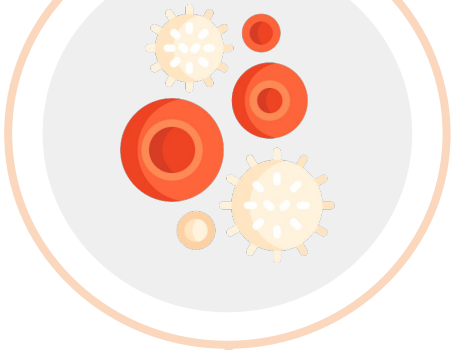
Practice file



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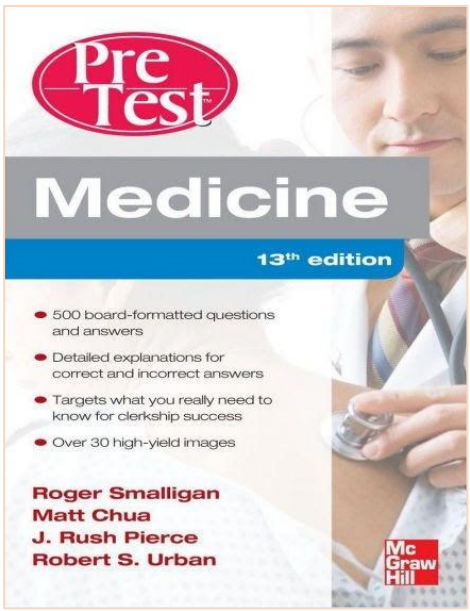
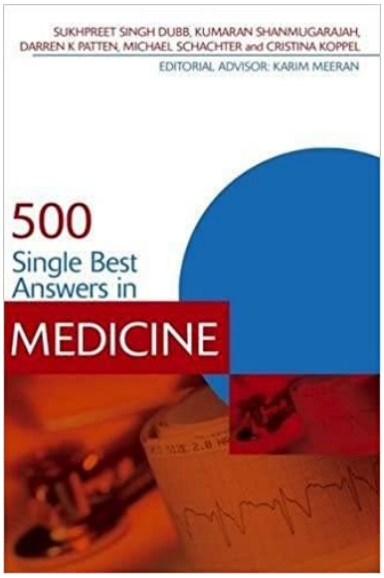
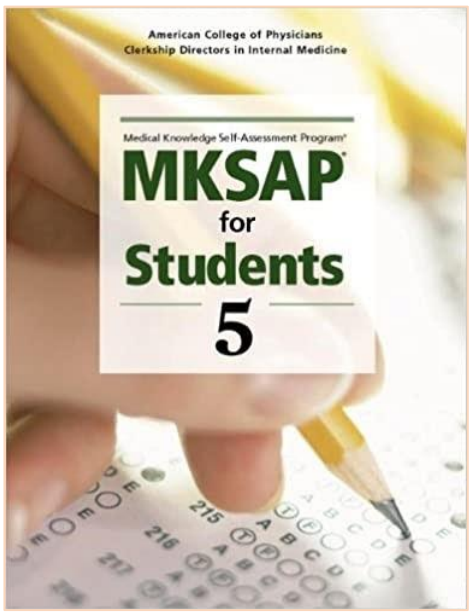
Resources







AMBOSS
medical knowledge distilled

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Bleeding disorders

Q1 (MKSAP): A 79-year-old woman is evaluated in the hospital for sepsis secondary to pyelonephritis. The patient was well before this illness and has no other medical problems. On physical examination, temperature is 38.9°C (102.0°F), blood pressure is 90/50 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. She has bleeding at phlebotomy sites and around her intravenous access insertion and many ecchymoses on her arms and legs. Examination of the peripheral blood smear shows many fragmented erythrocytes and diminished platelets. Which of the following is the most likely cause of her bleeding disorder?

Hemoglobin	9 mg/dL (90 g/L)
Platelet count	60,000/μL (60 × 10^9/L)
Prothrombin time	15 s
Activated partial thromboplastin time	30 s
D-dimer	Elevated
Fibrinogen	Reduced

A- Disseminated intravascular coagulation
B- Hemolytic uremic syndrome
C- Immune thrombocytopenic purpura
D- Thrombotic thrombocytopenic purpura

Explanation: The diagnosis of disseminated intravascular coagulation is based on a prolonged prothrombin time, activated partial thromboplastin time, and thrombin time; a high D-dimer titer; a reduced serum fibrinogen level and platelet count; and microangiopathic hemolytic anemia.

Q2 (500Best): A 16-year-old boy presents to his GP complaining of nosebleeds and bleeding after brushing his teeth. He is unsure of how long this has been occurring but decided to seek advice after having to continually excuse himself from lessons. On examination you notice he has some skin bruises. A blood test shows a prolonged bleeding time and activated partial thromboplastin time (APTT), while platelet count and prothrombin times are all normal. The most likely diagnosis is:

A. Von Willebrand disease
B. Liver disease
C. Disseminated intravascular coagulation
D. Congenital afibrinogenaemia
E. Glanzmann's thrombasthenia

Explanation: Von Willebrand disease (A) affects an important glycoprotein present in the blood plasma. In response to various stimuli, such as endothelial damage, von Willebrand factor (vWF) is released from cells and platelets. Its main function is to facilitate the adhesion of platelets to endothelial cells which are often exposed in vascular injury, it also acts to stabilize factor VIII. In vWF deficiency the most common symptoms include nosebleeds, bruising, gum bleeding and prolonged bleeding from minor wounds. Laboratory tests can be used to investigate bleeding disorders and include prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time, platelet counts and thrombin time (TT). A prolonged PT (>16–18 s) suggests abnormalities in the common (factors I, II, V, X) or extrinsic pathway (factor VII). A prolonged APTT (>30–50 s) suggests abnormalities in the common (factors I, II, V, X) or intrinsic pathway (factors VIII, IX, XI, XII). Importantly, factor VII does not cause any anomalies in APTT times. A prolonged TT suggests fibrinogen deficiency while abnormal bleeding times suggest platelet deficiencies. In liver disease (B) the PT, APTT, bleeding time and platelet counts would be abnormal alongside peripheral stigmata of liver disease. Disseminated intravascular coagulation (C) causes abnormalities of PT, APTT, bleeding time and platelets. In congenital afibrogenaemia (D), the PT, APTT, TT and bleeding times would be abnormal while the platelet count would be normal. Glanzmann's thrombaesthenia (E), a platelet abnormality whereby glycoprotein IIb/IIIa is absent preventing platelet bridging with fibrinogen, the bleeding time is significantly prolonged while PT, APTT and platelet counts are normal.

Q3 (500Best):A 45-year-old man collapses at home and is brought to accident and emergency. He has a fever at 39.5°C and blood pressure is 90/60 mmHg, although he is in a lucid state. Bruises can be seen on his skin which he remembers being present before he fell. Blood tests show the patient to have a normocytic anaemia with a low platelet count and increased fibrin split products. The most likely diagnosis is:

A. Warm autoimmune haemolytic anaemia
B. Cold autoimmune haemolytic anaemia
C. Paroxysmal nocturnal haemoglobinuria
D. Disseminated intravascular coagulation
E. Thalassaemia minor

Explanation: This patient is suffering from disseminated intravascular coagulation (DIC), which may have resulted from an infection, in this case causing septicaemia. DIC is characterized by the systemic activation of the coagulation system such that fibrin deposition occurs usually within the microvasculature. RBCs are damaged when crossing such fibres and coagulation factors and platelets are also consumed predisposing to severe bleeding. DIC has various causes. In this case a systemic inflammatory response such as occurs in sepsis is the most likely underlying cause. Thalassaemia (E) tends to produce chronic normocytic or microcytic anaemia without serious bleeding risk.

Answers: Q1:A | Q2:A | Q3:D

Bleeding disorders

Q4 (500Best): During a busy ward round you are asked to visit a patient the consultant has not had an opportunity to see. The only details you are given are that the patient is female and was admitted the previous day with bleeding abnormalities, you are given the results of her blood investigations:

A. Factor V deficiency
B. Warfarin therapy
C. Glanzmann's thrombasthenia
D. Bernard Soulier syndrome
E. Von Willbrand disease

Prothrombin time	Unaffected
Partial thromboplastin time	Prolonged
Bleeding time	Prolonged
Platelet count	Unaffected

Explanation: Investigations of the vascular system can provide essential information and support a diagnosis made alongside the ever important history and examination. Blood vessel abnormalities can be detected using the bleeding time, this investigation alongside platelet counts is also helpful in determining platelet dysfunction. Investigations of the coagulation cascade can be shown by the PT which reflects the extrinsic pathway and the PTT which measures the intrinsic pathway. This patient is likely to be suffering from Von Willbrand's disease (E) whereby Von Willebrand factor, important in platelet adhesion and Factor VIII function, is deficient. Patient's therefore have normal PT and platelet counts but bleeding time and PTT are abnormal. In Factor V (A) deficiency, the PT and PTT are prolonged while bleeding time and platelet counts would be unaffected. These findings are also found in Factor X deficiency, vitamin K deficiency and warfarin therapy (B). In Glanzmann's thrombaesthenia (C) platelets lack glycoprotein IIb/IIIa therefore fibrinogen bridging between platelets is disrupted, bleeding time is therefore the only abnormal result. In Bernard Soulier syndrome glycoprotein Ib, a receptor for Von Willebrand factor, is deficient therefore clot formation is disrupted and again only bleeding time would be affected.

Q5 (pretest): A 70-year-old intensive care unit patient complains of fever and shaking chills. The patient develops hypotension, and blood cultures are positive for gram-negative bacilli. The patient begins bleeding from venipuncture sites and around his Foley catheter. Laboratory studies are as follows: Hct: 38% WBC: 15,000/µL Platelet count: 40,000/µL (normal 150,000-400,000) Peripheral blood smear: fragmented RBCs PT: elevated PTT: elevated Plasma fibrinogen: 70 mg/dL (normal 200-400). Which of the following is the best course of therapy in this patient?

A. Begin heparin
B. Treat underlying disease
C. Begin plasmapheresis
D. Give vitamin K
E. Begin red blood cell transfusion

Explanation: This patient with gram-negative bacteremia has developed disseminated intravascular coagulation (DIC), as evidenced by multiple-site bleeding, thrombocytopenia, fragmented red blood cells on peripheral smear, prolonged PT and PTT, and reduced fibrinogen levels from depletion of coagulation proteins. Initial treatment is directed at correcting the underlying disorder—in this case, infection. Although heparin was formerly recommended for the treatment of DIC, it is now used rarely and only in unusual circumstances (such as acute promyelocytic leukemia). For the patient who continues to bleed, supplementation of platelets and clotting factors (with fresh frozen plasma or cryoprecipitate) may help control life-threatening bleeding. Red cell fragmentation and low platelet count can be seen in microangiopathic disorders such as thrombotic thrombocytopenic purpura (TTP), but in these disorders the coagulation pathway is not activated. Therefore, in TTP the prothrombin time, partial thromboplastin time, and plasma fibrinogen levels will be normal. Plasmapheresis, vitamin K therapy, and RBC transfusion will not correct the underlying cause.

Q6 (AMBOSS): A 13-year-old girl is brought to the emergency department by her father because of a severe nosebleed. She takes no medications and has no history of serious medical illness but has had frequent nosebleeds in the past. Physical examination shows brisk bleeding from the right nare and pooled blood in the posterior pharynx. Laboratory studies showed, The bleeding time is 11 minutes (N = 2–7). Which of the following is the most appropriate pharmacotherapy?

A. Prothrombin complex concentrate
B. Intravenous immunoglobulin
C. Rituximab
D. Desmopressin

Hemoglobin	8 g/dL
Platelet count	195,000/mm^3
Prothrombin time	12 sec
Partial thromboplastin time	49 sec
Fibrin split products	negative

Explanation: Recurrent epistaxis, prolonged partial thromboplastin and bleeding times combined with a normal platelet count suggest von Willebrand disease. Desmopressin stimulates von Willebrand factor (vWF) release from endothelial cells and can be used for the treatment of bleeding due to von Willebrand disease (vWD). Patients with vWD are often asymptomatic; treatment is only required if symptoms such as recurrent epistaxis occur, as seen in this patient. Desmopressin can also be used for the treatment of bleeding due to uremic platelet dysfunction and hemophilia A and is also used for the treatment of diabetes insipidus.

Answers: Q4:E | Q5:B | Q6:D

Bleeding disorders

Q7 (AMBOSS): A 22-year-old woman comes to the physician for evaluation of heavy menstrual bleeding. Two years ago, she had prolonged bleeding after wisdom tooth extraction. She follows a vegan diet and does not eat any animal products. Physical examination shows no abnormalities. Laboratory studies show a platelet count of 151,000/mm3 and a bleeding time of 13 minutes (N = 2–7). Prothrombin time and partial thromboplastin times are within the reference ranges. Peripheral blood smear shows normal platelet morphology. Which of the following is the most likely diagnosis?

A. Vitamin K deficiency
B. Bernard-Soulier syndrome
C. Von Willebrand disease
D. Hemophilia A
E. Immune thrombocytopenic purpura

Explanation: Investigations of the vascular system can provide essential information and support a diagnosis made alongside the ever important history and examination. Blood vessel abnormalities can be detected using the bleeding time, this investigation alongside platelet counts is also helpful in determining platelet dysfunction. Investigations of the coagulation cascade can be shown by the PT which reflects the extrinsic pathway and the PTT which measures the intrinsic pathway. This patient is likely to be suffering from Von Willbrand's disease (E) whereby Von Willebrand factor, important in platelet adhesion and Factor VIII function, is deficient. Patient's therefore have normal PT and platelet counts but bleeding time and PTT are abnormal. In Factor V (A) deficiency, the PT and PTT are prolonged while bleeding time and platelet counts would be unaffected. These findings are also found in Factor X deficiency, vitamin K deficiency and warfarin therapy (B). In Glanzmann's thrombaesthenia (C) platelets lack glycoprotein IIb/IIIa therefore fibrinogen bridging between platelets is disrupted, bleeding time is therefore the only abnormal result. In Bernard Soulier syndrome glycoprotein Ib, a receptor for Von Willebrand factor, is deficient therefore clot formation is disrupted and again only bleeding time would be affected.

Q8 (AMBOSS): An otherwise healthy 23-year-old man comes to the physician because of a 3-day history of mild persistent bleeding from the site of a tooth extraction. He has no prior history of medical procedures or surgeries and no history of easy bruising. He appears well. Vital signs are within normal limits. Laboratory studies showed, Deficiency of which of the following coagulation factors is the most likely cause of this patient's condition?

A. Factor V
B. Factor X
C. Factor XIII
D. Factor VII
E. Factor II

Hemoglobin	12.4 g/dL
Platelets	200,000/mm^3
Serum	
Prothrombin time	25 seconds
Partial thromboplastin time (activated)	35 seconds

Explanation: The patient's elevated prothrombin time and normal partial thromboplastin time (activated) indicate a coagulation defect in the extrinsic pathway. Factor VII is the only coagulation factor listed here that is part of the extrinsic hemostatic pathway. The extrinsic pathway is activated by traumatic tissue injury, such as this patient's tooth extraction, which exposes tissue factor (factor III) located beneath the endothelium. Factor III then activates factor VII, forming a complex to trigger the common pathway by activating factor X. Hereditary factor VII deficiency is rare and is caused by a mutation of the F7 gene on chromosome 13. Factor VII deficiency presents with features similar to those of hemophilia (factor VIII or factor IX deficiency), such as bleeding following dental extraction and hemarthrosis. However, in patients with factor VII deficiency, the PT would be prolonged (due to an extrinsic pathway defect) and the aPTT would be normal. Conversely, in patients with hemophilia, the aPTT is prolonged (due to an intrinsic pathway defect) and the PT is normal.

Answers: Q7:C | Q8:D

Bleeding disorders

Q9 (AMBOSS): A previously healthy 4-year-old boy is brought to the emergency department because of a 1-day history of pain and swelling of his left knee joint. He has not had any trauma to the knee. His family history is unremarkable except for a bleeding disorder in his maternal uncle. His temperature is 36.9°C (98.4°F). The left knee is erythematous, swollen, and tender; range of motion is limited. No other joints are affected. An x-ray of the knee shows an effusion but no structural abnormalities of the joint. Arthrocentesis is conducted. The synovial fluid is bloody. Further evaluation of this patient is most likely to show which of the following findings?

A. Decreased platelet count
B. Prolonged prothrombin time
C. Prolonged partial thromboplastin time
D. Elevated antinuclear antibody levels
E. Elevated erythrocyte sedimentation rate

Explanation: Prolonged partial thromboplastin time (aPTT) is a diagnostic feature of hemophilia A, an X-linked recessive disease characterized by defect factor VIII. A principal clinical feature is hemorrhage into a single weight-bearing joint, which can occur spontaneously or following minimal trauma. Repeated hemarthrosis can lead to joint destruction over time. Further hemorrhages may occur in the CNS, in gastrointestinal and genitourinary tracts, and from mucous membranes. Blood tests show a prolonged aPTT, normal prothrombin time, and normal platelet count. The diagnosis is confirmed through mixing studies and quantitative assessment of factor VIII activity levels.

Q10 (AMBOSS): A 25-year-old man comes to the physician for the evaluation of a 6-month history of recurrent spontaneous nosebleeds. He states that he is able to stop the bleeding within 10 minutes by lightly pinching his nose at the nostrils. He has no history of serious illness except for prolonged bleeding following wisdom teeth extraction 2 years ago. He does not smoke or drink alcohol. He takes no medications. Vital signs are within normal limits. Examination of the nose shows no abnormalities. There are several bruises on the lower extremities. The remainder of the examination shows no abnormalities. Laboratory studies showed, Which of the following is the most likely diagnosis?

A. Bernard-Soulier Syndrome
B. Hemophilia A
C. Factor X deficiency
D. Von Willebrand disease

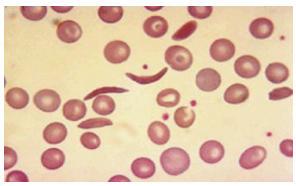
Hemoglobin	15 g/dL
Leukocyte count	6000/mm^3
Platelet count	220,000/mm^3
Bleeding time	9 minutes (N = 2–7)
Prothrombin time	13 sec
Partial thromboplastin time	50 sec

Explanation: This patient presents with recurrent epistaxis, a previous episode of heavy bleeding following tooth extraction, and multiple bruises. His laboratory studies show prolonged bleeding time despite normal platelet count and prolonged PTT. These features are consistent with the most common congenital hemostatic disorder. Von Willebrand disease occurs when there is a deficiency or defect in von Willebrand factor (vWF). The deficiency hinders the ability of platelets to adhere to subendothelial collagen and inhibits platelet activation, which leads to a prolonged bleeding time. PT and PTT are generally in normal ranges in patients with this condition because the clotting factors are unaffected. However, factor VIII is bound to vWF in the blood to prevent rapid breakdown. Thus, half of the patients with vWD can also present with mildly prolonged PTT, as seen in this patient.
Desmopressin is the treatment of choice for vWD types 1 and 2 because it stimulates vWF release from endothelial cells. Desmopressin is not an effective treatment in type 3 because of the complete absence of vWF.

Answers: Q9:C | Q10:D

Anemia

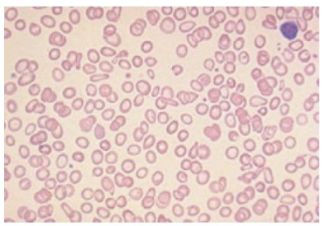
Q1 (MKSAP): A 13-year-old girl is hospitalized because of the sudden development of left hemiparesis and aphasia. A peripheral blood smear is shown. Which of the following is the most likely diagnosis?



A- Hereditary spherocytosis
B- Iron deficiency anemia
C- Sickle cell disease
D- Thalassemia minor

Explanation: It is highly likely that this adolescent has homozygous sickle cell disease and has had occlusion of a major vessel in the distribution of the left middle cerebral artery causing right hemiparesis and aphasia. The peripheral blood smear shows characteristic sickle cells (elongated crescent- and spindle-shaped cells). Patients with sickle cell disease commonly have target cells characterized by a central dense area of hemoglobin surrounded by a rim of pallor, giving it a "bull's-eye" appearance. Normal erythrocytes have an area of central pallor. Strokes due to occlusion of a large vessel are not uncommon in patients with sickle cell disease and are an indication for chronic blood transfusion therapy to maintain the peripheral blood hemoglobin S level below 50%.

Q2 (MKSAP): previously healthy 65-year-old man is evaluated for easy fatigability. He has no significant medical history, has never had a screening colonoscopy or other colon cancer screening, and does not drink alcohol. The patient takes no medications. His hemoglobin level 1 year ago was 14.3 g/dL (143 g/L). Results of physical examination are normal except for the finding of pallor. Laboratory examination reveals a hemoglobin level of 8.6 g/dL (86 g/L). Testing of stool for occult blood is negative. A peripheral blood smear is shown. Which of the following is the most likely diagnosis?



A- Hereditary spherocytosis
B- Iron deficiency anemia
C- Sickle cell anemia
D- Thalassemia minor

Explanation: The findings on the peripheral blood smear are suggestive of iron deficiency anemia. The erythrocytes show hypochromia, anisocytosis (changes in size), and poikilocytosis (changes in shape) and are also likely to be microcytic. If a confirmatory test (for example, serum ferritin determination) supports the diagnosis of iron deficiency anemia, a source of gastrointestinal blood loss should be sought, regardless of whether the stool is positive or negative for occult blood. A gastrointestinal lesion, such as colon cancer or gastritis, is far more likely than dietary inadequacies or malabsorption in an otherwise healthy adult.

Q3 (MKSAP): A 64-year-old man is evaluated in the office for a gradual decrease in exercise tolerance over the past 2 months. He has ostearthritis of the right knee but no other medical problems. His only medication is over-the-counter ibuprofen. Results of routine screening colonoscopy 4 months ago were normal. On physical examination, heart rate is 90/min, respiration rate is 20/min, and blood pressure is 140/80 mm Hg. Laboratory study findings include a hemoglobin level of 9.6 g/dL (96 g/L) and mean corpuscular volume of 76 fL. Results of routine serum chemistry analysis are normal. Serum iron, serum ferritin, and transferrin saturation levels are all low, and the total iron-binding capacity is elevated. Stool is positive for occult blood. Upper endoscopy reveals chronic gastritis, and the ibuprofen is stopped. Which of the following is the most appropriate treatment for this patient's anemia?

A- Blood transfusion
B- Erythropoietin
C- Intravenous iron
D- Oral iron

Explanation: This patient has iron deficiency anemia, as confirmed by the low mean corpuscular volume, low serum iron level, elevated total iron-binding capacity (TIBC), and low transferrin saturation (iron/TIBC). Iron deficiency is best treated by using oral iron salts; ferrous sulfate, 325 mg three times daily, is the least expensive preparation.

Answers: Q1:C | Q2:B | Q3:D

Anemia

Q4 (MKSAP): A 28-year-old woman has a 3-month history of easy bruising and bleeding gums. She feels otherwise well. Medical and family histories are unremarkable, and she takes no medications. On physical examination, vital signs are normal. Petechiae are present on the buccal mucosa and pretibial areas, and ecchymoses are noted on the upper thighs. There is no lymphadenopathy or splenomegaly. A peripheral blood smear shows no circulating blasts. The platelets are decreased in number but otherwise normal. Bone marrow examination shows hypoplastic marrow (<20% cellularity) with normal maturation of all cellular elements and normal iron stores. There are no findings suggesting an infiltrative disease and no fibrosis. Which of the following is the most likely diagnosis?

A- Aplastic anemia
B- Autoimmune hemolytic anemia
C- Immune thrombocytopenic purpura
D- Iron deficiency anemia

Explanation: This patient has aplastic anemia. Patients with this disorder have pancytopenia, a low reticulocyte count, and a hypoplastic bone marrow (<20% cellularity) with normal maturation of all cell lines. Aplastic anemia is a fatal disorder in which myeloid progenitor cells and stem cells are severely diminished or absent in the bone marrow because of either an intrinsic defect of the stem cells or immune-mediated stem cell destruction, which leads to transfusion-dependent anemia, thrombocytopenia, and severe neutropenia. Initial management involves withdrawal of any potentially causative agents and a CT scan of the chest to rule out an associated thymoma.

Q5 (500best):A 44-year-old Asian female presents with a two-month history of shortness of breath and lethargy. She denies any intolerance to the cold or any changes in her weight and on examination appears slightly pale. She states that she has recently become a vegetarian. A blood film shows the presence of elliptocytes and blood results show the following:
The most likely diagnosis is:

Haemoglobin	9.9 g/dL
Mean cell volume (MCV)	75 fL
Ferritin	Low

A. Iron deficiency anaemia
B. Sideroblastic anaemia
C. Anaemia of chronic disease
D. Thalassaemia trait
E. Hereditary elliptocytosis

Explanation: This patient is suffering from iron deficiency anaemia (A). The classic symptoms of anaemia include tiredness, shortness of breath and pallor. Signs can include koilonychia (spoon-shaped nails), while a blood film may show elliptocytes and hypersegmented neutrophils. Sideroblastic anaemia (B) is an abnormality whereby, despite the availability of iron, the body is unable to utilize it due to a genetic anomaly or in relation to the myelodysplastic syndrome. The ferritin is low here, therefore this cannot be the correct answer although a microcytic anaemia does occur. The three important causes of microcytic anaemia are iron deficiency anaemia, anaemia of chronic disease and thalassaemia trait. Ferritin helps to distinguish iron deficiency anaemia from the other causes. In anaemia of chronic disease (C), which can be caused by long-term illnesses such as rheumatoid arthritis, the action of cytokines interrupt iron homeostasis in red blood cells. As a result, iron is unable to leave red blood cells or ferritin stores so that ferritin measurements are classically normal or high. In thalassaemia trait, a genetic abnormality of the globin chains creates abnormal haemoglobin. The haemoglobin and MCV are therefore also reduced, however ferritin usually remains normal. In hereditary elliptocytosis (E), the majority of red blood cells are oval-shaped, predisposing to haemolytic anaemia. However, this does not present as microcytic anaemia.

Answers: Q4:A | Q5:A

Anemia

Q6 (500Best): A 47-year-old teacher complains of difficulty maintaining her concentration at work teaching secondary school children. She states that over the last four months she has become increasingly tired and easily fatigued. She has noticed it has become more difficult for her to lift books, rise from her chair and she has also noticed a tingling sensation in her fingers. Examination shows a positive babinski sign and absent reflexes. A blood test reveals the following:
The most likely diagnosis is:

Haemoglobin	10 g/dL
MCV	103 fL

A. Hypothyroidism
B. Vitamin B12 deficiency
C. Folic acid deficiency
D. Liver disease
E. Alcohol toxicity

Explanation: This patient has a macrocytic anaemia, the most common causes of which include vitamin B12 and folic acid deficiency, liver disease, alcohol toxicity and hypothyroidism. Vitamin B12 is important in DNA synthesis and maintaining the neurological system. In vitamin B12 deficiency (B), patients usually present with derangements in tissues with high cell turnover, such as the gastrointestinal system, epithelial surfaces and bone marrow. Symptoms therefore include weakness, fatigue, glossitis and changes in bowel habit. The classic triad of tiredness, glossitis and paraesthesia is not always present but strongly suggests B12 deficiency. Neurological consequences of B12 deficiency typically includes peripheral neuropathy, optic atrophy, dementia and subacute combined degeneration of the spinal cord (pyramidal tract weakness). Patients therefore present with paraesthesia, muscle weakness, visual impairments, psychiatric disturbance and difficulty walking. Folic acid is also important in DNA synthesis and in folic acid deficiency (C) many of the same features as described in B12 deficiency are present, such as fatigue and weakness. However, neurological symptoms are not as prominent and patients tend to have a history of malnutrition. Hypothyroidism (A) can present very similarly to patients with anaemia. Symptoms such as fatigue, tiredness and weakness are common to both pathologies. In hypothyroidism, a macrocytic anaemia is also present, however neurological symptoms tend to differ. In hypothyroidism, pseudomyotonic reflexes tend to occur whereby a prolonged relaxation phase occurs. Liver disease (D) and alcohol abuse can cause a macrocytic anaemia presentation. However, in liver disease, there are other peripheral stigmata such as gynaecomastia, spider naevia, caput medusae, etc). In alcohol abuse, malnutrition may cause anaemia or direct toxicity to the bone marrow. There is usually a history of alcohol abuse and other features, such as Wernicke's encephalopathy, can develop.

Q7 (500best):A 55-year-old man complains of a 4-week history of general malaise and fatigue, he has also noticed his trousers have become more loose fitting. A blood test shows the following results:
The most likely diagnosis is:

Haemoglobin	12 g/dL
MCV	90 fL
Platelet count	250×10^9/L
WBC	10×10^9/L
Serum iron	10 µmol/L
Total iron-binding capacity	40 µmol/L
Serum ferritin	160 µg/L

A. Thalassaemia
B. Iron deficiency anaemia
C. Anaemia of chronic disease
D. Macrocytic anaemia
E. Aplastic anaemia

Explanation: This patient is suffering from anaemia of chronic disease (C). The blood test values show a normocytic anaemia, normal platelet count and serum iron, increased ferritin concentration and reduced total iron binding capacity (TIBC). In anaemia of chronic disease, an underlying disease causes an inflammatory process involving cytokines to occur. Factors such as CRP and erythrocyte sedimentation rate (ESR) are raised. The effect of these cytokines is to interrupt the homeostasis of iron. Erythropoietin is inhibited, iron is unable to flow out of red blood cells, ferritin production is increased and RBC death is increased. The impact of these actions causes anaemia with raised ferritin levels and, if prolonged, serum iron is also eventually reduced. By definition, in iron-deficiency anaemia (B), the serum iron is reduced as well as the MCV, which is not the case here, there is also an increase in the TIBC. In anaemia of chronic disease, protein production can be reduced such that this increase does not occur. A macrocytic anaemia (D) would be accompanied by an increased MCV while aplastic anaemia (E) is unlikely in light of the normal platelet and white blood cell count. In thalassaemia, the haemoglobin and MCV are reduced but serum iron, ferritin and transferrin can be normal.

Q8 (500best):A 43-year-old woman suffers from Crohn's disease. A blood test shows the following results:
The most likely diagnosis is:

Haemoglobin	10.5 g/dL
MCV	120 fL
Platelet count	300×10^9/L

A. Vitamin B12 deficiency
B. Iron deficiency
C. Hypothyroidism
D. Folic acid deficiency
E. Anaemia of chronic disease

Explanation: This patient is suffering from vitamin B12 deficiency (A). Her blood test shows a macrocytic anaemia. In iron deficiency anaemia (B) there is usually a microcytic anaemia. Vitamin B12 and folate deficiency (D) are the most common causes of a macrocytic anaemia. Crohn's disease can involve the terminal ileum which is where vitamin B12 is absorbed, folate is absorbed in the proximal duodenum. Hypothyroidism (C) is unlikely as the classic symptoms of thyroid pathology, such as changes in weight, appetite and intolerance to room temperature, etc., are not present. In anaemia of chronic disease (E), a normocytic or microcytic blood film is more typical.

Answers: Q6:B | Q7:C | Q8:A

Anemia

Q9 (500Best): A 23-year-old Asian man presents to his GP complaining of shortness of breath following exercise. He has always been a little unfit and decided to start going to the gym but noticed that even after 4 weeks he is still quite short of breath. He denies any coughing or wheezing and on examination you notice mild pallor but the patient says he has always been slightly pale in colour. Investigation results are given below:
The most likely diagnosis is:

Haemoglobin	12 g/dL
MCV	70 fL
Serum iron	14 umol/L
Ferritin	60 ug/L
Transferrin saturation	35 per cent
Mean cell haemoglobin	22 pg
Haemoglobin electrophoresis	HbA2 increased

A. α thalassaemia trait
B. Anaemia of chronic disease
C. β thalassaemia trait
D. Haemoglobin H disease
E. Iron deficiency anaemia

Explanation: This patient is suffering from a microcytic anaemia with normal iron parameters. The differential diagnoses of a microcytic anaemia include iron deficiency anaemia, anaemia of chronic disease and thalassaemia disease. The normal iron parameters eliminate iron deficiency anaemia (E) while serum iron tends to be low and ferritin tends to be high in an anaemia of chronic disease (B). This leaves a disease of thalassaemia, α thalassaemia trait (A) usually results from gene deletion on chromosome 16 (β thalassaemia is coded on chromosome 11). There are two α globin genes from each parent so that adults have a total of four α globin genes. A single or double deletion causes a mild, usually asymptomatic anaemia known as α+ and α− disease, respectively. Haemoglobin H disease (D) involves three α deletions causing a significant anaemia beginning in childhood with target cells, Heinz bodies and splenogmegaly. In β thalassaemia trait (C) points to mutations of a single β globin gene allele. This causes a mild microcytic anaemia, electrophoresis shows an increased haemoglobin A2.

Q10 (500best):A 29-year-old woman complains of a 1-week history of weakness and malaise, she has recently become a vegetarian and eats mostly green vegetables and drinks lots of tea during the day. She is apyrexial and has a C-reactive protein (CRP) <5. You suspect an abnormality of the patient's iron stores. What is the most appropriate investigation to determine iron store levels?

A. Bone marrow biopsy
B. Serum ferritin
C. Serum transferrin
D. Total iron binding capacity
E. Serum iron

Explanation: Iron deficiency can be an important cause of anaemia in patients. In this case vitamin B12 and folic acid are less likely to be important given the patient's diet, however tea is alkaline and reduces the body's ability to effectively absorb iron. Measuring the patient's serum ferritin (B) provides an accurate reflection of the body's iron stores since the serum ferritin originates from the storage pools in the bone marrow, spleen and liver. Be aware that ferritin measurements are only accurate when CRP is normal since both ferritin and CRP are acute phase reactants. The serum transferrin (C) level reflects the levels of protein that bind to iron and transports it around the body and is usually 33 per cent saturated, hence not providing the most accurate level of iron. The serum iron level (E) is a poor reflection of iron stores since this can change dependent on disease states. In iron deficiency anaemia, the serum iron and iron stores are low, however in anaemia of chronic disease iron stores are increased yet the serum iron level is reduced. The total iron binding capacity (D) specifically saturates transferrin in order to measure the iron-carrying capacity in the body rather than iron stores and so would not be appropriate here. A bone marrow biopsy (A) is a very sensitive test since iron staining reflects iron stores in macrophages. However, it is both expensive and invasive and therefore not the most appropriate test compared to serum ferritin.

Answers: Q9:C | Q10:B

Anemia

Q11 (500Best): A 52-year-old woman presents complaining of a two-month history of increasing fatigue and numbness in both of her arms and legs. She lives at home with her husband and has found it difficult coping with the daily activities of living. She suffers from hypothyroidism which is well controlled with thyroid replacement medication. A peripheral blood smear shows hypersegmented neutrophils. A blood test reveals the following:
The most likely diagnosis is:

Haemoglobin	10 g/dL
Mean corpuscular volume	110 fL
Platelets	150×10^9/L
Liver function tests:	
ALT	25 IU/L
AST	27 IU/L
GGT	22 IU/L
ALP	100 IU/L
Urea	5 mmol/L
Creatinine	100 µmol/L

A. Thrombotic thrombocytopenic purpura
B. Iron deficiency
C. Folic acid deficiency
D. Liver disease
E. Pernicious anaemia

Explanation: This patient is suffering from a megaloblastic anaemia due to vitamin B12 deficiency secondary to pernicious anaemia. In a macrocytic anaemia two important differentials include folate and vitamin B12 deficiency. Folate deficiency (C) is commonly associated with alcohol disease as it is required to metabolize alcohol, poor diet and skin disease. Hypersegmented neutrophils can be associated with B12 or folic acid deficiency, some studies have also found relations with iron deficiency anaemia, however neurological deficits such as limb paraesthesia and numbness are more characteristic of vitamin B12 deficiency. Pernicious anaemia (E) is an autoimmune disease whereby antibodies bind intrinsic factor produced by the parietal cells in the gastric fundus. Intrinsic factor is essential in the absorption of vitamin B12 via the ileum. Associated conditions can include thyroid disease which compound symptoms of anaemia. Iron deficiency anaemia (B) is characterized by a microcytic anaemia rather than a macrocytic anaemia, which is present in this case. A thrombotic thrombocytopenic purpura (A) is defined by fever, transient neurologic abnormalities, thrombocytopenia, haemolytic anaemia and acute renal failure, which are not present in this case. Liver disease (D) can produce a macrocytic anaemia, however there would likely be other accompanying abnormalities such as jaundice, clotting anomalies, as well as deranged liver function tests, which are not present here.

Q12 (500best):A 14-year-old girl is brought to clinic by her parents who have been worried about a fever the patient has had for the last week. The patient looks pale and unwell. Blood tests reveal a neutropenia with normal red blood counts (RBCs) and platelets. A bone marrow exam reveals no abnormalities. The patient has been otherwise fit and well. There is no organomegaly or lymphadenopathy. The most likely diagnosis is:

A. Acute myeloid leukaemia
B. Aplastic anaemia
C. Acute lymphoblastic leukaemia
D. Bacterial infection
E. Thrombotic thrombocytopenic purpura

Explanation: This patient is likely suffering from a dangerous septicaemia shown by the presence of fever alongside a neutropenia. Urgent broad spectrum antibiotics should be administered. In an acute myeloid leukaemia (A) or acute lymphoblastic leukaemia (C), a bone marrow examination would show more than 20 per cent myeloblasts or lymphoblasts, respectively. Although the WCC can be variable, a neutropenia, anaemia and thrombocytopenia is associated with AML and ALL. An aplastic anaemia (B) is a failure of the bone marrow and presents with a hypocellular bone marrow and pancytopenia. A thrombotic thrombocytopenic purpura (E)is the pentad of fever, thrombocytopenia, microangiopathic haemolytic anaemia, renal failure and neurological symptoms.

Q13 (500best):A 27-year-old man presents with increasing tiredness and shortness of breath. A macrocytic anaemia with reticulocytes is discovered on blood tests and smear. Genetic analysis reveals the patient has glucose-6-phosphate dehydrogenase deficiency. What cell type is most likely to have been seen on the blood smear?

A. Target cells
B. Pencil cells
C. Spherocytes
D. Elliptocytes
E. Schistocytes

Explanation: Schistocytes (E), fragments of red blood cells, are the strongest indicator of red blood cell haemolysis. Target cells (A) have an accumulation of haemoglobin at their centre with pallor around them. They are indicative of obstructive jaundice, hepatic pathology, haemoglobinopathy and hyposplenism. Pencil cells (B) are hypochromic variations of elliptocytes (D), the former occurring in iron deficiency while the latter occurs in both hereditary elliptocytosis and iron deficiency anaemia. Spherocytes (C) usually occur in hereditary spherocytosis and haemolytic anaemia.

Answers: Q11:E | Q12:D | Q13:E

Anemia

Q14 (500Best): A 33-year-old man travels to South Africa to take part in a safari. On arriving, the patient takes his antimalarial tablets. A few days into his course he becomes ill complaining of shortness of breath, pallor and bloody urine. Blood tests reveal anaemia and reduced haematocrit, while a blood smear shows the presence of Heinz bodies. The most likely diagnosis is:

A. Hereditary elliptocytosis
B. Glucose-6-phosphate dehydrogenase deficiency
C. Hereditary spherocytosis
D. Autoimmune haemolytic anaemia
E. Microangiopathic haemolytic anaemia

Explanation: This patient is most likely suffering from glucose-6-phosphate dehydrogenase deficiency (G6PD) (B). This is an important enzyme which maintains levels of glutathione, an important protective factor against oxidative stress. Exposure to drugs such as dapsone or antimalarials such as primaquine can denature haemoglobin which produces Heinz bodies with precipitant haemoglobin. Hereditary elliptocytosis (A)is usually associated with iron deficiency anaemia and is not greatly impacted by an additional stressor such as oxidant influences. Hereditary spherocytosis (C) occurs due to a defect in the cell membrane protein spectrin which predisposes such cells to become accumulated within the spleen and more fragile. Autoimmune haemolytic anaemia (D) is due to autoimmune mediated attacks upon RBCs, usually through the action of autoantibodies or complement. Microangiopathic haemolytic anaemia (E) is characterized by anaemia and schistocytes on blood smear produced from the shearing of RBCs upon fibrin meshes formed in the small vasculature, which most often forms due to increased activation of the coagulatory system.

Q15 (500best):A 29-year-old woman presents complaining of shortness of breath, especially when walking up stairs. She is starting to struggle with yoga classes, which were never a problem before. She does not suffer from any medical conditions and takes no regular medication. On examination there is pallor, heart rate is 90 and blood pressure 119/79 mmHg. The patient mentions that she has recently become a vegetarian and in the morning only has time for tea before heading to work. Which of the following would you expect to be increased in this patient?

A. Myoglobin
B. Ferritin
C. Haemoglobin
D. Serum iron
E. Transferrin

Explanation: This patient is most likely suffering from iron deficiency anaemia given her change to vegetarian diet, although there are many foods with good iron content such as green vegetables and whole grain cereals. However, most ingested iron is not absorbed by the body, an acidic pH increases absorption while an alkaline pH reduces it. The characteristic symptoms of iron deficiency anaemia are shortness of breath, pallor and malaise. Transferrin (E) is the principal iron carrying protein in the body. In iron deficiency anaemia, iron-binding capacity increases to compensate the reduced intake. Although haemoglobin (C) and myoglobin (A) contain iron, they are likely to be reduced in iron deficiency anaemia. Similarly, the iron stores of the body are ferritin (B) and over time these will be consumed if intake decreases, as does the serum iron (D).

Q16 (500best):A 65-year-old man presents with a chronic history of malaise, shortness of breath and paraesthesia in his hands. He appears tired and pale while speaking and on examination his heart rate is 115, respiratory rate 16. A Schillings test is positive while blood tests reveal a macrocytic anaemia and a Coombs test is negative. The most likely diagnosis is:

A. Iron deficiency anaemia
B. Haemorrhage
C. Anaemia of chronic disease
D. Pernicious anaemia
E. Autoimmune haemolytic anaemia

Explanation: This patient is most likely suffering from pernicious anaemia (D) whereby antibodies bind to gastric parietal cells reducing B12 absorption through deficiency of intrinsic factor. Vitamin B12 deficiency can cause a megaloblastic anaemia which presents with an increased MCV on blood tests. Diseases of the small bowel can compound this anaemia such as coeliac's and Crohn's disease. Blood loss (B) is likely to have caused a positive faecal occult blood test and usually presents with a normocytic anaemia. Iron deficiency anaemia (A) and anaemia of chronic disease (C) usually cause a microcytic anaemia. Although autoimmune haemolytic (E) anaemia can cause a macrocytic anaemia, a Coomb's test would be positive.

Answers: Q14:B | Q15:E | Q16:D

Anemia

Q17 (500Best): A 44-year-old woman presents with recurrent fever, pallor, malaise and shortness of breath. She has noticed a petechial rash on her skin and small bruises on her arms. A blood test reveals a pancytopenia. During examination, you palpate a large spleen. Which investigation would differentiate between hypersplenism and aplastic anaemia?

A. Reticulocyte test
B. Direct Coombs test
C. Metabisulfite test
D. Ham's test
E. Osmotic fragility test

Explanation: The reticulocyte test (A) would show reduced counts in aplastic anaemia while it is raised in hypersplenism. The metabisulphite (C) can be added to blood smears to mimic accelerated deoxygenation. RBCs with high haemoglobin S concentrations undergo sickling in a reduced oxygen environment and therefore this is a useful test for sickle cell anaemia. Ham's test (D) is used to diagnose paroxysmal nocturnal haemoglobinuria. The direct Coomb's test (B) is used to investigate causes of autoimmune haemolytic anaemia. The osmotic fragility test (E) is used to investigate hereditary spherocytosis.

Q18 (500best):A 66-year-old man presents complaining of a three-month history of weakness, tingling in the limbs and a sore tongue. The patient notes an undesired 5 kg weight loss over 2 weeks. A peripheral blood smear shows a macrocytic anaemia, a Schilling test shows impaired vitamin B12 absorption and a diagnosis of pernicious anaemia is made. Which of the following antibodies is most closely associated with pernicious anaemia?

A. Anti-mitochondrial antibodies
B. Anti-intrinsic factor antibodies
C. Anti-gliadin antibodies
D. Anti-centromere antibodies
E. Anti-smooth muscle antibodies

Explanation: Pernicious anaemia is an autoimmune disease whereby anti-intrinsic factor antibodies (B) bind intrinsic factor produced by the parietal cells in the gastric fundus. Intrinsic factor is essential in the absorption of vitamin B12 via the ileum. Associated conditions can include thyroid disease which compound symptoms of anaemia. Anti-mitochondrial antibodies (A) are associated with primary biliary cirrhosis, anti-gliadin antibodies (C) are associated with coeliac disease. Anti-centromere antibodies (D) are associated with limited and occasionally diffuse scleroderma. Anti-smooth muscle antibodies (E) are associated with autoimmune hepatitis.

Q19 (500best):A 64-year-old man presents to accident and emergency following a collapse. He describes a blackout, subsequently regaining consciousness when on the floor. He presently feels well and describes no other symptoms. However, he mentions that he has unintentionally lost some weight over the past few months. There is no past medical history. Blood tests reveal a haemoglobin level of 9 g/dL with a mean cell volume on 71 fL. The most appropriate next investigation of this patient is:

A. Flexible sigmoidoscopy
B. Endoscopy
C. Colonoscopy
D. Endoscopy and colonoscopy
E. Profile of tumour markers

Explanation: The patient in the case outlined has presented with a microcytic anaemia.The most common cause of a microcytic anaemia is iron deficiency. In pre-menopausal women, the most common cause of iron deficiency anaemia is menstrual blood loss. However, blood loss from the gastrointestinal tract is the most common cause in men and post- menopausal women. Therefore, the case outlined in this question should raise the suspicion of a gastrointestinal cancer, such as gastric or colonic carcinoma. Colorectal cancer is more prevalent in males and the peak age of onset is in patients aged over 70 years. Therefore, this must be kept in mind for a patient such as this. Left-sided colonic lesions may commonly present with change in bowel habit, PR bleeding, abdominal pain or bowel obstruction. However, caecal and right-sided colonic lesions are often asymptomatic. Similarly, gastric cancers may also be asymptomatic. While non-malignant gastrointestinal causes such as oesophagitis, gastritis, gastric erosions and coeliac disease can cause iron-deficiency anaemia, there must be a low threshold of suspicion for cancer. Therefore, the correct answer in this case is endoscopy and colonoscopy (D). Flexible sigmoidoscopy (A) is limited in that it does not view the whole of the large bowel. This is particularly important in this case as the patient does not have any gastrointestinal symptoms. Endoscopy (B) and colonoscopy (C) alone are not the correct answers as blood loss may come from the upper or the lower gastrointestinal tract, as explained. Profile of the tumour markers (E) may be useful but endoscopy and colonoscopy are the investigations of choice as they allow direct visualization of a lesion and intervention and biopsy if necessary.

Answers: Q17:A | Q18:B | Q19:D

Anemia

Q20 (Pretest): A 55-year-old man is being evaluated for constipation. There is no history of prior gastrectomy or of upper GI symptoms. Hemoglobin is 10 g/dL, mean corpuscular volume (MCV) is 72 fL, serum iron is 4 µg/dL (normal 50-150 µg/dL), iron-binding capacity is 450 µg/dL (normal 250-370 µg/dL), saturation is 1% (normal 20%-45%), and ferritin is 10 µg/L (normal 15-400 µg/L). Which of the following is the best next step in the evaluation of this patient's anemia?

A. Red blood cell folate
B. Serum lead level
C. Colonoscopy
D. Bone marrow examination
E. Hemoglobin electrophoresis with A2 and F levels

Explanation: The patient has a microcytic anemia. A low serum iron, low ferritin, and high iron-binding capacity all suggest iron-deficiency anemia. Most iron-deficiency anemia is explained by blood loss. The patient's symptoms of constipation point to blood loss from the lower GI tract. Colonoscopy would be the highest-yield procedure. Barium enema misses 50% of polyps and a significant minority of colon cancers. Even patients without GI symptoms who have no obvious explanation (such as menstrual blood loss or multiple prior pregnancies in women) for their iron deficiency should be worked up for GI blood loss. Folate deficiency presents as a megaloblastic anemia with macrocytosis (large, oval-shaped red cells) and hypersegmentation of the polymorpho-nuclear leukocytes. Lead poisoning can cause a microcytic hypochromic anemia, but this would not be associated with the abnormal iron studies and low ferritin seen in this patient. Basophilic stippling or target cells seen on the peripheral blood smear would be important clues to the presence of lead poisoning. Although a bone marrow examination will prove the diagnosis by the absence of stainable iron in the marrow, the diagnosis of iron deficiency is clear from the serum studies. Thalassemia (diagnosed by hemoglobin electrophoresis) is not associated with abnormal iron studies. The most important issue is now to find the source of the iron loss.

Q21 (Pretest):A 50-year-old woman complains of pain and swelling in her proximal interphalangeal joints, both wrists, and both knees. She complains of morning stiffness. She had a hysterectomy 10 years ago. Physical examination shows swelling and thickening of the PIP joints. Hemoglobin is 10.3 g/dL, MCV is 80 fL, serum iron is 28 µg/dL, iron-binding capacity is 200 µg/dL (normal 250-370 µg/dL), and saturation is 14%. Which of the following is the most likely explanation for this woman's anemia?

A. Occult blood loss
B. Vitamin deficiency
C. Anemia of chronic disease
D. Sideroblastic anemia
E. Occult renal disease

Explanation: Patients with chronic inflammatory or neoplastic disease often develop anemia of chronic disease. Cytokines produced by inflammation cause a block in the normal recirculation of iron from reticuloendothelial cells (which pick up the iron from senescent red blood cells) to the red cell precursors (normoblasts). The peptide hepcidin is felt to be the main mediator of the effect. This defect in iron reutilization causes a drop in the serum iron concentration and a normocytic or mildly microcytic anemia. The inflammatory reaction, however, also decreases the iron- binding capacity (as opposed to iron-deficiency anemia, where the iron-binding capacity is elevated), so the saturation is usually between 10% and 20%. The anemia is rarely severe (Hb rarely < 8.5 g/dL). The hemoglobin and hematocrit will improve if the underlying process is treated. Diseases not associated with inflammation or neoplasia (ie, congestive heart failure, diabetes, hypertension, etc) do not cause anemia of chronic disease. Blood loss causes a lower serum iron level, an elevated iron-binding capacity, and a lower iron saturation. The serum ferritin (low in iron deficiency, normal or high in anemia of chronic disease) will usually clarify this situation. Vitamin B12 and folate deficiencies are associated with macrocytic anemia. Sideroblastic anemia can be either microcytic or macrocytic (occasionally with a dimorphic population of cells, some small and some large), but is associated with an elevated iron level. In addition, this patient's history (which suggests an inflammatory polyarthritis) would not be consistent with sideroblastic anemia. The diagnosis of sideroblastic anemia is made by demonstrating ringed sideroblasts on bone marrow aspirate. In the anemia of chronic renal insufficiency, the iron studies are normal and the red cells are normocytic.

Answers: Q20:C | Q21:C

Anemia

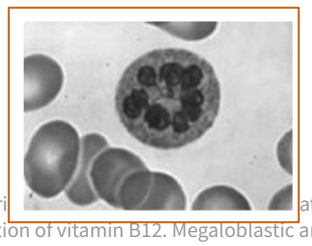
Q22 (Pretest): A 35-year-old woman presents with several days of increasing fatigue and shortness of breath on exertion. She was recently diagnosed with Mycoplasma pneumoniae. Physical examination reveals BP 113/67, HR 114 beats/minute, and respiratory rate 20 breaths/minute. She appears icteric and in mild respiratory distress. Her hemoglobin is 9.0 g/dL and MCV is 110. Which of the following is the best next diagnostic test?

A. Serum protein electrophoresis
B. Flow cytometry
C. Peripheral blood smear
D. Glucose-6-PD level
E. Bone marrow biopsy

Explanation: Macrocytic anemia and indirect hyperbilirubinemia suggest hemolysis, which in this patient is likely due to immune-mediated IgM antibodies which may follow Mycoplasma infections. These antibodies are also called cold-reacting antibodies as they react at temperatures less than 37°C (98°F). Examination of the peripheral blood smear is the first step in evaluation of hemolytic anemia. The young red cells (which would show up as reticulocytes when properly stained) are much larger than mature RBCs, accounting for the macrocytosis (the MCV can be as high as 140 with vigorous reticulocytosis). The presence of micro-spherocytes suggests immune-mediated hemolysis, while the presence of fragmented RBCs or schistocytes suggest a mechanical cause of hemolysis, as seen in the microangiopathic hemolytic anemias. Serum protein electrophoresis is useful to diagnose multiple myeloma, which is rarely associated with hemolysis, but this would not be the best initial test; the anemia in multiple myeloma is normocytic. Flow cytometry can detect surface proteins like CD55, CD59 on granulocytes, and red blood cells in paroxysmal nocturnal hemoglobinuria (a rare cause of hemolysis), but again is not the best first test. Glucose-6-PD levels might be useful once hemolytic anemia is established by a peripheral smear and negative Coombs test. Bone marrow biopsy would show erythroid hyperplasia, but is usually not required to diagnose hemolytic anemia.

Q23 (Pretest):A 60-year-old man develops numbness of the feet. On physical examination he has lost proprioception in the lower extremities and is noticed to have a wide based gait with a positive Romberg sign. His past medical history includes hypertension, hypothyroidism, and previous gastrectomy for gastric cancer. The peripheral blood smear is shown below. What is the most likely cause of his symptoms?

A. Folic acid deficiency
B. Vitamin B12 deficiency
C. Vitamin K deficiency
D. Iron deficiency
E. Thiamine deficiency



Explanation: This is a classic presentation of a patient with vitamin B12 deficiency. This is commonly seen in patients with gastri atients with gastric resection lose intrinsic factor production from parietal cells. Loss of intrinsic factor leads to decreased absorption of vitamin B12. Megaloblastic anemia with hypersegmented neutrophils (as seen on this patient's peripheral blood smear) can be found in both folic acid and vitamin B12 deficiency. Folic acid deficiency does not produce neurologic findings. B12 deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the posterior and pyramidal tracts of the spinal cord and, less frequently, optic atrophy or cerebral symptoms. Iron deficiency anemia would show micro-cytic and hypochromic red blood cells on peripheral blood smear. Vitamin K deficiency results in a coagulopathy but does not cause neurologic symptoms or hypersegmented neutrophils on peripheral blood smear. Thiamine deficiency causes beriberi; this vitamin does not depend on gastric factors for absorption.

Q24 (pretest): A 20-year-old black man presents to the emergency room complaining of diffuse bone pain and requesting narcotics for his sickle cell crisis. Which of the following physical examination features would suggest an alternative diagnosis to sickle cell anemia (hemoglobin SS)?

A. Scleral icterus
B. Systolic murmur
C. Splenomegaly
D. Ankle ulcers
E. Leukocytosis

Explanation: Splenomegaly is not typical of sickle cell anemia. Recurrent splenic infarcts usually occur during childhood and lead to a small, infarcted spleen with functional asplenia. These patients often have Howell-Jolly bodies on peripheral blood smear (indicative of asplenia) and have an increased incidence of infection with encapsulated organisms. The presence of an enlarged spleen in a patient with sickled cells on peripheral blood smear is most often seen in hemoglobin SC disease. Any hemolytic anemia can result in an unconjugated hyperbilirubinemia and scleral icterus. Anemia results in a hyperdynamic circulation and a systolic ejection murmur. Ankle ulcers and other chronic skin ulcers may be persistent problems in patients with SS disease, particularly in those with severe anemia. Patients with sickle cell crisis often present with leukocytosis, related both to stress and to the asplenia.

Answers: Q22:C | Q23:B | Q24:C

Anemia

Q25 (pretest): A 30-year-old black man plans a trip to India and is advised to take prophylaxis for malaria. Three days after beginning treatment, he develops pallor, fatigue, and jaundice. Hematocrit is 30% (it had been 43%) and reticulocyte count is 7%. He stops taking the medication. The next step in treatment should consist of which of the following?

A. Splenectomy
B. Administration of methylene blue
C. Administration of vitamin E d. Exchange transfusions
E. No additional treatment is required

Explanation: This woman is at high risk of recurrent breast cancer, an ultimately fatal event. Adjuvant therapy has been shown to decrease the chance of recurrence by 40%. This translates into a proven survival advantage for the woman; the advantages of treatment far outweigh the risk of side effects. Therefore, no therapy or only local therapy (eg, radiation therapy) would represent inadequate treatment. Postmenopausal women who are ER or PR positive are generally treated with adjuvant hormonal therapy. Premenopausal women, or women whose tumor does not contain ER or PR, will usually need adjuvant chemotherapy. Both aromatase inhibitors (eg, letrozole, anastrozole) and tamoxifen (a selective estrogen receptor modulator) are effective in decreasing the rate of recurrence. Aromatase inhibitors are modestly more effective than tamoxifen and are the usual drugs chosen in a postmenopausal woman. Osteoporosis and musculoskeletal pains are common side effects of aromatase inhibitors. In a woman 5 or more years after menopause, the ovaries produce inconsequential amount of estrogens. Therefore oophorectomy, sometimes used in the premenopausal woman, is an inappropriate choice for this patient.

Answers: Q25:E

Common solid tumors

Q1 (MKSAP): A 45-year-old woman is evaluated for a lump in the right breast that has been present for 3 months. The patient is gravida 1, para 1. She has menses every 28 days. She is otherwise healthy. No family history of breast cancer exists. Her mother died of endometrial cancer at the age of 63 years.
On physical examination, vital signs are normal. A firm and nontender 2-cm mass in the upper outer quadrant of the right breast is palpated. No other masses or axillary
adenopathy are noted.
A mammogram is BI-RADS 2 (benign findings).
Which of the following is the most appropriate next step in the management of this patient?

A- Obtain a fine needle aspirate
B- Obtain an ultrasound of the right breast
C- Repeat mammogram in 1 year
D- Test for BRCA-1 and BRCA-2 genes

Explanation: The next management step for this patient is to obtain an ultrasound of the right breast. The Breast Imaging Reporting and Data System (BI-RADS) is a standardized reporting system for mammography findings and a source of recommendations for further management. Category assignments are either incomplete (category 0) or final assessment (categories 1 through 6). Category 2 findings correspond to findings compatible with benign nodules or cysts or benign calcifications. But because this patient's mass has persisted through several menstrual cycles, she needs further evaluation despite the normal mammogram. Because she is older than 30 years and the mammogram is classified as BI-RADS 2, the ultrasound is the next appropriate test. This is true for mammograms rated BI-RADS 1-3. Ultrasound serves to distinguish cystic from solid masses. A cystic mass should be aspirated and the fluid sent for cytologic evaluation if bloody or recurrent. A solid mass requires biopsy by fine-needle aspiration, core needle, or excision. If the mammogram is classified as BI-RADS 4 or 5, malignancy is much more likely and a tissue diagnosis with fine needle aspirate or biopsy is the most appropriate management.
Inherited germline abnormalities in BRCA-1 and BRCA-2 genes confer very high risk for breast and ovarian cancer (absolute risk of breast cancer greater than 60% by age 50 years). Fewer than 5% of all cases of breast cancer are attributed to germline abnormalities in these genes, however, and the prevalence of these abnormalities in the general population is approximately 1/800. Testing for BRCA-1 and BRCA-2 genes should be performed only in women who appear to have a genetic risk (multiple relatives with breast or ovarian cancer, especially with early-onset of disease). These women and their families should be referred to a genetic counselor for discussion and consideration of these complex issues. This patient does not have an increased genetic risk for breast cancer and testing for BRCA-1 and BRCA-2 genes is not indicated.

Q2 (MKSAP): A 49-year-old woman is evaluated after noticing a small lump in her right breast 3 weeks ago. It is painless and has not changed in size. She has no other pertinent medical history. Her last menstrual period was 2 weeks ago. Her mother had breast cancer at age 55 years; there is no other family history of cancer.
On physical examination, vital signs are normal. There is a 1.0 × 1.5-cm firm, discrete, mobile mass in the upper outer quadrant of the right breast. There is no lymphadenopathy or other abnormalities on examination.
A bilateral mammogram does not reveal any suspicious lesion in either breast.
Which of the following is the most appropriate management option for this patient?

A- Aspiration or biopsy
B- Clinical reevaluation in 1 month
C- MRI of both breasts
D- Repeat mammography in 6 months

Explanation: The most appropriate management option is fine-needle aspiration or biopsy of the breast mass. A patient with a breast mass requires triple assessment: palpation, mammography with or without ultrasonography, and surgical evaluation for biopsy. Mammograms may be normal in 10% to 15% of patients with breast lumps, some of which may be cancerous. After performance of bilateral diagnostic mammography, the initial focus of the workup of a dominant breast mass is to distinguish a simple cyst from a solid mass by fine-needle aspiration (FNA) or ultrasonography. If the fluid from FNA is bloody, the fluid should undergo cytologic evaluation. Women with simple cysts should undergo a breast examination 4 to 6 weeks after cyst aspiration to evaluate for cyst recurrence or a residual lump. A solid mass requires a tissue diagnosis by fine- needle aspiration biopsy (FNAB), core-needle biopsy, or excisional biopsy. Patients with benign FNAB or core-needle biopsy results and negative mammogram require close clinical follow-up of the breast abnormality.

Answers: Q1:B | Q2:A

Common solid tumors

Q3 (MKSAP): A 52-year-old woman undergoes evaluation after a recent diagnosis of invasive ductal adenocarcinoma of the right breast. Her aunt died of breast cancer at age 85 years, but there is no other family history of breast or ovarian cancer. The patient is otherwise healthy. Her physical examination is normal.
The patient undergoes tumor resection and a sentinel lymph node biopsy of the right axilla. On pathologic examination, a 1.2-cm invasive ductal adenocarcinoma with free margins is confirmed, and the lymph node reveals no metastases. Complete blood count, metabolic profile, and liver chemistry tests are normal as are diagnostic mammography and chest radiography.
Which of the following will be most helpful in directing the approach to management of this patient?

A- Full right axillary lymph node dissection
B- Genetic testing for the BRCA1/2 mutation
C- Tumor estrogen and progesterone receptor assay
D- Whole-body positron emission tomography

Explanation: The next step is a tumor estrogen-receptor (ER) and progesterone-receptor (PR) assay. This patient has early-stage breast cancer (stage I) based on the tumor size (<2 cm); absent lymph node involvement; and no apparent metastases based on her symptoms, physical examination findings, and routine blood tests. The step that would be most helpful in directing the approach to management of this patient is to perform an assay for expression of ER and PR to determine the optimal systemic treatment, and this evaluative step should be performed in all cases of primary breast cancer. Endocrine therapy (for example, tamoxifen, aromatase inhibitors, fulvestrant, and megestrol acetate) is beneficial only in patients with ER-positive or PR-positive tumors. Patients whose tumors are hormone receptor-negative are refractory to endocrine treatment and should receive chemotherapy instead.
In patients with early-stage breast cancer, the routine evaluation is limited to a thorough history and physical examination, diagnostic mammography, chest radiography, and routine blood tests (including liver chemistry tests). The use of additional imaging studies or blood tests is not warranted in the absence of specific symptoms because they may lead to the detection of abnormalities of no significance (a false-positive test result).

Q4 (MKSAP): A 48-year-old postmenopausal woman is evaluated after a recent diagnosis of breast cancer. Her annual screening mammogram revealed a new 1.5-cm area of microcalcification in the left breast without any associated mass. Stereotactic biopsy revealed grade 2, estrogen receptor-progesterone receptor-negative and HER2-negative infiltrating ductal carcinoma. She is otherwise healthy.
Her physical examination is normal except for ecchymosis at the biopsy site.
Which of the following is the most appropriate next step in management?

A- Left lumpectomy and tamoxifen
B- Left lumpectomy followed by breast irradiation
C- Left lumpectomy with sentinel lymph node biopsy and tamoxifen
D- Left lumpectomy with sentinel lymph node biopsy followed by breast irradiation

Explanation: This patient should undergo breast lumpectomy plus sentinel lymph node biopsy followed by radiation therapy. Breast lumpectomy plus radiation therapy is known as "breast-conserving therapy." Breast-conserving therapy consists of excision of the primary tumor followed by radiation to the remaining ipsilateral breast tissue and is generally indicated for patients with focal disease and small tumors for which conservation will offer a good cosmetic result. However, patient preferences must be considered in the surgical decision-making process. The survival rate for women undergoing breast-conserving therapy is equivalent to that of those who undergo mastectomy, with breast-conserving therapy resulting in improved cosmetic outcomes and less morbidity than mastectomy. Most patients treated with lumpectomy without radiation therapy have a high risk for local recurrence; therefore, this treatment modality cannot be recommended. In addition, sentinel lymph node biopsy is a safe and accurate method for screening the axillary lymph nodes for metastases in women with small breast tumors. Sentinel lymph node biopsy has replaced full axillary lymph node dissection for the staging of disease in many women with early-stage, clinically lymph node-negative breast cancer. The first draining (or sentinel) lymph node is identified by injecting blue dye and radioactive colloid into the tumor site. If the sentinel lymph node does not contain metastases, it is unlikely that more distal axillary lymph nodes will contain metastases; consequently, no further surgery is indicated in this setting, and the toxicity from a full axillary lymph node dissection is avoided. However, if the sentinel lymph node shows metastatic involvement, then axillary lymph node dissection is performed to determine the number of involved lymph nodes.
Selective estrogen receptor modulators such as tamoxifen are not indicated in patients with estrogen receptor-negative tumors.

Answers: Q3:C | Q4:D

Common solid tumors

Q5 (MKSAP): A 51-year-old woman is evaluated during a routine health maintenance examination. She is healthy and takes no medications. She does not smoke or drink alcohol. She is up to date on all of her immunizations and cancer screening tests. Her most recent screening colonoscopy was performed at age 50 years. The only new addition to her history is a recent diagnosis of colorectal cancer in her 55-year-old brother. What is the best colorectal cancer screening strategy for this patient?

A- APC gene mutations screening
B- Colonoscopy at age 55 years and then every 3 to 5 years
C- Colonoscopy at age 60 years and then every 10 years
D- Colonoscopy now and then every 2 years

Explanation: The best colorectal cancer screening strategy for this patient is colonoscopy at age 55 years and then every 3 to 5 years. A family history of colorectal cancer or adenomatous polyps significantly increases a person's risk for colorectal cancer. The presence of colorectal cancer in a first-degree relative carries a twofold to threefold increased lifetime risk over the general population; that risk is doubled again if the affected relative was diagnosed before age 45 year.

Q6 (MKSAP): A 59-year-old man is evaluated for a change in his bowel habits over the past 2 months. Typically, he has a soft, formed bowel movement every other day, but he now passes hard, pellet-like stools alternating with loose stools associated with a sense of bloating and abdominal fullness; there is no blood. He has not lost weight. He has never undergone colon cancer screening.
On physical examination, vital signs are normal. Abdominal examination reveals normal bowel sounds and no evidence of tenderness or masses. Rectal examination is normal, and the stool is negative for occult blood. Routine screening chemistry tests are normal. Which of the following is the most appropriate next step in the management of this patient?

A- Colonoscopy
B- Contrast-enhanced abdominal CT scan
C- Flexible sigmoidoscopy
D- Testing three stools for occult blood

Explanation: This patient requires a colonoscopy. Common signs and symptoms of colorectal cancer are influenced by the site of the primary tumor and may include a change in bowel habits, diarrhea, constipation, a feeling that the bowel does not empty completely, bright red blood in the stool or melanotic stools, and stools that are narrower in caliber than usual. Other signs include general abdominal discomfort (frequent gas pains, bloating, fullness, or cramps), weight loss for no known reason, fatigue, and vomiting. Findings that should prompt investigation for colon cancer include a rectal or abdominal mass, hepatomegaly, abdominal tenderness, or iron deficiency anemia. A contrast-enhanced CT scan of the abdomen is not sensitive for diagnosing colon cancer. Options for colorectal cancer screening include colonoscopy, fecal occult blood testing, flexible sigmoidoscopy, or barium enema used alone or in combination for screening.

Q7 (MKSAP): A 58-year-old woman undergoes a general physical examination. She is asymptomatic and takes no medications or over-the-counter drugs. Family history is unremarkable. Her preferred method of colorectal cancer screening has been annual fecal occult blood testing (FOBT). Annual testing for the past 8 years has been negative for fecal occult blood. Physical examination is normal. Results of routine laboratory studies are also normal, including a hemoglobin level of 14.8 g/dL (148 g/L). One of three stool samples submitted by the patient for FOBT is positive. Which of the following is the most appropriate next step in evaluating this patient?

A- Colonoscopy
B- Flexible sigmoidoscopy
C- Repeat FOBT now
D- Repeat FOBT in 1 year

Explanation: This patient has a positive result on a screening test for colorectal neoplasia and should be evaluated next with colonoscopy. Fecal occult blood testing (FOBT) is associated with a 15% to 33% reduction in mortality rates from colorectal cancer when annual or biennial testing is done. Six-window FOBT is performed by taking two separate samples from each of three spontaneously passed stools (six samples). Even though only one of three of this patient's samples submitted for fecal occult blood testing was positive, she requires appropriate follow-up with a diagnostic test such as colonoscopy.

Answers: Q5:B | Q6:A | Q7:A

Common solid tumors

Q8 (500Best):A 39-year-old woman has undergone a wide local excision for a 0.5 cm ductal carcinoma of her right breast. Sentinal node biopsy, histology and staging scans have confirmed the disease as T1N0M0. Histology has confirmed the cancer as oestrogen and progesterone receptor positive. Which of the following statements is most accurate regarding this female's treatment options?

A. She should receive radiotherapy
B. She is not suitable for radiotherapy
C. She is not suitable for tamoxifen therapy
D. She requires no further treatment
E. She should be considered for cetuximab therapy

Explanation: This is a difficult question for the budding oncologist. The treatment options for breast cancer include surgery, radiotherapy, chemotherapy and endocrine therapy. The female in this question has early disease. For such patients, breast-conserving surgery (i.e. wide local excision) is now favoured and has been shown to achieve equivalent local control and survival to mastectomy. Radiotherapy (B) is recommended for all patients who have had wide local excisions and reduces the risk of local recurrence. Therefore, option (A) is incorrect. Radiotherapy may also be given post- mastectomy for tumours that have a high risk of local recurrence (such as large tumours, multifocal lesions, axillary lymph node involvement, high- grade tumours or proximity to surgical margins). Chemotherapy should be considered in all early breast cancer patients under the age of 70. In those above the age of 70, there is no clear evidence for or against the use of chemotherapy, but it should be considered for high-risk patients, with the advantages and disadvantages of chemotherapy evaluated for each specific patient. Chemotherapy in breast cancer is now being used on a neoadjuvant basis, to shrink a large operable cancer for which breast conserving surgery may then be possible in place of mastectomy. Tamoxifen is an oestrogen-receptor antagonist and is given to patients who have oestrogen and/or progesterone receptor positive disease. Therefore, the woman in the question should receive tamoxifen, making answers (C) and (D) incorrect. Finally, cetuximab (E) is a monoclonal antibody, which targets the epidermal growth factor receptor. It is used in colorectal and head and neck cancers, but not breast cancer.

Q9 (500Best): A 74-year-old man with T2N0M0 squamous cell carcinoma of the tongue is currently undergoing hyper-fractionated radiotherapy with curative intent. He has had no previous surgery. This type of therapy is best described by which of the following terms:

A. Adjuvant
B. Neoadjuvant
C. Palliative
D. Radical
E. Brachytherapy

Explanation: Treatment with curative intent is known as radical therapy (D). Adjuvant therapy (A) is treatment given following surgical resection of a cancer. The aim of such therapy is to reduce the chances of recurrence. Neoadjuvant therapy (B) is treatment given before surgery to reduce the size of a tumour and thus facilitate its removal. Palliative therapy (C) is given to those patients where cure is not possible and treatment aims are to reduce the tumour load and thus increase life expectancy and quality of life. Brachytherapy (E) is a form of radiotherapy where the radiation source is placed within or adjacent to the area requiring treatment. Examples of cancers where brachytherapy is used are cervical or prostate cancer.

Q10 (500Best): A 57-year-old woman with adenocarcinoma of the sigmoid colon with liver metastasis is attending for cycle six of her palliative FOLFOX chemotherapy. Which tumour marker can be measured in the blood test to indicate the effect of the chemotherapy?

A. α-fetoprotein (αFP)
B. β-human chorionic gonadotrophin (β-hCG)
C. CA 19-9
D. CA 125
E. CEA

Explanation: Tumour markers can be used for screening purposes, disease staging, assessing response to therapy and assessing disease recurrence. Carcinoembryonic antigen (CEA) (E) is associated with colorectal cancers and thus is the correct answer here. α-fetoprotein (A) is raised in hepatocellular carcinoma and teratomas. β-hCG (B) is raised in seminomas, teratomas and choriocarcinomas. CA 19-9 (C) is raised in pancreatic carcinoma. CA 125 (D) is raised in ovarian cancer. It is important to note that the tumour markers are nonspecific and the tumour markers listed may be raised by other malignancies or non-cancerous pathologies. For example, CEA may be raised by gastric cancer, pancreatic cancer, cirrhosis, pancreatitis and smoking.

Answers: Q8:B | Q9:B | Q10:E

Common solid tumors

Q11 (pretest): A 66-year-old postmenopausal woman presents with a painless breast mass and is found to have a 3-cm infiltrating ductal breast cancer. Sentinel node sampling reveals metastatic cancer in the sentinel node; a formal axillary node dissection shows that 4 of 13 nodes are involved by the malignant process. Both estrogen and progesterone receptor are expressed in the tumor. There is no evidence of metastatic disease outside the axilla. In addition to lumpectomy and radiation therapy to the breast and axilla, what should her treatment include next?

A. No further treatment at this time
B. Radiation therapy to the internal mammary nodes
C. Platinum-based adjuvant chemotherapy
D. Bilateral oophorectomy
E. Adjuvant hormonal therapy (aromatase inhibitor or tamoxifen)

Explanation: This woman is at high risk of recurrent breast cancer, an ultimately fatal event. Adjuvant therapy has been shown to decrease the chance of recurrence by 40%. This translates into a proven survival advantage for the woman; the advantages of treatment far outweigh the risk of side effects. Therefore, no therapy or only local therapy (eg, radiation therapy) would represent inadequate treatment. Postmenopausal women who are ER or PR positive are generally treated with adjuvant hormonal therapy. Premenopausal women, or women whose tumor does not contain ER or PR, will usually need adjuvant chemotherapy. Both aromatase inhibitors (eg, letrozole, anastrozole) and tamoxifen (a selective estrogen receptor modulator) are effective in decreasing the rate of recurrence. Aromatase inhibitors are modestly more effective than tamoxifen and are the usual drugs chosen in a postmenopausal woman. Osteoporosis and musculoskeletal pains are common side effects of aromatase inhibitors. In a woman 5 or more years after menopause, the ovaries produce inconsequential amount of estrogens. Therefore oophorectomy, sometimes used in the premenopausal woman, is an inappropriate choice for this patient.

Q12 (pretest): A 37-year-old woman presents for evaluation of a self-discovered breast mass. There is no family history of breast cancer; she is otherwise healthy. Examination reveals a 1.5-cm area of firmness in the right upper outer quadrant. No skin changes or axillary lymphadenopathy are noted. Ultrasonography reveals a solid lesion; a mammogram is ordered and is normal. Which of the following is the most appropriate next step in management?

A. Refer the patient for further evaluation to a surgeon or comprehensive breast radiologist.
B. Reevaluate the patient in 6 months.
C. Give oral contraceptives to decrease ovulation and help shrink the lesion.
D. Recommend tamoxifen to decrease her chance of developing cancer.
E. Reassure the patient.

Explanation: A breast mass, even in a young woman, requires definitive evaluation. Although most such masses are benign, breast cancer is still the most common cause of cancer death in this age group. Risk factor assessment cannot provide sufficient reassurance. A negative mammogram never rules out breast cancer. Either excisional biopsy or core needle biopsy under sonographic or stereotactic guidance will be needed to detect cases of breast cancer before metastases outside the breast have occurred. Reassurance and reevaluation in 6 months may lead to delay in diagnosis of breast cancer. Neither oral contraceptives nor tamoxifen are indicated prior to a definitive diagnosis. A breast mass, even in a young woman, requires definitive evaluation. Although most such masses are benign, breast cancer is still the most common cause of cancer death in this age group. Risk factor assessment cannot provide sufficient reassurance. A negative mammogram never rules out breast cancer. Either excisional biopsy or core needle biopsy under sonographic or stereotactic guidance will be needed to detect cases of breast cancer before metastases outside the breast have occurred. Reassurance and reevaluation in 6 months may lead to delay in diagnosis of breast cancer. Neither oral contraceptives nor tamoxifen are indicated prior to a definitive diagnosis.

Answers: Q11:E | Q12:A

Lymphomas

Q1 (Pretest): A 43-year-old woman complains of fatigue and night sweats associated with itching for 2 months. On physical examination, there is diffuse nontender lymphadenopathy, including small supraclavicular, epitrochlear, and scalene nodes. CBC and chemistry studies (including liver enzymes) are normal. Chest x-ray shows hilar lymphadenopathy. Which of the following is the best next step in evaluation?

A- Excisional lymph node biopsy
B- Monospot test
C- Toxoplasmosis IgG serology
D- Serum angiotensin-converting enzyme level
E-Percutaneous aspiration biopsy of the largest lymph node

Explanation: The long-term nature of these symptoms, the fact that the nodes are nontender, and their location (including scalene and supraclavicular) all suggest the likelihood of malignancy. Although infectious mononucleosis and toxoplasmosis can cause diffuse lymphadenopathy, these infections are usually associated with other evidence of infection such as pharyngitis, fever, and atypical lymphocytosis in the peripheral blood. It would be unusual for the lymphadenopathy associated with these infections to persist for 2 months. Serum angiotensin-converting enzyme level is a nonspecific test for sarcoidosis but is also elevated in other granulomatous diseases and is not sensitive or specific enough to be used as an initial diagnostic test. Lymphadenopathy associated with sarcoidosis requires a biopsy for diagnosis. In this patient, an excisional biopsy is necessary primarily to rule out malignancy, particularly lymphoma. Needle aspiration biopsy, useful for the diagnosis of metastatic carcinoma, is insufficient to diagnose suspected lymphoma, where assessment of the lymph node architecture is important.

Q2 (Pretest): A 19-year-old woman presents for evaluation of a nontender left axillary lymph node. She is asymptomatic and denies weight loss or night sweats. Examination reveals three rubbery firm nontender nodes in the axilla, the largest 3 cm in diameter. No other lymphadenopathy is noted; the spleen is not enlarged. Lymph node biopsy, however, reveals mixed-cellularity Hodgkin lymphoma. Liver function tests are normal. Which of the following is the best next step in evaluation?

A- Bone marrow biopsy
B- Liver biopsy
C- Staging laparotomy
D- Erythrocyte sedimentation rate
E-CT scan of chest, abdomen, and pelvis

Explanation: The staging of Hodgkin disease is important so that proper treatment can be planned. Stage I (single lymph node bearing area) or stage II (more than one lymph node site on the same side of the diaphragm) patients with good prognostic features may be treated with radiation therapy. Those with stage III (affected lymph nodes on both sides of the diaphragm) or stage IV (extranodal disease) are treated with combination chemotherapy. CT or MRI of the abdomen and pelvis will show evidence of lymph node involvement below the diaphragm. Staging laparotomy with splenectomy, formerly done to provide pathology of the periaortic nodes and spleen, is rarely done today. Gallium scans can be useful in difficult cases. Bone marrow biopsy can later be performed to exclude bone marrow disease, which would imply stage IV, if less invasive studies have not clarified the proper stage. Liver biopsy is rarely indicated and the ESR is a nonspecific test.

Q3 (pretest): A 62-year-old woman has noted fever to 38.3°C (101°F) every evening for the past 3 weeks, associated with night sweats and a 15-lb weight loss. Physical examination reveals matted supraclavicular lymph nodes on the right; the largest node is 3.5 cm in diameter. She also has firm rubbery right axillary and bilateral inguinal nodes. Excisional biopsy of one of the nodes shows diffuse replacement of the nodal architecture with large neo-plastic cells which stain positively for B-cell markers. No Reed-Sternberg cells are seen. Which statement most accurately reflects her prognosis?

a. This is an indolent process which will respond to corticosteroids.
b. This is an aggressive neoplasm which responds poorly to chemotherapy and will likely be fatal in 6 months or less.
c. This is an aggressive neoplasm, but it may be cured with chemotherapy in up to 60% of the cases.
d. The neoplasm often responds to chemotherapy but almost always relapses.
e. Radiation therapy is curative.

Explanation: This is a classic presentation of diffuse large cell lymphoma. These neoplasms usually present with a rapidly enlarging nodes and B symptoms (fever, night sweats, >10% weight loss). Extranodal disease (eg, gastric involvement) is occasionally seen, whereas extra-lymphatic disease is unusual in the more indolent small cell lymphomas. Although Hodgkin disease can also present in this fashion, the histological features are those o non-Hodgkin lymphoma. Untreated large cell lymphomas are progressive and rapidly fatal. Usually, however, they respond to combination therapy (multidrug chemotherapy, often combined with the anti-CD 20 antibody rituximab). As opposed to indolent lymphomas, which respond but almost always relapse, most large cell lymphomas are cured with therapy. Exceptions are mantle cell lymphomas and primary central nervous system lymphomas, which are more refractory to therapy.

Answers: Q1:A | Q2:E | Q3:C

Lymphomas

Q4 (AMBOSS): A 27-year-old woman comes to the physician because of a 4-month history of fatigue, recurrent night sweats, and a 5-kg (11-lb) weight loss despite no change in appetite. She also reports multiple swellings on her neck and in both armpits, which she first noticed 1 month ago. She has no history of serious illness and takes no medications. She does not smoke cigarettes or drink alcohol. She is 160 cm (5 ft 3 in) tall and weighs 56 kg (123 lb); BMI is 22 kg/m2. Vital signs are within normal limits. Physical examination shows firm, nontender cervical and axillary lymphadenopathy. The remainder of the examination shows no abnormalities. A PET/CT scan shows multiple enlarged fluorodeoxyglucose-avid nodules at the neck, axillae, and abdominal aorta. An excisional axillary lymph node biopsy shows granuloma formation and large binucleate cells that are CD15/CD30-positive. Which of the following is the most appropriate next step in management?

A- Immunotherapy
B- Lymph node dissection
C- Chemotherapy
D- Bone marrow aspiration

Explanation: Weight loss, night sweats, and nontender lymphadenopathy in a young adult should raise concern for Hodgkin lymphoma (HL). The histopathologic findings of this patient's lymph node biopsy show Reed-Sternberg cells, which are pathognomonic for this condition. Combination chemotherapy with the ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine) is the treatment of choice for patients with HL. According to the Lugano classification, this patient has stage III disease, which is defined by the involvement of lymph node regions on both sides of the diaphragm (i.e., neck, axillae, and abdominal aorta) without the involvement of extralymphatic organs. While radiation therapy is part of the standard treatment of early-stage HL (stages I-II), it is only recommended in certain patients with advanced disease (stages III-IV), such as patients with bulky disease and/or incomplete response to chemotherapy.

Q5 (AMBOSS): A 67-year-old woman comes to the physician because of a 3-week history of fatigue and worsening back and abdominal pain. During this period, she has also had excessive night sweats and a 4.6-kg (10-lb) weight loss. She has had swelling of the neck for 3 days. She does not smoke or drink alcohol. Vital signs are within normal limits. Physical examination shows a 4-cm, supraclavicular, nontender, enlarged and fixed lymph node. The spleen is palpated 2 cm below the left costal margin. A CT scan of the thorax and abdomen shows massively enlarged paraaortic, axillary, mediastinal, and cervical lymph nodes. Histopathologic examination of an excised cervical lymph node shows lymphocytes with a high proliferative index that stain positive for CD20. Which of the following is the most likely diagnosis?

A- Hodgkin lymphoma
B- Follicular lymphoma
C- Marginal zone lymphoma
D- Diffuse large B-cell lymphoma

Explanation: This patient presents with B symptoms, painless lymphadenopathy, anemia, and an increased serum lactate dehydrogenase (LDH). In conjunction with the detection of the pan B-cell marker CD20 on malignant lymphocytes and evidence of extensive lymph node involvement within 3 weeks of the onset of symptoms suggest a highly aggressive B-cell lymphoma. This patient's features are consistent with diffuse large B-cell lymphoma (DLBCL), which is the most common non-Hodgkin lymphoma in adults, accounting for ~ 25% of cases (see “B-cell lymphomas” table.). DLBCL is an aggressive (high-grade) type of lymphoma that occurs spontaneously or secondary to numerous low-grade B-cell lymphomas (e.g., chronic lymphocytic leukemia, MALT lymphoma). Patients with high-grade B-cell non-Hodgkin lymphoma are typically first treated with curative intent, often with R-CHOP..

Answers: Q4:C | Q5:D

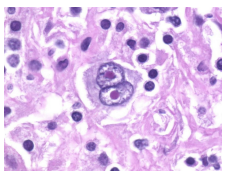
Lymphomas

Q6 (AMBOSS): A 60-year-old man comes to the physician because of a 2-month history of chest pain, dry cough, and shortness of breath. He describes two painless masses in his neck, which he says appeared 4 months ago and are progressively increasing in size. During this time, he has had week-long episodes of fever interspersed with 10-day periods of being afebrile. He reports that his clothes have become looser over the past few months. He drinks alcohol occasionally. His temperature is 38.0°C (100.4°F), pulse is 90/min, and blood pressure is 105/60 mm Hg. Physical examination shows two nontender, fixed cervical lymph nodes on either side of the neck, which are approximately 2.2 cm and 4.5 cm in size. The tip of the spleen is palpated 3 cm below the left costal margin. An x-ray of the chest shows discrete widening of the superior mediastinum. Which of the following is most appropriate to confirm the diagnosis?

A- Excisional biopsy
B- Fine needle aspiration
C- Bone marrow aspiration
D- CT scan of the chest

Explanation: Excisional biopsy of a lymph node is the most appropriate next step in confirming the diagnosis of suspected malignant lymphoma. Histopathological analysis of the biopsy specimen allows for the distinction between Hodgkin lymphoma and non-Hodgkin lymphoma, which is essential for determining further staging and a proper treatment regimen. Painless, fixed, slowly progressing lymph node enlargement (generalized or localized) should always raise suspicion for malignant disease

Q7 (AMBOSS): A 53-year-old man comes to the physician because of a 6-month history of recurring fever and night sweats. The fevers persist for 7 to 10 days and then subside completely for about a week before returning again. During the past 6 months, has had a 8-kg (18-lb) weight loss and has also noticed painless lumps on his neck that have gradually increased in size. Two years ago, he had a severe sore throat and fever, which was diagnosed as infectious mononucleosis. He has smoked a pack of cigarettes daily for the past 10 years. He does not drink alcohol. His job involves monthly international travel to Asia and Africa. He takes no medications. His temperature is 39°C (102.2°F), pulse is 90/min, respirations are 22/min, and blood pressure is 105/60 mm Hg. Physical examination shows enlarged, nontender, fixed cervical lymph nodes on each side of the neck. A photomicrograph from a biopsy of a cervical lymph node is shown. Which of the following additional findings is most likely present in this patient?



A- Proliferation of monomorphic lymphocytic cells
B- IgG and IgM antibodies against a viral capsid antigen
C- CD15/30 positive cells
D- Leukocyte count > 500,000/µL

Explanation: Lymph node biopsies in cases of Hodgkin lymphoma (HL) can show Reed-Sternberg cells, which are CD15/30-positive, polynuclear giant cells that originate from B cells. Reed-Sternberg cells are pathognomonic for HL and confirm the diagnosis. Past primary infection with Epstein-Barr virus (EBV), i.e., infectious mononucleosis, is a risk factor for HL. The most common histological types of EBV-associated HL are mixed cellularity HL and lymphocyte-depleted HL, and the median time to the onset of EBV-associated HL is approx. 3 years after the primary infection.

Q8 (AMBOSS): A 55-year-old man comes to the physician because of fatigue and worsening abdominal pain for 4 weeks. He also reports excessive night sweats and a 5.4-kg (12-lb) weight loss during this time. He has a neck swelling for 4 days. Physical examination shows a nontender, enlarged, and fixed supraclavicular lymph node. There is splenomegaly. A CT scan of the thorax and abdomen shows massively enlarged axillary, mediastinal, and cervical lymph nodes. Analysis of an excised cervical lymph node shows lymphocytes with a high proliferative index that stain positive for CD20. Which of the following is the most likely diagnosis?

A- Burkitt lymphoma
B- Mantle cell lymphoma
C- Diffuse large B-cell lymphoma
D- Hodgkin lymphoma

Explanation: The combination of B symptoms and painless lymphadenopathy raise suspicion for lymphoma. The detection of the pan B-cell marker CD20 on malignant lymphocytes indicates a B-cell origin. Evidence of extensive lymph node involvement within 4 weeks of the onset of symptoms and the high proliferation index suggest a highly aggressive B-cell lymphoma. This patient most likely has a diffuse large B-cell lymphoma (DLBCL), which is the most common type of non-Hodgkin lymphoma (NHL) in adults, accounting for approx. 25% of cases. DLBCL is an aggressive (high-grade) type of lymphoma occurring spontaneously or secondary to various types of low-grade B-cell lymphomas (e.g., CLL, MALT lymphoma).

Answers: Q6:A | Q7:C | Q8:C

Hypercoagulable state

Q1 (500Best): A 22-year-old Caucasian woman presents with a 1-day history of a painful right leg which is erythematous on appearance and tender on palpation. She states that she has had this problem many times in the last few years and her family has also suffered from similar problems. Her grandmother died of a pulmonary embolism. The most likely diagnosis is:

A. Antithrombin deficiency
B. Factor V Leiden mutation
C. Protein S deficiency
D. Lupus anticoagulant
E. Protein C deficiency

Explanation: This patient is suffering from deep vein thrombosis (DVT) and appears to have a history of recurrent DVTs, the occurrence of which at a young age is suggestive of an inherited disorder of coagulation. Factor V Leiden (B) is a mutation of factor V which makes it resistant to the action of protein C. The increased presence of factor V therefore creates a procoagulant state predisposing to pathology such as DVTs. Factor V Leiden is one of the most common causes of an inherited procoagulant state, present in approximately 5 per cent of the Caucasian population. Although protein C (E), protein S (C) and antithrombin deficiency (A) would also cause a procoagulant state, they are much rarer. Lupus anticoagulant (D) antibodies
cross-react with phospholipids and can be associated with patients with systemic lupus erythematosus (SLE). The antibodies also create a procoagulant state and patients may suffer from arterial and venous thrombosis.

Q2 (500Best):A 65-year-old man presents with a chronic history of headaches and occasional dizziness. He hesitantly mentions that he experiences severe pruritus, especially after hot showers and baths. Blood pressure is 160/85 mmHg. A full blood count (FBC) reveals a haemoglobin of 20 g/dL, MCV of 94 fL, platelet count of 470 × 10 9/L and WBC count of 7.8 × 10 9/L
The most likely diagnosis is:

A. Polycythemia vera
B. Idiopathic erythrocytosis
C. Essential thrombocythaemia
D. Myelofibrosis
E. Chronic myeloid leukaemia

Explanation: This patient is most likely suffering from polycythaemia vera (A), one of the myeloproliferative disorders. A V167F mutation in the JAK2 kinase causes uncontrolled stem cell proliferation, usually of the RBC cell line. Patients usually present with headaches, dizziness and, in severe cases, stroke. Hypermast cell degranulation can cause severe pruritus characteristically after hot baths/showers (aquagenic), as well as peptic ulcers. Patients may also present with gout (due to elevated cell turnover), splenomegaly and plethora. An idiopathic erythrocytosis (B) is an isolated erythrocytosis with no change in WBC or platelets, there is a high risk of AML progression. Essential thrombocythaemia (C) tends to occur in middle-aged and elderly patients, causing a thrombocytosis of dysfunction platelets which are often in excess of 600 × 10 9/L. Haemoglobin, WCC and haematocrit tend to be preserved. Myelofibrosis (D) describes the fibrosis of the bone marrow due to abnormal megakaryocytes which produce excess fibrosing factors. Extramedullary haemopoiesis occurs as compensation causing massive splenomegaly and hepatomegaly while WCC, platelets and haemoglobin initially increase, then are reduced. Chronic myeloid leukaemia (CML) (E) is characterized by a hypercellular bone marrow, elevated granulocytes and white cells.

Q3 (500Best):A 27-year-old woman who suffers from rheumatic mitral stenosis develops atrial fibrillation. She is placed on warfarin therapy. What is the most appropriate target international normalized raio (INR) range?

A. <1.0
B. 1.0–2.0
C. 2.0–3.0
D. 3.0–4.0
E. >5.0

Explanation: The INR is the ratio between the prothrombin time compared to a control sample and provides a means of monitoring bleeding risk. The normal INR is between 0.9 and 1.3 (B), an INR <1.0 (A) suggests a high thrombotic risk. The SIGN guidelines state a patient suffering from rheumatic mitral valve disease with/without atrial fibrillation should have a target INR of 2.5 with a range between 2.0 and 3.0 (C). An INR between 3 and 4 (D) would be appropriate in a patient with lupus anticoagulant syndrome or suffering from venous thromboembolism. It would also be appropriate following a mitral valve replacement with a metallic valve where a high INR is important. An INR >5.0 (E) indicates a high bleeding risk.

Answers: Q1:B | Q2:A | Q3:C

Hypercoagulable state

Q4 (pretest): A 60-year-old woman develops deep venous thrombosis after a 14-hour plane flight from New Zealand. The diagnosis is confirmed by a venous Doppler. There is no evidence of pulmonary embolism, and she is started on subcutaneous low-molecular-weight heparin. She has no family history of venous thrombosis, and she is on no medications that would increase her risk of clotting. In addition to routine monitoring of coagulation parameters and a CBC, what diagnostic tests should be ordered next?

A. Functional test for factor V Leiden (activated protein C resistance)
B. Protein C, protein S, and antithrombin III levels
C. Antiphospholipid antibody test
D. Genetic testing for prothrombin G20210A gene mutation
E. No further testing

Explanation: Testing for thrombophilia is generally reserved for patients who develop unprovoked venous thromboses, especially when those events occur before age 40 in a patient with a positive family history of abnormal clotting. This patient should simply be treated with low- molecular-weight heparin followed by 3 to 6 months of warfarin in the standard fashion. If she develops recurrent DVT, thrombophilia testing would be considered. The prothrombin gene mutation (G20210A) and factor V Leiden are the commonest genetic factors associated with DVT, but they cause only a modestly increased risk of DVT and their presence may not change the management of the patient. Patients with factor V Leiden who are taking oral contraceptives have a 35-fold increased risk of DVT, but OCPs should be avoided if possible in women with any history of DVT. Protein C, S, and AT III deficiencies confer a much greater risk, but are significantly less common. Their presence will usually be identified by the history including family history. Remember that these genetic conditions have been associated with an increased risk of venous, not arterial, thrombosis. Only the antiphospholipid antibody syndrome and elevated homocysteine levels have been associated with arterial thromboses.

Questions 5 to 7, Match the most appropriate answer for each following question. Each lettered option may be used once, more than once, or not at all.

A. Rivaroxaban
B. Low-molecular-weight heparin
C. Warfarin
D. Low dose aspirin (81 mg/d)
E. Inferior vena cava filter placement
F. Antithrombin III level
G. Factor V Leiden gene mutation analysis

Q5 (pretest): A 62-year-old man is evaluated in the ER for sudden onset of swelling of the right calf with pain for past 2 days. The patient noticed the swelling after he woke up from sleep and had pain while walking. He cannot recollect any history of trauma, denies any recent travel, and has never had a blood clot in the past His medical history is remarkable for hypertension, adequately controlled with lisinopril, and stage-III squamous cell carcinoma of the lung for which he recently completed six cycles of chemotherapy. On physical examination, there is tender swelling of the right calf without erythema. His D-dimer is 640 ng/mL. Venous Doppler of the right leg reveals occlusive thrombi in the deep veins. A plan is made to initiate anticoagulation and to extend the treatment for 6 months. What will be the drug of choice for anticoagulation for this patient?

Q6 (pretest): A 27-year-old woman is evaluated in the ER for sudden onset shortness of breath for 3 hours.
The patient mentions that she was sleeping last night peacefully and woke up with breathing difficulty. She denies fever, chills, cough, nausea, vomiting, chest trauma, or any other unusual symptoms prior to the onset of her dyspnea. There is no history of recent travel or prolonged immobility. She does not smoke, drink alcohol, or use recreational drugs. She is not on oral contraceptive pills. She mentions, however, that 2 years ago she had an episode of deep vein thrombosis in her right leg for which she was on Coumadin (warfarin) for 3 months. Her mother was diagnosed with unprovoked DVT twice in her lifetime. Her blood pressure is 142/88 mm Hg, pulse 112/min, temperature 36.6°C (98°F), respiratory rate 22/min, and oxygen saturation 91% on room air. Her lungs are clear, and the rest of the physical examination is normal. CT angiogram of the chest reveals right-sided pulmonary embolism. She is started on weight-based low-molecular-weight heparin therapy. Which additional test(s) should be ordered to detect an underlying hypercoagulable disorder?

Answers: Q4:E | Q5:B | Q6:G

Hypercoagulable state

Q7 (pretest): A 56-year-old man is evaluated for recent onset painful skin lesion which involves his abdominal wall. The lesion started 3 days ago as a small erythematous macule which has gradually. increased in size to a large purpuric lesion with bulla formation. He is afebrile and does not recall any trauma. His medical history is significant for atrial fibrillation; he was recently switched from oxaban to warfarin due to the high cost of rivaroxaban. What is the most probable cause of the condition?

Explanation: Malignancy is a recognized risk factor for venous thromboembolism (VTE), and VTE is the second leading cause of death in cancer patients. Procoagulant molecules expressed both by cancer cells and host tissue contribute to this condition. Low-molecular-weight heparin (LMWH) is the preferred anticoagulant for long-term treatment in patients with cancer. When compared with warfarin, LMWH reduces the rate of recurrent VTE without significant risk of bleeding. Newer anticoagulants such as rivaroxaban have not been adequately tested for cancer-induced VTE yet. Young patients with unprovoked VTE, a history of unexplained VTE, or family history of VTE raise the suspicion of an inherited hypercoagulable disorder. The common inherited hypercoagulable disorders are Factor V Leiden mutation, prothrombin gene mutation, protein S deficiency, protein C deficiency, antithrombin III deficiency, dysfibrinogenemia, and antiphospholipid antibody syndrome. When inherited hypercoagulable disorders are strongly suspected, tests for above mentioned disorders can be ordered. In the event of an acute thrombosis, however, it is not recommended to test for protein C, protein S, and anti-thrombin III since active coagulation can reduce the plasma concentration of these proteins resulting in false-positive result. To avoid confusion, it is recommended to order only Factor V Leiden mutation, prothrombin gene mutation, and antiphospholipid antibody with acute VTE or when patients are on warfarin. Warfarin-induced skin necrosis results from a transient hypercoagulable state. Warfarin initially affects all the vitamin K-dependent clotting proteins (Factors II, VII, IX, X, and proteins C and S). Since Protein C has a short half-life (8-12 hours), the serum protein C concentration drops quickly to 50% of normal in first 24 hours. Since circulating levels of other vitamin K-dependent proteins are still high, this gives rise to a hypercoagulable state which may cause microthrombi in the dermal and subcutaneous vessels, resulting in skin necrosis. The risk is particularly high in case of congenital protein C deficiency; nearly one-third cases of warfarin-induced skin necrosis are associated with congenital protein C deficiency.

Answers: Q7:C

Leukemia

Q1 (MKSAP): A 57-year-old woman is evaluated in the emergency department for fever and shaking chills of 8 hours' duration. The patient has a 1-year history of myelodysplastic syndrome treated with azacitidine. On physical examination, temperature is 39.2°C (102.6°F), blood pressure is 100/70 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Physical examination findings are otherwise unremarkable, with no rash, lymphadenopathy, costovertebral angle tenderness, abdominal tenderness, or splenomegaly. A chest radiograph is normal. A peripheral blood smear shows a myeloblast with Auer rods. Auer rods are clumps of azurophilic, needle-shaped crystals made from primary cytoplasmic granules.

Hemoglobin	10.6 g/dL (106 g/L)
Leukocyte count	33,600/μL (33.6 × 10^9/L)
Platelet count	88,000/μL (88 × 10^9/L)
Urinalysis	Normal

A- Acute lymphoblastic leukemia
B- Acute myeloid leukemia
C- Acute promyelocytic leukemia
D- Chronic myeloid leukemia

Explanation: The most likely diagnosis is acute myeloid leukemia (AML). Myelodysplastic syndromes are clonal disorders of the hematopoietic stem cells in patients older than 50 years and are characterized by ineffective hematopoiesis and peripheral cytopenia. Although the natural history of distinct subtypes of myelodysplasia ranges from indolent chronic anemia to rapid death from progression to acute leukemia, most patients eventually progress to leukemic syndromes or die from complications of bone marrow failure.

Q2 (MKSAP): A 58-year-old man is evaluated for increasing fatigue of 2 months' duration. He has no other medical problems and is not taking any medications. On physical examination, vital signs are normal. There is no lymphadenopathy or peripheral edema. The spleen is palpable 4 cm below the left costal margin. A peripheral blood smear shows an increased number of granulocytic cells in all phases of development but with a marked left shift and no Auer rods in the blasts. Bone marrow examination shows hypercellular marrow (80% cellularity) with marked granulocytic hyperplasia, a left shift in the granulocytes, and 3% myeloblasts. Cytogenetic testing reveals a BCR/ABL translocation. Which of the following is the most likely diagnosis?

Hemoglobin	12.1 g/dL (121 g/L)
Leukocyte count	55,200/μL (55.2 × 10^9/L)
Platelet count	105,000/μL (105 × 10^9/L)

A- Acute lymphoblastic leukemia
B- Acute myeloid leukemia
C- Acute promyelocytic leukemia
D- Chronic myeloid leukemia

Explanation: This patient has chronic myeloid leukemia (CML). The prototype of the myeloproliferative syndromes, CML results from a balanced translocation between chromosomes 9 and 22 [t(9;22), the Philadelphia chromosome], which creates a unique gene designated BCR-ABL; this gene codes a 210-kDa protein (p210) that functions as tyrosine kinase. A t(9;22) is not only diagnostic of CML but is also the causative genetic event and a therapeutic target. The diagnosis of CML in this patient is based on the presence of the BCR/ABL oncogene, peripheral blood smear findings showing increased granulocytes with a marked left shift, and hypercellular bone marrow with marked myeloid proliferation.

Q3 (500Best): A 5-year-old girl presents with her parents who have become concerned about the small petechiae and ecchymoses on her skin. An abdominal examination reveals hepatosplenomegaly. You suspect an acute leukaemia. The most appropriate initial investigation for diagnosis is:

A. Chromosomal analysis of bone marrow cells
B. Cytochemical analysis of bone marrow cells
C. Direct microscopy of bone marrow cells
D. Electron microscopy
E. Flow cytometry

Explanation: In order to diagnose an acute leukaemia, defined as ≥20 per cent of bone marrow cells being blasts, an examination of a bone marrow aspirate under microscopy (C) is necessary. Flow cytometry (E) is useful in distinguishing AML from ALL. Electron microscopy (D) has a reduced role with advanced immunotyping techniques available. (A) and (B) are useful investigations once a leukaemia is confirmed.

Answers: Q1:B | Q2:D | Q3:C

Leukemia

Q4 (MKSAP): A 60-year-old man comes to the office for follow-up evaluation 1 month after being seen for symptoms of an upper respiratory tract infection. Physical examination findings at his initial visit were normal; laboratory study results showed a leukocyte count of 18,000/μL (18 × 109 /L), with 60% lymphocytes. The patient's upper respiratory tract infection symptoms have since resolved completely, and he notes no other medical problems or symptoms. Physical examination findings during this visit are again normal, with no evidence of lymphadenopathy or splenomegaly. The repeated leukocyte count remains the same, and the comprehensive metabolic profile and lactate dehydrogenase concentration are normal. Peripheral blood smear reveals morphologically mature-appearing lymphocytes.
Which of the following is the most likely diagnosis?

A- Acute lymphocytic leukemia
B- Acute myeloid leukemia
C- Chronic lymphocytic leukemia
D- Chronic myeloid leukemia

Explanation: The most likely diagnosis for this patient is chronic lymphocytic leukemia (CLL), which is characterized by abnormal accumulation of morphologically mature-appearing lymphocytes with a characteristic immunophenotype (CD5+, CD20+, and CD23+ B cells) in the blood, bone marrow, or lymphatic tissues. The diagnosis often is established by flow cytometry to avoid the need for bone marrow aspiration or biopsy. CLL occurs in patients after age 40 years, with increasing frequency in successive decades of life. The disease is often found incidentally on routine blood workup as a lymphocytosis without other evident disease. Long periods of stability or very slow progression of disease may occur over many years.

Q5 (500Best):A 29-year-old woman complains of tiredness, especially during activity. On examination the patient appears pale. Auer rods and schistocytes can be seen on peripheral blood smear. The patient is referred for a bone marrow biopsy and the extracted cells are sent for cytogenetic analysis. The most likely results are:

A. t(8:21)
B. t(15;17)
C. t(9:22)
D. t(14;18)
E. t(8;14)

Explanation: This patient is suffering from an acute promyelocytic leukaemia, a subtype (M3) of AML. It is due to t(15;17) translocation (B) which causes the proliferation of promyelocytes. The most worrisome complication is diffuse intravascular coagulation, potentially leading to massive haemorrhage. The t(8;21) (A) abnormality part of the acute myelogenous leukaemia disorders (M2 variant) and is associated with variable WCC, anaemia, neutropenia and thrombocytopenia. The t(9;22) (C) translocation occurs in CML and in 95 per cent of patients is associated with the Philadelphia chromosome. Patients have elevated WCC, basophils, neutrophils and myelocytes with a hypercellular bone marrow. A t(14;18) (D) karyotype occurs in follicular lymphoma, a tumour of follicles consisting of centrocytes. A t(8;14) (E) abnormality occurs in Burkitt's lymphoma secondary to a latent Epstein–Barr (EBV) infection and usually affects the maxilla or mandible.

Q6 (500Best):A 65-year-old man presents to you reporting he has become increasingly worried about his lack of energy in the last 2 weeks. He mentions he has been increasingly tired, sleeping for long periods and has suffered from fevers unresponsive to paracetamol. He became increasingly worried when he noticed bleeding orginating from his gums. A blood film shows auer rods, hypogranular neutrophils and stains with Sudan black B. The most likely diagnosis is:

A. Acute lymphoblastic leukaemia
B. DiGeorge syndrome
C. Disseminated intravascular coagulation
D. Acute myeloid leukaemia
E. Afibrinogenaemia

Explanation: This patient is suffering from an acute myeloid leukaemia (D). There are many mutations that cause the disorder and it can occur in young or old patients, peak presentations tend to be in middle-aged males. Blood investigations may show a variable WCC, anaemia, thrombocytopenia and neutropenia. A blood smear may have auer rods and leukoerythroblastic cells. ALL (A) may have a similar count to AML although the lymphoblasts are usually seen on blood smear and stain with Periodic acid achiff stain. DiGeorge's syndrome (B) is a genetic disorder caused by a deletion at 22q11, young patients present with cardiac anomalies (Tetralogy of Fallot's), abnormal facies, thymic aplasia, cleft palate and hypocalcaemia. Disseminated intravascular coagulation (C) is a consumptive coagulopathy which does not feature auer rods. Congenital afibrinogenemia (E) is characterized by blood clotting disorder rather than increased predispositions to infections.

Answers: Q4:C | Q5:B | Q6:D

Leukemia

Q7 (500Best): A 70-year-old woman complains of tiredness, fatigue and weight loss. Blood tests reveal an elevated WCC and on examination splenomegaly is palpated. Cytogenetics are positive for the Philadelphia chromosome and the patient is diagnosed with chronic myeloid leukaemia. The most appropriate treatment is:

A. Hydroxycarbamide
B. Imatinib
C. Venesection
D. Stem cell transplant
E. Dasatinib

Explanation: Chronic myeloid leukaemia occurs due to the reciprocal translocation of chromosome 9 (Abl) and 22 (BCR) causing the BCR/ABL fusion gene, otherwise termed the Philadelphia chromosome, which has uncontrolled tyrosine kinase activity. Treatment begins with imatinib (B), a tyrosine kinase inhibitor which blocks the activity of BCR/ABL. Over time, the action of multiple drug resistance proteins which pump out imatinib and a change in the shape of the active site of BCR/ABL cause resistance. Dasatinib (E) and eventually stem cell transplantation (D) are then required for treatment. Hydroxycarbamide (A) is a chemotherapy drug used primarily in the treatment of polycythaemia rubra vera alongside venesection (C) to reduce viscosity and haematocrit.

Q8 (500Best):A 65-year-old woman who is currently receiving chemotherapy for acute myeloid leukaemia is found on blood testing to have urea of 10.1 mmol/L, creatinine of 190 mol/L, potassium of 6.1 mmol/L, phosphate of 8.5 mg/dL and corrected calcium of 2.00 mmol/L. The patient is asymptomatic. Her electrolyte levels were normal prior to the start of treatment. What is the most likely cause of this electrolyte disturbance?

A. Tumour lysis syndrome
B. Hypovolaemia
C. Haemolytic uraemic syndrome
D. Neutropenic sepsis
E. Disease progression

Explanation: Tumour lysis syndrome (A) occurs when there is rapid cell death of neoplastic cells. This may occur when patients with rapidly proliferating cells, such as leukaemia, lymphoma or myeloma, start chemotherapy. This syndrome is characterized by a rise in serum urate, potassium and phosphate and a drop in the calcium. Renal failure may be precipitated and the condition may become life threatening. Hypovolaemia (B) may cause acute renal impairment and can cause a rise in the serum potassium. However, it is unlikely to produce hyperphosphataemia and hypocalcaemia as well. Haemolytic uraemic syndrome (C) is usually caused by Escherichia coli 0157 and is characterized by intravascular haemolysis with red cell fragmentation, thrombocytopenia and acute renal failure. The patient has not demonstrated any of the clinical features of sepsis, thus neutropenic sepsis (D) is not the correct answer. The development of this picture of electrolyte imbalance suggests rapid cell death of tumour cells. Thus disease progression (E) is the incorrect answer.

Answers: Q7:B | Q8:A

Leukemia

Q9 (pretest): A 68-year-old man is evaluated in ER for generalized weakness. He also has shortness of breath and cough with productive sputum for 6 days. Two months ago, he had been treated with levofloxacin for community-acquired pneumonia. He works as a volunteer in a local church. He does not have a history of excessive alcohol consumption or recreational drug use. On physical examination, his blood pressure is 132/87 mm of Hg, pulse 107/min, temperature 38°C (100°F), and respiratory rate 22/min. He looks pale and has mild crackles in right base. No lymphadenopathy or hepatosplenomegaly is appreciated. Neurological examination is normal. Laboratory results reveal: hemoglobin 8.6 gm/dL, hematocrit 28, MCV 106 fL, leukocyte count 3600/µL, platelet count 71,000/ µL, ferritin 68 ng/mL, iron 156 µg/dL, transferrin saturation 48%, aPTT 32s, INR 1.1, total protein 6.2 g/dL, albumin 3.8 g/dL, LDH 128 u/L (normal), and total bili-rubin 1.5 mg/dL. Peripheral blood film examination reveals evidence of dysplasia in the red and white blood cell series. A chest x-ray reveals right basilar infiltrate; a CT scan of the abdomen is negative for any significant visceral abnormality. What is the next best step to diagnose the hemato-logical abnormality?

A. Liver biopsy
B. Bone marrow biopsy
C. Hemoglobin electrophoresis
D. JAK2 mutation analysis
E. Methylmalonic acid measurement

Explanation: This patient's pancytopenia is likely caused by myelodysplastic syndrome (MDS), and the next best step for diagnosis will be a bone marrow biopsy. MDS is a hematopoietic stem cell disorder resulting in dysplastic and ineffective blood cell production. The disease is most evident in sixth or seventh decade of life and usually presents with variable decrease in blood cell lineage (anemia, leukopenia, and thrombocytopenia), high MCV, and dysplastic cells in peripheral smear. Many patients are asymptomatic. Some patients present with symptomatic anemia or infection, as in this case. There is a risk transformation to acute leukemia. Bone marrow biopsy usually reveals hypercellular marrow with dysplasia. The blast cells represent less than 20% of the total cells of the bone marrow aspirate. Hemoglobin electrophoresis is recommended for diagnosis of hemoglobinopathies such as thalassemia or sickle cell disease. JAK2 mutation is considered for polycythemia vera and methylmalonic acid level for confirming vitamin B12 deficiency. Liver biopsy would be normal in MDS.

Q10 (pretest): A 47-year-old woman complains of fatigue, weight loss, and itching after taking a hot shower. Physical examination shows plethoric facies and an enlarged spleen, which descends 6 cm below the left costal margin. Her white cell count is 17,000 with a normal differential, the platelet count is 560,000, and hemoglobin is 18.7. Liver enzymes and electrolytes are normal; the serum uric acid level is mildly elevated. What is the most likely underlying process?

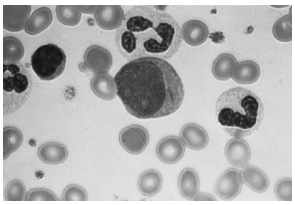
A. Myelodysplastic syndrome
B. Myeloproliferative syndrome
C. Paraneoplastic syndrome
D. Cushing syndrome
E. Gaisböck syndrome

Explanation: This patient has polycythemia vera, a clonal proliferative disorder of the bone marrow in which all three cell lines (red blood cells, platelets, and myelocytes) are overproduced. The other classic myeloproliferative disorders are chronic myeloid leukemia, essential thrombocythemia, and myelofibrosis. In polycythemia vera, nearly 98% patients are JAK2 mutation positive. It is important to distinguish myeloproliferative syndromes (where one or more cell lines proliferate) from myelodysplastic syndromes (where one or more cell lines—usually red cells—are deficient). In myelodysplastic disorders, white blood cells and platelets are normal, at least initially. These patients present with anemia, often in association with mild macrocytosis and other features of altered marrow maturation (ringed sideroblasts, hypolobulated polys, etc). Splenomegaly and cellular overproduction are not features of the myelodysplastic syndromes. Cushing syndrome can cause facial plethora but would not account for the splenomegaly or hematological changes. Gaisböck syndrome causes erythrocytosis with a normal red cell mass (resulting from diminished plasma volume) but does not cause splenomegaly, leukocytosis, or thrombocytosis. Polycythemia vera does not occur as part of a paraneoplastic process.

Answers: Q9:B | Q10:B

Leukemia

Q11 (pretest): A 50-year-old man presents with 3 daydenies any sick contacts. On examination, there is conjunctival pallor, dried blood on the nasal mucosa, and petechiae on both lower extremities. There is no lymphadenopathy or hepatosplenomegaly. CBC shows hemoglobin 7.9 g/dL, leukocyte count 23,600, and platelet count 14,000. Urinalysis and chest x-ray are normal. The peripheral blood smear is shown in the following figure. What is the most likely diagnosis?



A. Multiple myeloma
B. Myelofibrosis
C. Acute myeloid leukemia (AML)
D. Chronic myeloid leukemia (CML)
E. Acute lymphocytic leukemia (ALL)

Explanation: Patients with acute myeloid leukemia (AML) usually present with nonspecific symptoms such as fever, bone pain, headache, night sweats, and fatigue. Bone pain is attributed to the expansion of the marrow by leukemic cells. Laboratory abnormalities include anemia and thrombocytopenia. Patients with French American British (FAB) classification M3 variety (acute promyelocytic leukemia) of AML can also present with symptoms of disseminated intravascular coagulation (DIC) or can develop it during treatment. Nearly 95% cases of acute promyelocytic leukemia have balanced translocation t(15;17) involving the retinoic acid receptor-alpha gene on chromosome 17 and the PML gene on chromosome 15. As a result, all-trans retinoic acid is used as a chemotherapeutic agent in cases of acute promyelocytic leukemia with good success. The blood smear in this patient shows a leukemic myeloblast containing an Auer rod. Auer rods are formed by fusion of lysosomal granules and appear as clumps of azurophilic, granular, needle-shaped material found in the cytoplasm of blast cells. Myelofibrosis would have a more insidious course and is usually associated with splenomegaly. Multiple myeloma can present with bone pain, but patients usually have chronic pain that is localized to the back or ribs. Acute lymphocytic leukemia (ALL) is less common in adults, and patients usually have generalized lymphadenopathy. Auer rods are found in myeloblasts but not in lymphoblasts of ALL. In ALL bone marrow biopsy would show a predominant lymphocytic pattern rather than myeloid predominance.

Q12 (AMBOSS): A 60-year-old man comes to the physician because of recurrent nose bleeds that occur with light trauma or at random times during the day. Over the past 6 months, the patient has felt weak and fatigued and has had a 10-kg (22-lb) weight loss. He has poor appetite and abdominal discomfort. He does not have night sweats. Temperature is 37.5°C (99.5°F), pulse is 72/min, and blood pressure is 130/70 mm Hg. The spleen is palpated 10 cm below the left costal margin. Multiple bruises are noted on both upper extremities. Laboratory studies showed, A peripheral blood smear detects tartrate-resistant acid phosphatase activity. Which of the following is the most appropriate initial treatment for this patient?

A- Rituximab
B- Cladribine
C- Transfusion of platelets
D- Cyclophosphamide

Explanation: Chemotherapy with cladribine is the first-line treatment for hairy cell leukemia. Treatment is indicated in patients with symptoms of cytopenia, splenomegaly, and/or constitutional symptoms. The majority of patients achieve complete remission with cladribine. Pentostatin is another purine analog that can be used as an initial treatment for hairy cell leukemia or as an alternative to cladribine if the initial treatment fails.

Answers: Q11:C | Q12:B

General hematology

Q1 (MKSAP): A 55-year-old woman undergoes preoperative evaluation before elective laparoscopic cholecystectomy. Medical history includes three pregnancies and full-term deliveries with no complications or health problems. She has had no previous surgeries. Physical examination findings are normal. Which of the following is the best screening approach to detect any bleeding disorders in this patient?

A- Clinical history
B- INR
C- INR, prothrombin time (PT), and partial thromboplastin time (PTT)
D- INR, PT, PTT, and bleeding test

Explanation: The best screening approach to detect bleeding disorders is by taking a thorough clinical history. The clinical history should focus on the presence of any systemic illnesses and previous bleeding. In the absence of a personal or family history of abnormal bleeding, liver disease, significant alcohol use, malabsorption, or anticoagulation therapy, the likelihood of a bleeding disorder is low, and no further preoperative testing is required

Q2 (Pretest): A 38-year-old woman presents with repeated episodes of sore throat. She is on no medications, does not use ethanol, and has no history of renal disease. Physical examination is normal. Hgb is 9.0 g/dL, MCV is 85 fL (normal), white blood cell count is 2000/µL, and platelet count is 30,000/µL. Which of the following is the best approach to diagnosis?

A- Erythropoietin level
B- Serum B12
C- Bone marrow biopsy
D- Liver spleen scan
E- Therapeutic trial of corticosteroids

Explanation: This patient has an unexplained pancytopenia. If all three elements (red blood cells, white blood cells, and platelets) are affected, the cause is usually in the bone marrow (although peripheral destruction from hypersplenism can cause pancytopenia as well). In this patient without a history of liver disease or palpable splenomegaly on physical examination, a bone marrow production problem is the most likely culprit. Although B12 deficiency can cause pancytopenia, usually a macrocytic anemia is the most prominent feature; a serum B12 level would be reasonable, but the most productive approach would be to examine the bone marrow. Leukemia can present without leukocytosis (so-called aleukemic leukemia), but the most likely diagnosis would be aplastic anemia. In the elderly patient, myelodysplastic syndrome (MDS) may present with pancytopenia. Decreased levels of erythropoietin can cause decreased RBC production, but will not cause pancytopenia. A corticosteroid trial is not warranted until a diagnosis is established.

Q3 (Pretest):A patient with bacterial endocarditis develops thrombophlebitis while hospitalized. His course in the hospital is uncomplicated. On discharge he is treated with penicillin, rifampin, and warfarin. Therapeutic prothrombin levels are obtained on 15 mg/d of warfarin. After 2 weeks, the penicillin and rifampin are discontinued. Which of the following is the best next step in management of this patient?

A- Cautiously increase warfarin dosage.
B- Continue warfarin at 15 mg/d for about 6 months.
C- Reduce warfarin dosage.
D- Stop warfarin therapy.
E-Restrict dietary vitamin K.

Explanation: Rifampin induces the cyto-chrome P450 that metabolizes warfarin; higher doses of warfarin are required to overcome this effect. When rifampin is stopped, the dose of warfarin necessary to produce a therapeutic prothrombin time will decrease. Barbiturates also accelerate the metabolism of warfarin. Many drugs interfere with the metabolism and clearance of warfarin. Drugs such as nonsteroidal anti-inflammatories can compete with warfarin for albumin-binding sites and will lead to an increased prothrombin time. The list of medications that can either increase or decrease the effect of warfarin is long; all patients given this drug should be advised to contact their physician before taking any new drug. They should also be counseled about over-the-counter drugs (aspirin and NSAIDs) and even health food supplements (such as ginkgo biloba) which can affect the prothrombin time in these patients. A stable intake of vitamin K–containing foods (ie, green leafy vegetables) is recommended.

Answers: Q1:A | Q2:C | Q3:C