise healthy.

On physical examination, vital signs are normal. A 2- to 3-cm solid mass is palpated in the right testicle. The remainder of the examination is unremarkable.

Serum α-fetoprotein level is normal, serum lactate dehydrogenase (LDH) level is 450 U/L, and serum β-human chorionic gonadotropin level is less than 5 U/L.

Testicular ultrasound confirms the presence of a hypoechoic solid right testicular mass.

Right radical inguinal orchiectomy is performed, and pathological examination reveals seminoma. Subsequent CT scan of the abdomen and pelvis shows no lymphadenopathy or evidence of metastatic disease. The tumor is stage I based on surgical and radiographic findings and tumor marker studies. LDH is normal following orchiectomy.

Which of the following is the most appropriate management for this patient?

A

Active surveillance

B

Hematopoietic stem cell transplantation

C

Platinum-based chemotherapy

D

Retroperitoneal lymph node dissection

Answer & Critique

Correct Answer: A

Educational Objective: Manage a patient following radical inguinal orchiectomy for early-stage seminoma.

Key Point

Active surveillance is the recommended management strategy for patients with stage I seminoma diagnosed after radical inguinal orchiectomy; other options are adjuvant single-agent carboplatin or para-aortic lymph node irradiation.

Active surveillance is appropriate for this patient with stage I seminoma following resection. Testicular germ cell tumors are divided into pure seminomas and nonseminomatous germ cell tumors (NSGCT). Recommended postsurgical treatments vary based on histologic findings and tumor stage. In general, pure seminoma is associated with a better prognosis than NSGCT. For men with stage I seminoma (disease confined to the testis), radical inguinal orchiectomy is curative in at least 80% of patients. This high cure rate with initial surgical treatment coupled with the ability to treat recurrent disease with curative intent makes active surveillance the lowest-risk approach with an expected good outcome. Active surveillance refers to a regimen of regular assessment with serum tumor marker measurement, CT scans of the abdomen and pelvis, and chest radiographic imaging. As this requires close and regular monitoring, it requires a reliable and motivated patient to be successful.

Other management options after surgery include adjuvant therapy with either single-agent carboplatin or para-aortic lymph node irradiation, although neither approach has been shown to improve overall survival. In addition, neither of these alternatives appears superior to the other, but they might be reasonable to consider in patients who wish to decline active surveillance.

Hematopoietic stem cell transplantation is used for treatment of patients with recurrent or refractory disease, usually only after treatment with multiple chemotherapeutic agents, in selected patients following adjuvant chemotherapy.

Platinum-based chemotherapy (specifically the combination of bleomycin, etoposide, and cisplatin) is the standard regimen for patients with more advanced seminoma, as well as for those with

NSGCT. This regimen is not recommended for patients with stage I seminoma because of their very good prognosis and the significant potential for side effects associated with these drugs.

Retroperitoneal lymph node dissection is often used in the treatment of NSGCT but has no role in the treatment of patients with stage I seminoma.

Question 124

A 59-year-old woman undergoes follow-up evaluation for management of limited-stage small cell lung cancer diagnosed during care for an episode of pneumonia.

The patient was treated with a course of chemotherapy and radiation therapy. CT scan of the chest following treatment showed near-complete resolution of the lung mass and lymphadenopathy.

On physical examination, vital signs are normal. Auscultation of the chest is unremarkable, and the remainder of her examination is normal.

Which of the following is the most appropriate next step in the management of this patient?

A

Maintenance chemotherapy

B

PET/CT scan

C

Prophylactic cranial irradiation

D

Surgical removal of the residual lung mass

Answer & Critique

Correct Answer: C

Educational Objective: Treat a patient who responds to treatment for small cell lung cancer with prophylactic cranial irradiation.

Key Point

Patients with small cell lung cancer who experience a complete or near-complete response following treatment with chemotherapy or combined chemotherapy and radiation therapy should be offered prophylactic cranial irradiation to reduce the incidence of brain metastases and improve overall survival.

Prophylactic cranial irradiation (PCI) is indicated. Following evaluation for pneumonia, this patient was diagnosed with limited-stage small cell lung cancer (SCLC). The definition of limited-stage disease consists of disease limited to one hemithorax, with hilar and mediastinal lymphadenopathy that can be encompassed within one tolerable radiotherapy portal. Combined chemotherapy and radiation therapy induced a significant near-complete response in this patient. At initial diagnosis and following treatment, there was no evidence of cerebral metastatic disease. Despite these results, she remains at significant risk for recurrence of small cell lung cancer. In addition, approximately one third of patients without cerebral metastatic disease at initial diagnosis will have brain metastases at the time of disease recurrence. Randomized trials assessing the role of PCI in patients with primary treatment–responsive SCLC have identified both a reduced incidence of brain metastases and an improvement in overall survival after irradiation. PCI is currently considered standard management following response to primary treatment in these patients.

Although limited-stage SCLC tumors are one of the most chemosensitive types of tumors, there are recurrences in 90% to 95% of patients. To date, attempts to improve outcomes by providing maintenance chemotherapy, adding other agents to the standard chemotherapy regimen, or by using high-dose chemotherapy with stem cell support have been unsuccessful.

PET/CT is not a standard imaging modality to assess patients with primary treatment–responsive SCLC and would provide no new information for this patient, given her CT imaging findings.

SCLC is considered a systemic disease at diagnosis, even if a potentially resectable peripheral lesion is the only finding after diagnostic studies are completed. All patients with SCLC now

receive systemic chemotherapy as the mainstay of treatment. Surgery has no role in the management of patients with SCLC.

Question 125

A 68-year-old man undergoes follow-up evaluation. The patient has stage IIIB nodular sclerosing Hodgkin lymphoma that was initially diagnosed 3 years ago. Complete remission was achieved following administration of six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. Two months ago, stage IIIB Hodgkin lymphoma was again diagnosed. Salvage chemotherapy was initiated with dexamethasone, ifosfamide, cisplatin, and etoposide (DICE). The patient has now completed two cycles of DICE chemotherapy.

On physical examination, the patient is afebrile, blood pressure is 142/80 mm Hg, pulse rate is 80/min, and respiration rate is 12/min. There is no palpable lymphadenopathy. The remainder of the examination is unremarkable. Results of a complete blood count and serum chemistry panel are normal.

PET/CT imaging shows no residual disease.

Which of the following is the most appropriate treatment at this time?

A

Allogeneic hematopoietic stem cell transplantation

B

Autologous hematopoietic stem cell transplantation

C

Continued salvage DICE chemotherapy

D

Involved-field radiation therapy

Answer & Critique

Correct Answer: B

Educational Objective: Treat a patient with recurrent Hodgkin lymphoma who responds to salvage chemotherapy.

Key Point

Autologous hematopoietic stem cell transplantation is indicated for patients with recurrent Hodgkin lymphoma, particularly patients who achieve a complete response to salvage chemotherapy.

Autologous hematopoietic stem cell transplantation (HSCT) is the most appropriate treatment option for patients with recurrent Hodgkin lymphoma, particularly those who achieve a complete response to salvage chemotherapy. Prospective trials have consistently demonstrated a survival advantage when patients with chemotherapy-sensitive disease are treated with autologous HSCT compared with patients treated with continued salvage chemotherapy. Because this patient has achieved a complete remission following two cycles of dexamethasone, ifosfamide, cisplatin, and etoposide (DICE) chemotherapy, the next step is to administer hematopoietic growth factors, with or without chemotherapy, to mobilize, collect, and store hematopoietic progenitor cells. Once a sufficient quantity of hematopoietic progenitor cells are collected (>3 million CD34+ cells/kg patient body weight), high-dose multiagent chemotherapy followed by reinfusion of the stored progenitor cells can be completed.

Allogeneic HSCT is not indicated for patients with chemotherapy-sensitive recurrent Hodgkin lymphoma because of the significant risk of morbidity and mortality associated with allogeneic transplantation. The risk for fungal and viral infections occurring 3 months or more after transplantation is significantly greater after allogeneic than autologous transplantation. Lymphocytes derived from the donor can mount an immune response to the recipient's organs, leading to graft-versus-host disease, which may affect the skin, gastrointestinal tract, liver, ocular adnexa, lungs, bone marrow, and soft tissues. However, in patients with chemotherapy-resistant recurrent Hodgkin lymphoma, including patients who develop a relapse after autologous HSCT, allogeneic HSCT may result in prolonged disease-free survival.

Continuation of DICE chemotherapy is not optimal treatment for this patient because, as noted, patients with chemotherapy-sensitive Hodgkin lymphoma who are treated with autologous HSCT have a survival advantage compared with patients treated with continued salvage chemotherapy.

Radiation therapy in the salvage setting can be effective for patients with limited disease and may be associated with long-term disease-free survival. However, radiation therapy is much less likely to result in long-term disease-free survival in patients with advanced recurrent disease. In addition, radiation therapy would adversely affect the hematopoietic stem cells in patients being considered for autologous HSCT.

Question 126

A 44-year-old woman undergoes follow-up evaluation. Stage I cancer of the left breast was diagnosed 3 years ago (1.4-cm, grade 2 invasive ductal carcinoma, estrogen receptor positive, progesterone receptor positive, *HER2* negative, 0/2 positive sentinel lymph nodes, and a low score on 21-gene recurrence score testing). *BRCA1/2* testing results were negative. She underwent breast-conserving surgery and radiation therapy and then started tamoxifen. The patient is concerned about her risk of recurrence. Menses are irregular. She has occasional hot flushes and night sweats on tamoxifen but otherwise feels well. There is no family history of breast or ovarian cancer.

On physical examination, vital signs are normal. BMI has remained stable at 22.4. Well-healed left breast and left axilla incisions are present. There are no breast masses or lymphadenopathy. The remainder of the examination is unremarkable.

Results of a bilateral mammogram obtained 1 month ago were normal.

Which of the following is the most appropriate ne xt step in the management of this patient?

A Bilateral breast MRI

B Complete blood count, liver chemistry studies, and CEA and CA 15-3 measurement

C CT of the chest, abdomen, and pelvis and bone scan

D No diagnostic studies at this time

Answer & Critique

Correct Answer: D

Educational Objective: Manage concerns about disease recurrence in a breast cancer survivor.

Key Point

In asymptomatic patients with a history of early breast cancer, routine imaging studies (excluding annual mammography) or blood tests, including tumor marker studies, are not beneficial.

Diagnostic testing is not indicated for this patient at this time. She had stage I breast cancer treated 3 years ago and has no worrisome symptoms and no abnormal findings on physical examination. In asymptomatic patients with a history of early breast cancer, routine imaging studies (excluding annual mammography) or blood tests, including tumor marker studies, are not beneficial. These tests have a 10% to 50% false-positive rate, leading to unnecessary studies and procedures. Two randomized trials showed no survival benefit from intensive screening with routine blood and imaging tests compared with clinical evaluation alone in asymptomatic patients. One of the trials showed a decreased quality of life in the group undergoing more intensive screening.

Patients with cancer in one breast are at higher risk for contralateral breast cancer (absolute risk 0.5% to 1.0% per year), although this risk is decreased by use of antiestrogen therapy. All women with a diagnosis of breast cancer should have annual mammograms. Breast MRI is only indicated for patients with *BRCA1/2* mutations or other familial breast cancer syndromes or those with a very strong family history of breast cancer. None of these high-risk situations is present in this patient.

Except for patients with familial cancer syndromes, breast cancer survivors have no increased risks for other cancers except those related to certain treatments. Patients receiving adjuvant chemotherapy with cyclophosphamide and anthracyclines have a 0.5% risk of developing myelodysplasia and acute leukemia. Tamoxifen is associated with a 1/1000 per year risk of endometrial cancer in women over 55 years of age and a smaller risk of uterine sarcoma in this age group. These risks are low, however, and routine screening blood tests and imaging studies are not recommended in asymptomatic patients.

In addition to cancer surveillance, survivor issues that should be addressed at follow-up visits include menopausal symptoms (selective serotonin reuptake inhibitors that do not interfere with tamoxifen activation or gabapentin may be helpful), sexual dysfunction including dyspareunia due to vaginal dryness (lubricants and cautious use of very low-dose vaginal estrogen are options), arthralgia from antiestrogen therapy, cognitive dysfunction, depression, fatigue, weight gain, decreased bone density, cardiovascular disease due to radiation or chemotherapy, and thrombosis in patients taking tamoxifen.

Bibliography

Question 127

A 72-year-old man undergoes follow-up examination for prostate cancer. The patient was diagnosed with prostate cancer 2 years ago and was treated with external-beam radiation therapy. Six months ago, androgen deprivation therapy was added in response to a rising prostate-specific antigen level in the absence of local disease progression.

More recently, the patient developed worsening back and chest pain. A bone scan showed multifocal osseous metastases in the thoracic spine, lumbar spine, and ribs. CT scans of the chest, abdomen, and pelvis did not show enlarged lymph nodes or visceral metastases. His symptoms remain poorly controlled on opioid medications. Medications are extended-release morphine, oxycodone-acetaminophen, leuprolide, and flutamide.

On physical examination, blood pressure is 140/82 mm Hg, pulse rate is 97/min, and respiratory rate is 20/min. Physical examination reveals multiple tender areas involving the thoracic and lumbar spine. The remainder of the physical examination, including neurological examination, is normal.

In addition to a bisphosphonate, which of the following is the most appropriate treatment?

A

Bilateral orchiectomy

B

Estrogen therapy

C

External-beam radiation to the lumbar spine

D

Radium-223

nswer & Critique

Correct Answer: D

Educational Objective: Treat prostate cancer metastatic to bone with radium-223.

Key Point

The radiopharmaceutical agent radium-223 is associated with improvement in both symptoms and overall survival when used to treat patients with bone-limited or bone-predominant symptomatic metastatic prostate cancer.

This patient, who has recurrent prostate cancer metastatic to bone, should be treated with the radiopharmaceutical agent radium-223. Patients with metastatic prostate cancer who are found to have a biochemical recurrence (a rising serum prostate-specific antigen level and no evidence of local disease progression) will typically respond to androgen deprivation therapy. However, they will also eventually develop clinical metastatic disease. Once this occurs, optimal management depends on multiple factors, including the extent and sites of metastases and the symptoms associated with the disease. One important consideration in this setting is use of a bone-seeking radiopharmaceutical agent. These agents concentrate in bone, and recent data indicate radium-223 is associated with improvement in both symptoms and overall survival. Radium-223 is indicated specifically for patients with bone-limited or bone-predominant symptomatic metastatic disease, such as that present in this patient.

Bilateral orchiectomy, while a very effective form of antiandrogen therapy, would not be indicated in a patient who has already been demonstrated to be castrate resistant.

Estrogen therapy has uncertain benefit in the treatment of castrate-resistant prostate cancer, and would not be considered an appropriate treatment option for this patient, especially given that radium-223 has been associated with both improved survival and symptom burden.

External-beam radiation to metastatic sites can be considered for treatment of patients with spinal cord compression or for those with focal symptomatic bone metastases, neither of which this patient has.

Question 128

A 51-year-old woman undergoes a follow-up evaluation. The patient recently required surgery for stage I cancer of the right breast confirmed as a grade 3 invasive ductal carcinoma that was estrogen receptor negative, progesterone receptor negative, and *HER2* negative. Sentinel lymph nodes were negative. The patient currently states that she feels well. Medical history is otherwise unremarkable, and she is perimenopausal.

On physical examination, vital signs are normal. Healed incisions of the right breast and right axilla are present. There are no masses in either breast and no lymphadenopathy. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

A

Anastrozole

B

Anthracycline-based chemotherapy

C

Autologous hematopoietic stem cell transplantation

D

Bevacizumab

Answer & Critique

Correct Answer: B

Educational Objective: Treat early-stage triple-negative breast cancer with adjuvant chemotherapy.

Key Point

Adjuvant chemotherapy, typically anthracycline-based chemotherapy, is recommended for patients with triple-negative breast cancers who have no medical contraindications to this regimen.

Anthracycline-based chemotherapy is the most appropriate treatment. Although this patient has a stage I cancer (measuring 2 cm or less and lymph node negative), it is a high-grade, triple-negative tumor (negative for estrogen receptor, progesterone receptor, and *HER2* amplification), and she is at high risk for systemic recurrence. In patients with triple-negative cancers that are 0.6 cm or greater in size, adjuvant chemotherapy, typically anthracycline-based chemotherapy, is recommended if there are no medical contraindications. Chemotherapy is the mainstay of treatment for triple-negative breast cancers, both when used as adjuvant therapy and when used for more advanced cancers. Based on retrospective analysis, adding a taxane agent to adjuvant anthracycline-based chemotherapy is of greater benefit in patients with hormone receptor–negative cancers than in patients with hormone receptor–positive cancers.

Triple-negative cancers constitute about 15% of breast cancers and are usually of high grade. They occur more frequently in young black and Hispanic women than in other ethnic groups. Patients with triple-negative cancers have a higher risk of *BRCA1/2* mutations, and *BRCA1/2* genetic testing is recommended for women diagnosed with triple-negative breast cancers before age 60 years. Most breast cancers in women with *BRCA1* mutations are triple negative.

Antiestrogen therapies such as anastrozole are not effective in hormone receptor–negative cancers and would not be used in this patient's treatment regimen.

Autologous bone marrow transplantation is not used as adjuvant treatment for breast cancer. Clinical trials on its use in both the adjuvant setting and the metastatic setting showed no improvement in survival compared to treatment with standard therapy and its use in breast cancer has been discontinued.

Epidermal growth factor receptor–targeted therapy with bevacizumab has not been found to improve disease survival or overall survival when added to adjuvant chemotherapy for patients with triple-negative breast cancers.

uestion 129

A 38-year-old woman undergoes routine follow-up evaluation. The patient was treated with mantle irradiation for stage IIA Hodgkin lymphoma at age 19 years. She has done well and has no evidence of recurrence. Personal and family medical histories are noncontributory.

On physical examination, vital signs are normal. A healed incision from a previous lymph node biopsy is present in the right supraclavicular area. There is no lymphadenopathy, and breast examination is normal. The remainder of the examination is unremarkable.

No recent imaging studies have been obtained.

Which of the following is the recommended cancer screening program for this patient?

A

Begin annual mammograms now

B

Begin annual mammogram and breast MRIs now

C

Begin annual mammograms at age 40 years

D

Begin monthly breast self-examination now

Answer & Critique

Correct Answer: B

Educational Objective: Screen for breast cancer in a patient who has received chest radiation therapy.

Key Point

Women who received chest wall radiation (such as mantle radiation therapy for Hodgkin lymphoma) between the ages of 10 and 30 years are at high risk for developing breast cancer and should be screened with annual mammograms and breast MRIs.

This patient should now be screened with mammography and accompanying breast MRI on an annual basis. Women who received chest wall radiation (such as mantle radiation therapy for Hodgkin lymphoma) between the ages of 10 and 30 years are at high risk for developing breast cancer and, according to the American Cancer Society 2007 guidelines, should be screened with breast MRIs as well as annual mammograms. Such women have a 30% to 50% lifetime risk of developing breast cancer within the radiation field. A recent study from England and Wales reviewed the incidence of breast cancer in 5002 women treated with supradiaphragmatic radiation therapy for Hodgkin lymphoma before age 36 years. This study showed an increased breast cancer risk starting 10 years after radiation exposure and peaking 25 to 34 years after exposure. At the 40-year follow-up, the risk of breast cancer was 48% for patients who received 40 Gy or more of mantle radiation therapy at a young age. Breast MRI is more sensitive, although less specific, than mammography for the detection of invasive breast cancers and has been studied prospectively in women with a high risk of breast cancer. However, mammography may still detect cancers not seen on MRI; therefore, a dual imaging strategy is recommended. In one study, the combination of mammogram and breast MRI had a sensitivity of 0.94 for detecting invasive breast cancer compared with a sensitivity of 0.39 with mammogram alone.

For the reasons noted above, yearly mammograms alone are less effective than a screening program including breast MRI.

Some groups, including the American Cancer Society, recommend annual mammography starting at age 40 years for women with an average breast cancer risk, whereas the American College of Physicians and the United States Preventive Services Task Force suggest initiating discussion with patients between the ages of 40 to 49 years who are at average risk for breast cancer

regarding the risks and benefits of screening to determine the appropriate screening approach. Additionally, none of these groups recommends the use of MRI in screening for breast cancer in average risk women. This woman's breast cancer risk is far above average, and delaying mammography would be an inadequate screening approach for her.

There is no evidence that breast self-examination (BSE) decreases breast mortality. Some expert groups raise concerns about increased harm with BSE, such as unnecessary distress and procedures for benign lumps. Most guidelines from expert groups recommend against BSE, with a few recommending “breast self-awareness” or education about the benefits and limitations of BSE. BSE alone as a screening strategy in this high-risk patient is inadequate.

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Answer & Critique

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Question 130

A 55-year-old woman undergoes follow-up evaluation for a recent diagnosis of lung cancer. Initial evaluation included a plain chest radiograph that showed a right middle lobe mass confirmed as a 3-cm spiculated mass on chest CT. PET/CT identified hypermetabolic uptake in the mass but was otherwise normal.

On surgical resection, the tumor was identified as an intermediate-grade adenocarcinoma with clear margins and was negative for molecular genetic abnormalities. One hilar lymph node was positive, and 10/10 mediastinal lymph nodes were negative for tumor.

She has never smoked. Medical history is otherwise negative, and she takes no medications.

On physical examination, vital signs are normal. Her right thoracic surgical incisions are clean and dry. The lung fields are clear. The remainder of her examination is unremarkable.

Which of the following is the most appropriate next step in this patient's management?

A

Chemotherapy

B

Erlotinib

C

Radiation therapy

D

Observation

Answer & Critique

Correct Answer: A

Educational Objective: Treat non–small cell lung cancer with chemotherapy.

Key Point

Cisplatin-based adjuvant chemotherapy improves survival for selected patients who have undergone successful resection of stage II or stage III non–small cell lung cancer, regardless of histologic type.

Chemotherapy is most appropriate for this patient with stage II non–small cell lung cancer (NSCLC). Although several combination chemotherapeutic regimens have been studied, so far only a cisplatin-based regimen has been shown to be effective in selected patients with NSCLC. Currently available studies indicate that adjuvant cisplatin-based chemotherapy, given for a total of four cycles, improves survival in patients who have undergone successful resection of stage II or stage III NSCLC, regardless of histologic type.

Erlotinib is a tyrosine kinase inhibitor with activity against tumors expressing mutations in the epidermal growth factor receptor (EGFR). Although erlotinib is effective in the treatment of EGFR mutation–positive patients with metastatic NSCLC, its effectiveness in the adjuvant treatment setting has not been established.

Although radiation therapy may decrease locoregional recurrence, it has not been shown to improve survival in patients with stage II lung cancer with clear margins after resection and therefore is not given to such patients as adjuvant treatment.

Observation alone is inappropriate because of the survival advantage associated with adjuvant chemotherapy and because this patient has no apparent contraindications to administration of chemotherapy. Potential contraindications to chemotherapy include poor performance status following surgery and the presence of medical comorbidities that predict for an increase in toxicity associated with chemotherapy treatment.

Question 131

A 58-year-old woman is evaluated for a 6-month history of progressive lymphadenopathy. She is otherwise asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Cervical and axillary lymphadenopathy is palpated. Abdominal examination reveals splenomegaly; the liver is not enlarged. The remainder of the examination is unremarkable.

Laboratory studies indicate a leukocyte count of 12,000/μL (12.0×10^9/L), with 65% lymphocytes.

CT scans show diffuse cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following diagnostic studies should be performed next?

A

Bone marrow biopsy

B

Excisional biopsy of an enlarged lymph node

C

Fine-needle lymph node biopsy

D

Lumbar puncture

E

PET/CT scan

Answer & Critique

Correct Answer: B

Educational Objective: Evaluate a patient with possible lymphoma with an excisional lymph node biopsy.

Key Point

Excisional biopsy of an adequate tissue sample that preserves the architecture of the lymph node is required for the diagnosis of lymphoma.

This patient most likely has lymphoma, and excisional or core needle biopsy of an enlarged lymph node should be done next to establish a tissue diagnosis. Optimally, an excisional biopsy should be performed to preserve lymph node architecture which is important in differentiating reactive lymphadenopathy from lymphoma. Core needle biopsy is able to sample some structural aspects of the lymph node, and may be used for deep lymph nodes in place of excision. This patient's presentation of asymptomatic but progressive lymphadenopathy, splenomegaly, and lymphocytosis is highly suggestive of lymphoma. To determine the subtype of lymphoma and to guide therapy, the biopsy specimen is sampled for histopathologic, cytogenetic, and fluorescence in situ hybridization (FISH) analysis, as well as immunophenotype and gene expression profiling. Routine blood studies include a complete blood count with differential, erythrocyte sedimentation rate, and serum chemistry studies, including serum urate level. Serum lactate dehydrogenase, $?_2$-microglobulin, and immunoglobulin levels should also be determined. Screening for viral infections, including hepatitis B and C, HIV, human T-cell lymphotrophic virus type 1, human herpesvirus-8, and Epstein-Barr virus (and, when indicated, screening for bacterial infection due to *Helicobacter pylori*), needs to be performed because these infections can be causative drivers of lymphoma. As active infections may reduce lymphoma response rates and duration, it is essential to treat both the lymphoma and any underlying infections.

Although bone marrow biopsy, generally iliac crest bone marrow biopsy, is needed to complete the evaluation, excisional or core needle biopsy should be done first to establish a tissue diagnosis prior to staging.

Fine-needle lymph node biopsy should not be used because it will not preserve the architecture of the lymph node that is required for the diagnosis of lymphoma.

Patients with aggressive lymphoma presenting with involvement of the testes, sinuses, bone marrow, and ocular sites have an increased risk of central nervous system involvement and require lumbar puncture for cerebrospinal fluid examination. This procedure is only appropriate following the diagnosis and staging of non-Hodgkin lymphoma.

PET scanning is performed to complete staging but, again, should not be done until a tissue diagnosis is established. Early repeat PET scanning (after two to three cycles of chemotherapy) provides important prognostic information for patients with Hodgkin lymphoma but not for those with non-Hodgkin lymphoma.

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Question 132

A 79-year-old man is evaluated for a recent diagnosis of prostate cancer following detection of a left-sided prostate nodule during evaluation for worsening prostatic hyperplasia symptoms. Biopsy of the prostate nodule showed adenocarcinoma with a Gleason score of 3 + 4 = 7; additional core samples were negative for cancer. Medical history is also significant for myocardial infarction and heart failure. The patient has been hospitalized three times in the past 12 months because of exacerbations of heart failure. Medications are carvedilol, lisinopril, metoprolol, aspirin, furosemide, tamsulosin, and finasteride.

On physical examination, vital signs are normal. Mild bibasilar crackles are auscultated and there is trace lower extremity edema. The remainder of the physical examination is unremarkable.

Serum prostate-specific antigen level prior to biopsy was 4.9 ng/mL (4.9 μg/L).

Which of the following is the most appropriate management?

A

Active surveillance

B

Cryotherapy

C

External-beam radiation therapy

D

Radical prostatectomy

E

Observation

Answer & Critique

Correct Answer: E

Educational Objective: Manage early-stage prostate cancer in an elderly man with medical comorbidities.

Key Point

Observation is the appropriate management for an elderly man with newly diagnosed, low-risk prostate cancer and medical comorbidities that significantly limit life expectancy.

Observation, or watchful waiting, is most appropriate for this elderly man with newly diagnosed prostate cancer and medical comorbidities after the benefits and risks of this approach are discussed with the patient. Observation is based on an assessment that a patient would not benefit from definitive treatment of prostate cancer, either because of significant comorbidities or a shortened life expectancy, with the expectation that palliative treatment could be provided if the disease progresses. This patient's prostate-specific antigen (PSA) level, extent of disease based on biopsy findings, and Gleason score are all predictors of low-risk disease. Furthermore, he has a significant medical history, including worsening heart failure. Given that this patient has very low-risk prostate cancer and a life expectancy most likely less than 10 years, observation is the most appropriate management option for this patient.

Active surveillance, in contrast to observation, is the postponement of definitive therapy with the intent to pursue treatment of curative intent if there is evidence of disease progression. Active surveillance involves a program of regular assessment with physical examination, PSA testing, and prostate biopsy. It would not be appropriate for this patient, given his life expectancy related to significant medical comorbidities.

Cryotherapy is a technique that freezes prostatic cancer cells to treat localized prostate cancer. However, its role as a treatment option for localized prostate cancer has not been established at present.

Both external-beam radiation therapy and radical prostatectomy are reasonable alternatives for definitive treatment in patients considered appropriate candidates for therapy. However, the risks of either would likely outweigh the benefits of treatment in this patient with low-risk disease and significant medical comorbidities.

Question 133

A 77-year-old woman is evaluated for new-onset fatigue and anemia. She otherwise feels well. Medical history is unremarkable, and she takes no medications.

Physical examination findings, including vital signs, are normal. BMI is 22.

Colonoscopy identifies a 7-cm mass in the transverse colon. Biopsy of the mass shows poorly differentiated adenocarcinoma. Contrast-enhanced CT scans of the chest, abdomen, and pelvis show the mass, but no other abnormalities are identified.

Which of the following is likely to be the most important factor in determining this patient's prognosis?

A

Degree of differentiation of the tumor

B

Patient's performance status

C

Size of the tumor

D

Stage of the tumor

Answer & Critique

Correct Answer: D

Educational Objective: Determine the prognosis in a patient with newly diagnosed colon cancer.

Key Point

Tumor stage is usually the most important prognostic factor in determining outcome in a patient with newly diagnosed cancer.

Tumor stage is usually the most important prognostic factor in determining a patient's outcome. Staging typically involves ordering appropriate tests to identify the local extent of the primary tumor and to determine whether the disease has spread beyond the site of origin. Although specific staging will vary according to the unique anatomic and biologic features of the primary site, there are many common steps to the staging process. Most solid tumors are staged according to the American Joint Commission on Cancer (AJCC) TNM classification. “T” indicates the extent of the tumor (size and/or depth of penetration), “N” represents the number of locoregional lymph nodes that contain cancer, and “M” indicates whether metastases are present or absent. TNM scores are then classified on a scale of stage I to IV, with stage I tumors having the best prognosis and stage IV having the worst.

Although poorly differentiated tumors generally have a worse prognosis than well-differentiated tumors, this is a modest prognostic factor compared with staging.

Performance status, which is a designation of the patient's overall medical “wellness” and ability to perform routine daily activities, may have important prognostic implications within a particular stage of disease but is far less significant prognostically than the stage itself.

Tumor size may be a component of the “T” stage, but by itself has only modest prognostic significance relative to overall stage. Generally, the degree of lymph node involvement has a greater negative impact on prognosis than does a higher T stage, and the presence of metastatic disease beyond lymph node involvement has the worst prognosis.

Question 134

A 48-year-old woman is evaluated for a 6-month history of rectal pain and bright red blood per rectum upon defecation. She has a long-standing history of genital warts. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals no masses. Bowel sounds are normal, and the liver and spleen are not enlarged. Digital rectal examination reveals a hard, tender mass in the anal canal measuring approximately 2.5 cm in diameter. There is no inguinal lymphadenopathy.

Laboratory studies are unremarkable.

Contrast-enhanced CT scan of the pelvis confirms the anal mass and shows no associated lymphadenopathy or other abnormalities. Contrast-enhanced CT scans of the chest and abdomen are normal. Biopsy of the anal mass shows invasive squamous cell carcinoma.

Which of the following is the most appropriate treatment?

A

Radiation therapy

B

Radiation therapy with concurrent chemotherapy

C

Radiation therapy with concurrent chemotherapy followed by surgical resection

D

Surgical resection

Answer & Critique

Correct Answer: B

Educational Objective: Treat locally advanced anal cancer with radiation and concurrent chemotherapy.

Key Point

The standard treatment regimen for patients with stage I, II, or III anal squamous cell carcinoma is radiation therapy with concurrent chemotherapy consisting of mitomycin plus 5-fluorouracil.

This patient, who has locally invasive squamous cell carcinoma of the anus, requires pelvic radiation therapy and concurrent systemic chemotherapy, a regimen that is appropriate for patients with stage I, II, and III anal cancer. Compared with rectal cancer, which is typically adenocarcinoma for which resection is the initial therapeutic step, anal cancers are usually of squamous cell origin, with chemoradiation the primary treatment modality owing to increased cure rates. Mitomycin plus 5-fluorouracil (5-FU) has been used to treat patients with anal cancer since the 1970s and remains the standard chemotherapy regimen. Randomized clinical trials have demonstrated that radiation therapy plus chemotherapy is superior to radiation therapy alone and that the combination of 5-FU plus mitomycin is superior to use of 5-FU alone.

Radiation therapy alone is inadequate for treatment of anal cancer.

If radiation therapy and chemotherapy fail to eradicate this patient's anal cancer, surgery can be performed as salvage treatment. However, the procedure required to excise an anal cancer also requires removal of the anal sphincter and placement of a permanent colostomy. Consequently, surgery as either initial treatment or as a planned procedure following initial radiation therapy and chemotherapy without documentation of continuing metastases would not be appropriate because of the unacceptable level of morbidity.

Anal cancer is a squamous cell carcinoma that arises in the squamous epithelium of the anus and is typically associated with human papillomavirus exposure. It is a distinct entity from rectal cancer, which arises in the columnar epithelium of the rectum, is an adenocarcinoma, and is typically treated with a combination of radiation therapy, chemotherapy, and definitive surgery.

Question 135

A 62-year-old man undergoes follow-up evaluation. The patient received an examination 2 weeks ago following a minor bicycle accident during which a firm, nontender, palpable liver edge 2 cm below the right costal margin was found incidentally. Examination findings were otherwise unremarkable.

A contrast-enhanced CT scan of the abdomen showed a slightly enlarged liver with numerous (>10) hypodense lesions ranging in size from 0.5 to 1.5 cm. Needle biopsy of a liver lesion showed a low-grade, well-differentiated neuroendocrine tumor with fewer than 2 mitoses per 50/hpf. An indium-111 pentetreotide scan (radiolabeled octreotide scan) confirmed the presence of multiple small-volume liver lesions, as well as an approximately 1-cm area of increased avidity in the mesentery consistent with a small bowel carcinoid primary tumor.

Medical history is otherwise unremarkable. He has not had diarrhea, constipation, flushing of the skin, or wheezing. He takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable except for the palpable liver edge.

Laboratory studies:

Alkaline phosphatase	115 U/L
Alanine aminotransferase	Normal
Aspartate aminotransferase	Normal
Total bilirubin	Normal
Serotonin	Normal

Which of the following is the most appropriate management?

A

Hepatic artery embolization

B

Octreotide therapy

C

Radiofrequency ablation of the liver lesions

D

Repeat abdominal imaging in 3 to 4 months

ESystemic chemotherapy

Answer & Critique

Correct Answer: D

Educational Objective: Manage a patient with a low-grade metastatic carcinoid tumor.

Key Point

Appropriate management for a patient with an incidental finding of a metastatic low-grade carcinoid tumor that is asymptomatic and hormonally nonfunctional consists of expectant observation and repeat imaging studies several times each year to determine whether the disease is progressing.

Repeat abdominal imaging with a contrast-enhanced CT scan of the abdomen in 3 to 4 months is most appropriate. This patient has an incidental finding of a metastatic low-grade carcinoid tumor that is asymptomatic and hormonally nonfunctional. It is impossible to know how long the tumor has been present. However, given the benign presentation and near-normal liver function studies, the tumor has probably been present for many years. Because urgent intervention is unlikely to be needed, expectant observation and repeat imaging studies in 3 to 4 months will be useful in establishing disease progression. For many patients, little or no change is seen on serial scans, and these patients may be followed with serial imaging studies two to three times each year. If substantial tumor progression or tumor-related symptoms develop, intervention should be considered.

Hepatic artery embolization may be effective in decreasing tumor volume in the liver or decreasing hormone production in patients with neuroendocrine tumors. However, this is an invasive procedure that carries risks of morbidity and mortality and would not be appropriate for an asymptomatic patient with small-volume, hormonally nonfunctional disease.

This patient does have a positive radiolabeled octreotide scan, indicating that somatostatin receptors are present on the tumor (as they are in most neuroendocrine tumors). Therefore, treatment with octreotide, a somatostatin analogue, could be considered in the future if the disease progresses. Although actual tumor regression following octreotide administration is rare, octreotide has been demonstrated to stabilize and delay progression of carcinoid tumors and would be an appropriate consideration if progression of this patient's tumor is seen on serial imaging.

Radiofrequency ablation is another invasive procedure that can be used to treat patients with a small number of liver lesions. However, it has no role in the treatment of patients with numerous lesions, such as the patient described here.

Systemic chemotherapy would also not be indicated in a patient with an asymptomatic neuroendocrine tumor in the absence of disease progression or disease-related symptoms.

Question 136

A 55-year-old man is evaluated for a 1-year history of postprandial indigestion. Associated symptoms are nausea, oily stools, and a 4.5-kg (10.0-lb) weight loss over the past 6 months. His medical history is significant for a recent diagnosis of prediabetes. His current medications are ibuprofen, acetaminophen, and omeprazole.

On physical examination, vital signs are normal; BMI is 25. Scleral icterus is present. Abdominal examination reveals epigastric abdominal pain without guarding or rebound. The remainder of the examination is normal.

Upper endoscopy is normal. Contrast-enhanced CT scan shows a solid 2.5-cm hypoattenuating lesion suspicious for pancreatic adenocarcinoma confined to the head of the pancreas. Dilation of the upstream pancreatic duct and common bile duct is noted. There is no regional lymphadenopathy. The liver parenchyma appears normal.

Which of the following is the most appropriate management?

A

Endoscopic ultrasound–guided fine needle aspiration

B

Measurement of CA 19-9

C

Percutaneous needle biopsy

D

Surgical resection of the pancreatic mass

Answer & Critique

Correct Answer: D

Educational Objective: Diagnose and stage pancreatic adenocarcinoma.

Key Point

In patients who have imaging that is characteristic of resectable pancreatic cancer, tissue sampling prior to potential curative resection is not appropriate, and definitive resection without prior tissue confirmation should be pursued.

The most appropriate management is surgical resection of the pancreatic mass. This patient likely has localized and potentially resectable pancreatic adenocarcinoma. Strong supportive data include clinical risk factors (age ?50 years, cigarette smoking, new-onset diabetes mellitus), symptoms (weight loss, dyspepsia), and CT imaging findings (a discrete, solid, low-attenuating mass with dilation of the upstream pancreatic duct and common bile duct [“double-duct sign”]).

Percutaneous or endoscopic ultrasound?guided tissue sampling is generally not recommended in patients who are operative candidates with potentially resectable (localized) pancreatic cancer because negative results may simply represent sampling error and are insufficient to rule out the presence of cancer. Thus, they entail risk and do not affect management.

The tumor marker CA 19-9 has variable sensitivity and specificity for pancreatic cancer and is generally not recommended as a screening test; management will not be changed by the results of this test at this time, however, it can add prognostic value for patients diagnosed with metastatic pancreatic cancer.

Question 137

A 63-year-old woman is evaluated for a 2-month history of pain in her right chest and right ribs as well as right upper abdominal discomfort. Medical history is significant for stage II cancer of the right breast diagnosed 4 years ago and identified as an estrogen receptor–positive, progesterone receptor–negative, *HER2*-negative invasive ductal carcinoma with negative sentinel lymph nodes. She was treated with breast-conserving therapy, primary breast radiation therapy, and adjuvant chemotherapy and has been receiving adjuvant anastrozole since completing radiation.

On physical examination, vital signs are normal. There is tenderness over the anterior lower right ribs, but no mass or bone defects are present. There are no breast masses or lymphadenopathy. Abdominal examination shows no epigastric mass or tenderness. The liver and spleen are not palpable.

Chest and rib radiographs are normal. CT scans of the abdomen and pelvis show two liver lesions and lytic bone lesions in the spine and pelvis consistent with metastases.

Which of the following is the most appropriate management?

A

Anthracycline-based chemotherapy

B

Biopsy of a liver lesion

C

Exemestane combined with everolimus

D

PET/CT scan

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose metastatic breast cancer through biopsy of a suspicious lesion.

Key Point

Patients with a history of early breast cancer who develop findings suspicious for metastatic breast cancer should undergo biopsy of one of the suspected metastatic sites to confirm the diagnosis and to assess hormone receptor and *HER2* status, as these may differ from the original cancer.

Patients with a history of early breast cancer who develop findings suspicious for metastatic breast cancer should first have a biopsy of one of the suspected metastatic sites to confirm the diagnosis and to assess hormone receptor and *HER2* status, as these may differ from the original cancer. A study of suspected metastatic lesions in 121 women with newly metastatic breast cancer showed discordance between the primary and the metastatic site in 16% of specimens for estrogen receptor, 40% for progesterone receptor, and 10% for *HER2*. Biopsy led to a change in management in 14% of patients. Since bone biopsy specimens cannot be assessed for *HER2* status unless there is a soft tissue component, biopsy of an area other than bone is preferred, if possible.

Beginning chemotherapy is inappropriate before the diagnosis of metastatic breast cancer and its hormone receptor and *HER2* status are confirmed by biopsy.

Beginning antiestrogen therapy (for example, exemestane combined with everolimus) is also inappropriate before biopsy confirmation of metastatic breast cancer.

Although a PET/CT scan may be useful for staging disease and following response to treatment in patients with metastatic breast cancer, it is important first to establish the diagnosis by biopsy. In this patient, the ultrasound and CT scans have already identified an accessible location for biopsy, and a PET scan is not needed before proceeding to biopsy of one of the liver lesions.

Question 138

A 70-year-old woman is hospitalized for worsening generalized weakness, anorexia for several days associated with weight loss, and back pain responsive to NSAID administration. The patient recently completed chemotherapy for poorly differentiated adenocarcinoma of the right lung and metastasis-related pathologic compression of the L3 vertebral body without cord compression. Her Eastern Cooperative Oncology Group/World Health Organization performance status is 3 (confined to bed or chair more than 50% of waking hours).

At the time of diagnosis, the patient was treated with four cycles of carboplatin/paclitaxel chemotherapy. CT scans after completing chemotherapy showed an increase in the right lung mass, a new right pleural effusion, increased size of hilar and mediastinal lymph nodes, and new lesions in the liver, consistent with metastases.

On physical examination, the patient is afebrile, blood pressure is 95/57 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. Oxygen saturation is 94% on ambient air. Decreased breath sounds are auscultated over the right lower lung field. There is tenderness over the lumbosacral area. Neurological examination is normal.

Which of the following is the most appropriate next step in management?

A

Comprehensive palliative care assessment

B

Initiation of a different chemotherapy regimen

C

Initiation of artificial nutrition support

D

Placement of a thoracostomy tube

E

Radiation therapy to the L3 vertebral body

Answer & Critique

Correct Answer: A

Educational Objective: Manage a patient with metastatic lung cancer and poor performance status.

Key Point

Patients with lung cancer and poor performance status do not benefit from chemotherapy and should undergo a palliative care assessment.

Recommending comprehensive palliative care assessment for possible hospice care is indicated. Stage IV (metastatic) non–small cell lung cancer (NSCLC) is incurable. Because metastatic NSCLC is a systemic process, systemic chemotherapy is typically used as the primary treatment modality. Chemotherapy for stage IV NSCLC has been shown to prolong survival and improve quality of life. However, patients with poor performance status and advanced disease have a limited prognosis (less than 4 months) despite therapy. Goals of therapy for these patients are symptom palliation and possible prolongation of survival. This patient has progressive metastatic lung cancer based on imaging studies that were obtained after she completed four cycles of chemotherapy. She also has a clear decline in functional status. Based on these findings, hospice care would be most appropriate.

The response rate to second-line chemotherapy is very low in patients with NSCLC. In addition, all available evidence indicates that patients with an Eastern Cooperative Oncology Group/World Health Organization performance status of 2 or worse do not derive benefit from chemotherapy.

Providing artificial nutrition for patients with advanced cancer has not been shown to improve outcomes and is not usually recommended.

The pleural effusion identified on the most recent imaging studies is small and is not causing respiratory compromise. Thoracostomy tube drainage is therefore not indicated.

Radiation therapy should be considered to relieve pain, particularly bony pain, visceral pain (when secondary to capsular distension), or pain due to nerve/nerve root compression. Although this patient has pain due to a metastatic lesion involving the L3 vertebral body, the pain is mild,

managed with a NSAID, and there is no evidence of cord compression; consequently, radiation treatment is not needed for palliation.

Question 139

A 78-year-old man is evaluated for headaches, blurred vision, facial flushing, and mild right midback discomfort. The patient is a lifelong nonsmoker.

On physical examination, blood pressure is 150/95 mm Hg; other vital signs are normal. Oxygen saturation is 99% on ambient air. Facial plethora is present. There is no hepatosplenomegaly. The remainder of the examination is unremarkable.

Laboratory studies:

Erythropoietin	150 mU/mL (150 U/L)
Hematocrit	55.2%
Hemoglobin	18.2 g/dL (182 g/L)
Leukocyte count	8200/µL (8.2×10^9/L)
Platelet count	312,000/µL (312×10^9/L)

Urinalysis reveals microscopic hematuria.

Which of the following diagnostic studies should be performed next?

A

Bone marrow biopsy

B

CT of the abdomen and pelvis

C

JAK2 mutation testing

D

Peripheral blood flow cytometry

Answer & Critique

Correct Answer: B

Educational Objective: Diagnose renal cell carcinoma in a patient with erythrocytosis and a high serum erythropoietin level.

Key Point

The finding of a markedly elevated serum erythropoietin level in a patient with vague midback pain and microscopic hematuria suggests the presence of an underlying renal cell carcinoma.

This patient requires CT of the abdomen and pelvis to detect possible renal cell carcinoma. The findings of a markedly elevated serum erythropoietin level due to secondary erythrocytosis plus vague midback pain and microscopic hematuria suggest the presence of an underlying renal cell carcinoma. Renal cell carcinoma is associated with secondary erythrocytosis in about 1% to 3% of patients. Polycythemia vera (PCV), a myeloproliferative neoplasm that results in excessive and unregulated erythrocyte production, is associated with very low serum erythropoietin levels. In contrast, an elevated serum erythropoietin level indicates the presence of secondary erythrocytosis. Although the most common causes of secondary erythrocytosis are chronic hypoxia and elevated carboxyhemoglobin concentrations due to tobacco use, an important cause is an erythropoietin-producing tumor. Other tumors commonly associated with secondary erythrocytosis include hepatocellular carcinoma and pheochromocytoma.

Bone marrow biopsy is not indicated because of this patient's markedly elevated serum erythropoietin level, which suggests external erythropoietin production and not a bone marrow disorder as a cause of this patient's polycythemia.

JAK2 mutation testing, which would be appropriate to rule out PCV in a patient with a very low serum erythropoietin level, is not indicated for this patient who has a markedly elevated level that is not compatible with a diagnosis of PCV.

Peripheral blood flow cytometry would not add useful information because this patient has isolated polycythemia and no evidence of abnormal lymphocytes. Flow cytometry is best used to help establish a diagnosis when evaluating for a malignancy that would reveal a monoclonal population of cells with a specific phenotype.

Question 140

A 42-year-old man is evaluated for a 3-month history of dyspepsia and increasing episodes of nausea. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Examination of the abdomen is normal.

Upper endoscopy discloses a large (6-cm) mass in the wall of the proximal duodenum. Biopsy reveals a gastrointestinal stromal tumor staining positive for KIT protein (CD117). Contrast-enhanced CT scans of the chest and abdomen show no other abnormalities.

The patient undergoes complete resection of the mass with clear margins. The final pathology report confirms the original diagnosis and notes a high mitotic rate of 5 to 10 mitoses per 50/hpf. The tumor is classified as being at higher risk for recurrence on the basis of its mitotic rate, large size, and location in the small intestine.

Which of the following is the most appropriate adjuvant treatment?

A

Epirubicin, cisplatin, and 5-fluorouracil

B

Imatinib

C

Radiation therapy

D

Observation

Answer & Critique

Correct Answer: B

Educational Objective: Treat a localized gastrointestinal stromal tumor with imatinib after surgical resection.

Key Point

Patients with a localized gastrointestinal stromal tumor with a relatively higher risk for recurrence should be treated with imatinib for 3 years following resection of the tumor.

Imatinib for 3 years is the most appropriate adjuvant treatment for this patient, who has a localized gastrointestinal stromal tumor (GIST) associated with a relatively higher risk for recurrence. GISTs, although rare, are the most common sarcoma of the gastrointestinal tract. The most common site is in the stomach, but GISTs can arise anywhere in the digestive tract. Location outside the stomach, larger size, and higher mitotic index constitute relative high-risk factors for recurrence after resection. Patients with small gastric GISTs with low mitotic indices may often be managed with surgery alone. Higher-risk tumors, such as in this patient, require further treatment. A 3-year course of the oral tyrosine kinase inhibitor imatinib has been shown to improve outcomes when used as adjuvant therapy after surgical resection of localized higher-risk GISTs. Imatinib has also been shown to be highly active in treating patients with metastatic GISTs, in whom lifelong therapy is recommended. Finally, randomized clinical trials have shown a superior outcome for those patients with localized higher-risk GISTs who receive imatinib for 3 years compared with those receiving 1 year of treatment.

The MAGIC trial demonstrated the superiority of preoperative and postoperative chemotherapy (epirubicin, cisplatin, and 5-fluorouracil) compared with surgery alone for treatment of gastric and esophageal/gastroesophageal junction adenocarcinomas. In patients who undergo surgery as initial therapy, postoperative 5-fluorouracil and leucovorin plus radiation therapy have been shown to confer a survival benefit compared with postoperative observation alone. These therapies are not effective treatments for GISTs.

GISTs are relatively resistant to radiation, and adjuvant radiation therapy is not routinely indicated.

Observation following surgical resection is appropriate only for patients with GISTs associated with favorable risk factors, whereas this patient has a higher-risk tumor.

Question 141

A 37-year-old woman is evaluated in the emergency department for fever and rigors of 4 hours' duration. Medical history is significant for acute lymphoblastic leukemia for which she completed multiagent chemotherapy 10 days ago. Her medical history is otherwise noncontributory, and she takes no other medications.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 110/60 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. On pulmonary examination, the lungs are clear. The remainder of the physical examination is unremarkable.

Laboratory studies indicate a leukocyte count of 0.3/μL (0.0003×10^9/L) with 0 neutrophils. The remaining laboratory studies are normal.

A chest radiograph is normal. Blood and urine cultures are obtained.

Which of the following is the most appropriate next step in management?

A

Administer granulocyte-macrophage colony-stimulating factor

B

Await culture results before starting antimicrobial therapy

C

Begin piperacillin-tazobactam

D

Begin vancomycin

Answer & Critique

Correct Answer: C

Educational Objective: Manage neutropenia and fever in a patient with leukemia.

Key Point

Patients with a neutrophil count less than 1000/µL (1.0×10^9/L) or at any level in the presence of fever or other signs of infection require rapid administration of broad-spectrum antibiotics.

This patient requires immediate parenteral administration of a broad-spectrum antibiotic such as piperacillin-tazobactam while blood and urine cultures are pending. Neutropenia is defined as an absolute neutrophil count less than 1000/µL (1.0×10^9/L). Monotherapy with a ?-lactam agent with broad coverage of gram-positive and gram-negative organisms with antipseudomonal activity has been shown to be effective in treating neutropenic fever and is the most commonly used approach. Although combination antibiotic therapy is often used (such as the addition of an aminoglycoside for additional antipseudomonal coverage), no specific regimen has been shown to be superior to broad-spectrum monotherapy. It is also reasonable to further broaden directed antimicrobial therapy if a specific source is suspected, such as adding gram-positive coverage (for example, vancomycin) if a central catheter infection is considered likely. Antifungal agents are usually considered only for patients with mucosal barrier inflammation and prolonged neutropenia (>1 week), and antiviral agents are used only in patients whose disease or therapy is associated with immunosuppression. Antimicrobial therapy should be narrowed if a specific organism or organisms are identified on culture.

Because of resistance, fluoroquinolones are not frequently used as initial monotherapy for patients with neutropenic fever. However, they may have a role in selected low-risk patients with stable vital signs and an unremarkable physical examination who might be eligible for outpatient oral therapy at experienced centers with close monitoring capability. They may also be used as add-on therapy for specific infections or for directed therapy based on culture results.

Hematopoietic growth factors, including granulocyte-macrophage colony-stimulating factors, are effective in preventing neutropenia and allowing for continued full-dose chemotherapy when

appropriate. These agents also may reduce the duration of neutropenia and the length of hospitalization for patients admitted if fever develops in the setting of neutropenia. However, hematopoietic growth factors are not a replacement for immediate antimicrobial therapy in patients with fever and neutropenia and do not have a clear role in treatment.

Waiting for culture results before administering antimicrobial agents in patients with neutropenia and fever is never appropriate. If patients do not receive parenteral antimicrobials immediately after cultures are taken, their condition can rapidly deteriorate over 12 to 24 hours, and they can experience sepsis, shock, and death.

Although gram-positive organisms are the most commonly identified cause of neutropenic fever, initial monotherapy with vancomycin is not appropriate because of the potential virulence of gram-negative organisms. Vancomycin is usually not a routine component of empiric broad-spectrum antibiotic therapy for neutropenic fever without a specific indication.

Question 142

A 61-year-old man undergoes follow-up evaluation for prostate cancer diagnosed 6 months ago that was treated with radical prostatectomy. CT scans of the chest, abdomen, and pelvis at the time of diagnosis were normal. Bone scan at that time showed no evidence of metastatic disease. The serum prostate-specific antigen (PSA) level at the time of surgery was 12 ng/mL (12 µg/L), decreasing to 0.6 ng/mL (0.6 µg/L) 6 weeks after surgery.

Physical examination findings are unremarkable.

Serum PSA measurement obtained at the time of this visit is 10 ng/mL (10 µg/L). Repeat imaging studies were obtained, and no evidence of metastatic disease was identified.

Which of the following is the most a ppropriate management?

A

Androgen deprivation therapy

B

Chemotherapy

C

Continued monitoring of the serum PSA level

D

Salvage radiotherapy

Answer & Critique

Correct Answer: A

Educational Objective: Manage a patient with prostate cancer recurrence following radical prostatectomy.

Key Point

Men who have a persistently elevated serum prostate-specific antigen level immediately following surgery for prostate cancer have a high likelihood of harboring distant metastatic disease and should be started on androgen deprivation therapy.

Androgen deprivation therapy is indicated for this patient with possible metastatic prostate cancer. Following surgery for early-stage prostate cancer, the serum prostate-specific antigen (PSA) level should be undetectable. A postoperative serum PSA level of 0.2 ng/mL (0.2 µg/L) or greater is therefore diagnostic of residual or recurrent prostate cancer. Although this finding can represent either locally recurrent or distant metastatic disease, timing is an important discriminating factor in ascertaining the likelihood of local versus distant recurrence. Men who have a persistently elevated PSA level, particularly a rising level immediately following surgery (such as the patient described here), have a high likelihood of harboring distant metastatic disease. Androgen deprivation therapy is therefore indicated for this patient. Prostate cancer cells usually need testosterone to grow. Surgical or chemical castration is highly effective in reducing serum testosterone levels and suppressing prostate cancer cell growth.

Patients with metastatic prostate cancer are first treated with androgen deprivation therapy. Although prostate cancer initially is androgen dependent, over time, cancer cells become androgen independent. Chemotherapy has recently been shown to prolong life expectancy in many of these patients. Since this patient has not yet been treated with androgen deprivation therapy, chemotherapy is not indicated.

A rising PSA level indicates biochemical recurrence, and estimates of survival can be made from the time of completion of treatment to the rise in the PSA, the rate of that rise, and the initial Gleason score. Although recurrent disease after definitive therapy of early-stage prostate cancer is incurable, significant palliation can be achieved with hormone deprivation therapy and chemotherapy. Continuing to monitor the PSA level without initiating therapy is not recommended.

Identification of biochemical recurrence 2 or more years after surgery is more consistent with local recurrence. Studies have shown that salvage radiotherapy is beneficial for men diagnosed with a biochemical recurrence 2 or more years after surgery. In contrast, radiotherapy does not seem to benefit men in whom a PSA level remains detectable following surgery.

Question 143

A 72-year-old man is evaluated for a 4-month history of pain in the left side of his throat. He also has pain when swallowing and a 2-month history of dysphagia. The patient has a 15-pack-year smoking history but stopped smoking 5 years ago. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There is no palpable cervical adenopathy and there are no abnormalities on inspection or palpation of the oral pharynx and tongue.

Laryngoscopy identifies a mass centered in the left tongue base. Biopsy of the mass identifies moderately differentiated invasive squamous cell carcinoma. PET/CT scans show hypermetabolic uptake in the tongue base mass without any evidence of cervical lymph node involvement or distant metastasis. On PET/CT the tongue base mass measures 2.1 cm.

Which of the following is the most appropriate treatment approach for this patient?

A

Concurrent cisplatin-based chemotherapy followed by radiation

B

Radiation followed by adjuvant chemotherapy

C

Radiation therapy plus cetuximab

D

Radiation therapy or surgery alone

Answer & Critique

Correct Answer: D

Educational Objective: Treat locally advanced squamous cell carcinoma of the neck with radiation therapy or surgery alone.

Key Point

Patients with early stage head and neck cancer should be treated with either surgery or primary radiotherapy; use of combined chemotherapy and radiation is not indicated.

Either radiation therapy or surgical resection is the most appropriate treatment for this patient with early stage squamous cell carcinoma of the oropharynx. Because head and neck cancers tend to recur locally rather than spread systemically, radiation therapy and surgical resection are the primary treatment modalities for stage I and II disease (without lymph node involvement) of the oropharynx. These tumors are highly curable with either modality, with the specific treatment typically selected based on factors such as surgical accessibility of the tumor and the expected morbidity and functional outcomes anticipated with either approach. In patients treated with surgery as the initial approach, adjuvant radiation or combined chemotherapy and radiation may also be indicated for follow-up treatment based on findings at surgery such as close or positive surgical margins, the presence of lymphovascular or perineural invasion, or identification of more advanced (T3 or T4) disease. An important exception to this general treatment approach for early stage head and neck squamous cell malignancies is nasopharyngeal cancer, which is treated with radiation alone for stage I disease and combined chemotherapy and radiation for stage II and higher disease because of a higher risk of distant disease occurrence with these tumors.

Because of their higher rate of locoregional recurrence, more locally advanced tumors (lymph node involvement) are usually treated with surgery (for accessible oral cavity tumors) or combined modality therapy (for other oropharyngeal anatomic sites) that includes radiation along with concurrent chemotherapy with a radiation sensitizer; cisplatin is the most commonly used agent for this purpose. Multiple studies have found that use of combined modality therapy results in significantly improved patient outcomes. However, treatment for locally advanced disease with cisplatin chemotherapy and radiation in this patient with early stage cancer would not be indicated.

Radiation therapy is considered definitive treatment for early stage head and neck cancer. Therefore, adjuvant chemotherapy following radiation therapy is not indicated and would not be an appropriate treatment in this patient.

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, also has an established role in the treatment of locally advanced squamous cell carcinoma of the head and neck when given with radiation therapy. The addition of either cisplatin or cetuximab has been shown to improve survival when compared with radiation therapy alone in patients with locally advanced disease. However, this is not the standard of care treatment for patients with early stage disease who have a much better prognosis and who can be effectively treated with either primary radiation therapy or surgery alone.

Question 144

A 55-year-old man undergoes follow-up evaluation for pancreatic cancer. He underwent a pancreaticoduodenectomy (Whipple procedure), with the pathology report showing stage II pancreatic cancer. Because of postoperative complications and a slow recuperation period, he did not receive postoperative therapy. Nine months postoperatively, the patient was able to resume all activities, including full-time work and regular exercise. Three months later, however, he developed right upper quadrant pain. A CT scan showed postsurgical changes in the pancreatic bed and multiple liver metastases. The patient remains medically fit, has good oral intake, and maintains all activities. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 27. The abdomen is soft and nontender with normal bowel sounds. The liver is enlarged. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	12.8 g/dL (128 g/L)
Leukocyte count	7200/µL (7.2×10^9/L)
Platelet count	302,000/µL (302×10^9/L)
Albumin	Normal
Total bilirubin	Normal
Creatinine	Normal

Which of the following is the most appropriate management?

A

Multiagent systemic chemotherapy

B

Single-agent systemic chemotherapy

C

Radiation therapy to the liver

D Transarterial chemoembolization of liver lesions

Answer & Critique

Correct Answer: A

Educational Objective: Treat metastatic pancreatic cancer with multiagent systemic chemotherapy.

Key Point

Multiagent systemic chemotherapy with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) is appropriate treatment for metastatic recurrence of pancreatic cancer in patients with good performance status.

Multiagent systemic chemotherapy, with a preferred regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), is most appropriate for this patient, who has a history of stage II pancreatic cancer and now has developed a metastatic recurrence. Patients with pancreatic cancer remain at substantial risk of developing a metastatic recurrence within the first 2 years after undergoing appropriate surgical resection (Whipple procedure). For such patients who are otherwise medically fit and have good performance status, FOLFIRINOX chemotherapy is associated with improved outcomes compared with single-agent chemotherapy. More recently, the combination of nab-paclitaxel and gemcitabine has been shown to be modestly superior to gemcitabine alone.

Gemcitabine as single-agent therapy would be suitable for a patient with metastatic pancreatic cancer who is more debilitated (poor performance status) than the patient described here.

Radiation therapy to the liver might be appropriate for treatment of locally symptomatic liver disease but would not be effective for management of metastatic pancreatic cancer in a patient who is otherwise a good candidate for systemic chemotherapy.

Transarterial chemoembolization is used for treatment of metastatic lesions to the liver associated with a number of different cancers. It is most effective in treating larger, symptomatic metastatic lesions, but does not address systemic disease and would not be expected to be as effective as multiagent systemic chemotherapy.

Question 145

A 32-year-old man is evaluated in the emergency department for fever, neck pain, and a rapidly enlarging right cervical lymph node. The patient first noticed the lymph node 3 weeks ago. He has no significant medical history and takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 120/70 mm Hg, pulse rate is 110/min, and respiration rate is 17/min. A 16-cm firm, enlarged right cervical lymph node is palpated. There is no other lymphadenopathy and no splenomegaly. The remainder of the examination is unremarkable.

Laboratory studies:

Complete blood count	Normal
Creatinine	1.2 mg/dL (106.1 µmol/L)
Lactate dehydrogenase	830 U/L
Phosphorus	5.4 mg/dL (1.74 mmol/L)
Potassium	5.0 mEq/L (5.0 mmol/L)
Urate	8.0 mg/dL (0.47 mmol/L)

CT scans of the chest, abdomen, and pelvis reveal a 20-cm enlarged right cervical lymph node that is displacing the trachea to the left. Biopsy of the node shows CD20-positive Burkitt lymphoma. Treatment with hydration, furosemide, and allopurinol are initiated.

Which of the following is the most appropriate additional treatment?

A

Involved-field radiation therapy

B Clarithromycin, amoxicillin, plus omeprazole

C Rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD)

D Surgical debulking followed by radiation therapy

Answer & Critique

Correct Answer: C

Educational Objective: Treat Burkitt lymphoma with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R -hyper-CVAD).

Key Point

Patients with Burkitt lymphoma always warrant aggressive and immediate therapy with combination chemotherapy and aggressive intravenous hydration, urine alkalinization, and administration of allopurinol or rasburicase.

Combination chemotherapy consisting of rituximab plus hyperfractionated (rapidly cycled) cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD) is most appropriate for this patient with CD20-positive Burkitt lymphoma. The most aggressive forms of large cell lymphoma include Burkitt lymphoma and lymphoblastic lymphoma. Onset of disease is acute, and patients usually present with life-threatening metabolic and structural abnormalities (this patient has early tumor lysis syndrome and impending airway obstruction). Treatment with R-hyper-CVAD, which is also used to treat acute lymphoblastic leukemia, is associated with high response rates (80%) and is curative in nearly 50% of patients with CD20-positive disease. The International Prognostic Index (IPI) score was developed to assist in determining prognosis before therapy. The IPI score is based on the patient's age, serum lactate dehydrogenase level, number of extranodal sites, disease stage, and performance status. Patients with Burkitt lymphoma have high IPI scores and always warrant aggressive and immediate therapy. Careful monitoring is required when treating patients with Burkitt lymphoma because rapid cell turnover and cell death are exacerbated by initiation of chemotherapy. Aggressive intravenous hydration, urine alkalinization, and administration of allopurinol or rasburicase are indicated in addition to chemotherapy.

Although Burkitt lymphoma can be localized in presentation, it is considered a generalized disease process and is treated with systemic agents. Therefore, neither surgery nor involved-field radiation therapy is indicated as primary treatment.

Because of their association with *Helicobacter pylori* infection, gastric mucosa-associated lymphoid tissue lymphomas can often be induced into complete and durable remission with the

combination of antimicrobial agents and a proton pump inhibitor such as amoxicillin, clarithromycin, and omeprazole without the need for additional chemotherapy. This regimen is not effective for patients with aggressive large B-cell lymphoma, such as Burkitt lymphoma.

Question 146

A 45-year-old man undergoes follow-up evaluation for chronic lymphocytic leukemia. He was diagnosed 1 year ago after presenting with profound fatigue, decreased performance status, diffuse lymphadenopathy, and splenomegaly. He has been treated with rituximab, fludarabine, cyclophosphamide, and prednisone since the time of diagnosis without significant improvement in his symptoms or blood counts. He continues to complain of marked fatigue but minimal symptoms associated with lymphadenopathy or splenic enlargement. He reports no abnormal bleeding. Current medications are alemtuzumab and gamma globulin. Family history is significant for a mother with transfusion-dependent myelodysplastic syndrome and a sister and brother who are well.

On physical examination, vital signs are normal. Enlarged cervical, axillary, and inguinal lymph nodes are palpated. Splenomegaly extending 15 cm below the costal margin at the anterior axillary line is present. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 9.5 g/dL (95 g/L), a leukocyte count of 30,000/μL (30×10^9/L) with 70% small mature lymphocytes, and a platelet count of 40,000/μL (40×10^9/L).

Flow cytometry studies show small mature B cells co-expressing CD5 and CD23. Fluorescence in situ hybridization indicates a chromosome 17p deletion.

Chest radiograph is normal. CT scans show extensive cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following is the most appropriate next step in treatment?

A

Hematopoietic stem cell transplantation

B

Leukapheresis

C

Lymph node radiation

D

Splenectomy

Answer & Critique

Correct Answer: A

Educational Objective: Treat advanced chronic lymphocytic leukemia that is resistant to standard therapy.

Key Point

Allogeneic hematopoietic stem cell transplantation, a potentially curative therapy option, should be considered for a young patient with advanced chronic lymphocytic leukemia associated with a high risk of disease progression.

Hematopoietic stem cell transplantation (HSCT) is most appropriate for this patient who has aggressive B-cell chronic lymphocytic leukemia (CLL) refractory to therapy. CLL is the most common form of adult leukemia, accounting for 10% of all hematologic malignancies. Patients with CLL are usually diagnosed at a median age of 70 years. Many of these patients are asymptomatic at the time of diagnosis and are identified after detecting lymphocytosis on a complete blood count obtained for other purposes. The disease course is often indolent with many patients not requiring treatment. For those who do, newer therapies have improved the median survival for patients with CLL nearly to that of age-matched healthy controls. Although younger patients develop CLL less often, they usually have more aggressive disease as in this patient who had systemic symptoms at presentation in addition to significant lymphadenopathy and splenomegaly. In addition, his disease resistance to standard rituximab and multiagent chemotherapy, the presence of immune thrombocytopenia, and a 17p deletion together confer a limited likelihood of survival (median survival less than 3 years). Because of this, HSCT is the only therapeutic option for this patient that is associated with the potential for cure, and he has siblings who might serve as possible HLA-matched donors.

Leukapheresis is the selective removal of leukocytes from the blood and is typically used in patients with acute leukemias, particularly acute myelogenous leukemia, in which myeloblast counts typically exceeding 100,000/µL (100×10^9/L) result in leukostasis with resulting respiratory failure and central nervous system symptoms. Leukapheresis rapidly lowers the leukocyte count, decreasing leukostasis. However, leukostasis is rarely associated with CLL, and even with very high leukocyte counts, leukapheresis is not indicated in this patient without an extreme elevation of his leukocyte count or evidence of hyperviscosity.

The lymphocytes associated with CLL are usually exquisitely radiosensitive, and radiation of bulky lymph nodes may be helpful in managing symptoms associated with lymphadenopathy. It is frequently used in conjunction with other more definitive treatments or palliatively. However, this patient does not have significant symptoms related to his lymphadenopathy, and radiation therapy would also not address the underlying hematologic malignancy in this patient.

Splenectomy has been shown to be beneficial in patients with CLL who have marked splenomegaly or profound cytopenias in which splenomegaly may be a contributing factor. However, it is usually reserved for patients whose disease does not respond to chemotherapy or other treatments. Although this patient has evidence of splenomegaly and a low platelet count, he has no evidence of organ impingement from his enlarged spleen or bleeding from his thrombocytopenia. Therefore, there is no current indication for splenectomy at this time.

Question 147

A 76-year-old man is evaluated for a 1-month history of increasing fatigue, abdominal pain, decreased appetite, and a 4.5-kg (10-lb) weight loss. He does not have cough, dyspnea, or chest pain. Medical history is unremarkable, and he takes no medications. The patient is a lifelong nonsmoker.

On physical examination, the patient is afebrile, blood pressure is 130/80 mm Hg, pulse rate is 84/min, and respiration rate is 12/min. Abdominal examination reveals hepatomegaly. The remainder of the examination is unremarkable.

The serum alkaline phosphatase level is 225 U/L, the serum total bilirubin level is 2.0 mg/dL (34.2 µmol/L), and the serum creatinine level is 0.9 mg/dL (79.6 µmol/L).

Contrast-enhanced CT scans of the abdomen and pelvis show multiple liver metastases with 50% liver replacement and several metastases in the ribs and pelvic bones. CT-guided needle biopsy of the liver reveals high-grade poorly differentiated neuroendocrine cancer. A subsequent chest CT scan shows no evidence of tumor.

Which of the following is the most appropriate treatment?

A

Hepatic artery embolization

B

Octreotide

C

Platinum-based systemic chemotherapy

D

Radiation therapy for bone metastases

E

Radiofrequency ablation of liver metastases

Answer & Critique

Correct Answer: C

Educational Objective: Treat a high-grade neuroendocrine tumor of unknown primary site with platinum-based chemotherapy.

Key Point

High-grade poorly differentiated neuroendocrine tumors of unknown primary site often respond rapidly to systemic platinum-based chemotherapy, such as the regimens used to treat small cell lung cancer.

This patient has a high-grade poorly differentiated neuroendocrine tumor of unknown primary site; such tumors often respond rapidly to systemic platinum-based chemotherapy, such as the regimens used to treat small cell lung cancer. Although these regimens can have substantial side effects, the potential for clinical benefit, including improved symptom control and prolonged survival, is significant. Bone metastases are also likely to respond to this chemotherapy regimen.

Hepatic artery embolization is a locoregional therapy that is often used to treat patients with low-grade neuroendocrine tumors, but this technique is not effective for treating patients with high-grade neuroendocrine tumors and would not provide therapy for the bone metastases.

Octreotide is useful for treating patients with low-grade neuroendocrine tumors and for managing hormonal symptoms caused by hormonally functional tumors, but it is not effective for treating patients with high-grade neuroendocrine tumors.

Radiation therapy for bone metastases is inappropriate because it would delay chemotherapy for the visceral metastases, which are clinically more important. In addition, chemotherapy may also treat the bone metastases.

Radiofrequency ablation is useful for treating patients with a limited number of small metastases of low-grade neuroendocrine tumors but would not be appropriate for treating patients with high-grade neuroendocrine tumors or for managing patients with bulky liver metastases.

Question 148

A 43-year-old woman undergoes follow-up evaluation following a recent diagnosis of estrogen receptor–positive, progesterone receptor–positive, *HER2*-negative, grade 2 invasive ductal carcinoma of the left breast. The patient was treated with surgery, adjuvant chemotherapy, and radiation therapy. This is her first postradiation visit. She currently takes no medications. She is premenopausal.

On physical examination, vital signs are normal. Well-healed incisions of the left breast and left axilla are present. There is no lymphadenopathy and no right breast masses. The remainder of the examination is unremarkable.

Results of a complete blood count and serum chemistry panel are normal.

Which of the following is the most appropriate therapy?

A

Exemestane alone

B

Tamoxifen alone

C

Maintenance chemotherapy with oral capecitabine

D

No additional adjuvant therapy

Answer & Critique

Correct Answer: B

Educational Objective: Treat a premenopausal patient who has completed breast cancer therapy with antiestrogen therapy.

Key Point

The recommended adjuvant endocrine therapy following breast cancer treatment for a premenopausal patient is tamoxifen for at least 5—preferably 10—years.

This patient, who has completed breast surgery, adjuvant chemotherapy, and primary breast radiation, should now be started on antiestrogen therapy. Tamoxifen has been the standard treatment in premenopausal women. As her breast cancer is estrogen receptor positive, adjuvant antiestrogen therapy will reduce her risk of distant recurrence by 40% to 50%. For premenopausal women with hormone receptor–positive early-stage breast cancer, tamoxifen should be used for at least 5 years—preferably 10 years based on the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen Treatment Offers More (aTTom) trials.

Exemestane is an aromatase inhibitor that blocks peripheral conversion of androgens to estrogens. Aromatase inhibitors are therefore used only in postmenopausal women in whom the primary source of estrogen is peripheral conversion of adrenal androgens; therapy with exemestane alone would therefore not be appropriate in the woman with residual ovarian function. However, exemestane has recently been compared with tamoxifen in conjunction with ovarian suppression in premenopausal women. The Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) trials have shown improved disease-free survival at 5 years for exemestane with ovarian suppression compared to tamoxifen with ovarian suppression, and this is now an option that can be discussed with premenopausal patients, particularly those at high risk of recurrence. There is at present no difference in breast cancer mortality between these two treatments and the toxicity analysis of these treatments with ovarian suppression compared to tamoxifen alone has not yet been done.

There is no evidence that maintenance chemotherapy is effective in early stage breast cancer and it has not been used outside of a clinical trial.

Without antiestrogen adjuvant therapy, the patient's risk of distant recurrence will increase. As above, antiestrogen therapy reduces the risk of breast cancer distant recurrence by 40 to 50% and also decreases the risk of contralateral breast cancers by 50%. Its use should be recommended in this patient with hormone receptor–positive early-stage breast cancer.

Question 149

A 65-year-old man is seen in follow-up for a recent diagnosis of non–small cell lung cancer. He presented 2 weeks ago with a 3-month history of worsening shortness of breath, fatigue, and reduced appetite with a 35-pound weight loss. Medical history is notable for COPD with baseline shortness of breath with exertion, but no supplemental oxygen requirement. Medications are tiotropium and as-needed albuterol metered dose inhalers.

Physical examination at the time of diagnosis revealed decreased breath sounds in the left lung field. Chest radiograph showed near complete obliteration of the left lung field. CT scan of the chest confirmed the presence of a large left-sided pleural effusion and showed evidence of multiple hepatic and osseous metastatic lesions. He underwent left-sided large volume thoracentesis, and cytology confirmed squamous cell carcinoma.

He currently notes that despite fluid drainage, his breathing has not improved significantly and he is now using home oxygen. He remains weak, spending significant time in bed and requiring assistance in performing many of his daily self-care activities.

Chest auscultation reveals a clear improvement in left-sided breath sounds, and a chest radiograph shows a small amount of residual pleural fluid on the left.

Which of the following is the most appropriate management?

73%

A

Palliative care assessment

12%

B

Platinum-based chemotherapy

14%

C

Pleurodesis

1%

D Radiation to bone metastases

Answer & Critique

Correct Answer: A

Educational Objective: Manage non–small cell lung cancer and poor performance status with palliative care.

Key Point

Early palliative care has shown to improve symptom control and survival in patients with non–small cell lung cancer and associated poor performance status.

The most appropriate management for this patient with metastatic non–small cell lung cancer (NSCLC) and a poor performance status is a comprehensive palliative care assessment. While systemic chemotherapy treatment with a platinum-based doublet regimen has been shown to improve both overall survival and quality of life, this has only been shown for patients with good performance status (Eastern Cooperative Oncology Group/World Health Organization performance status of 2 or better). Patients with a performance status of 2 can carry out all self-care activities and they are also active more than 50% of waking hours. This patient clearly does not meet that definition, as he is spending significant time in bed and requires help with self-care activities. For a patient such as this, chemotherapy treatment has no benefit and instead is associated with potential harm and significant negative impact on quality of life. In contrast, palliative care instituted early in the disease course for patients with metastatic NSCLC has shown to improve symptom control and improve survival.

Pleurodesis, or obliteration of the pleural space, may be helpful in managing recurrent malignant pleural effusion. However, this patient has undergone thoracentesis without evidence of recurrent effusion. Therefore, pleurodesis would not be indicated in this patient.

Radiation treatment to sites of osseous metastases is indicated only for symptom control or for stabilization of a suspected impending fracture. Neither of these is indicated to be an issue for this patient.