100 SELF-ASSESSMENT QUESTIONS

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Questions

1. Brain Tumors

1. A 9-year-old boy presents to the emergency department with emesis and headache of 3 weeks' duration. MRI reveals a large heterogeneous mass in the cerebellum. He undergoes a resection, and the pathology is most consistent with a classic medulloblastoma.

Which of the following findings would classify the patient as a high-risk medulloblastoma?

A. Elevated serum and CSF AFP and beta-HCG tumor markers
B. WNT subgrouping on molecular classification
C. A presurgical spine MRI that reveals bulky tumor in the spine
D. A postoperative brain MRI with no signs of residual tumor

2. A 6-year-old boy is noted to have worsening visual acuity on serial eye exams. Recent MRI of his brain and orbits reveals an optic chiasm mass, most consistent with an optic pathway glioma. Upon further examination, the physician notes axillary freckling and numerous "spots" on the patient's skin.

This patient most likely has a which of the following genetic disorders?

A. Neurofibromatosis type-1 (NF1)
B. Li Fraumeni syndrome
C. Tuberous sclerosis
D. Cystic Fibrosis

3. An 8-year-old boy undergoes a resection of a tumor in the right cerebrum next to the lateral ventricle (supratentorial). The pathologist feels the histology is most consistent with an ependymoma. The tumor is sent for advanced molecular and genetic testing. Which of the following findings would further support a diagnosis of ependymoma?

A. BRAFKIAA1549 fusion
B. BRAFV600E mutation
C. RELA fusion
D. H3K27M mutation

4. A 5-year-old boy presents with a 3-week history of his right eye "not moving to the right side." The remainder of his neurologic exam is normal with the exception of a weak gag. MRI of the brain reveals a diffusely infiltrative mass in the pons.

If this patient were to undergo a stereotactic biopsy, what would be the most likely molecular finding?

A. BRAFKIAA1549 fusion
B. Trisomy 21
C. H3 K27M mutation
D. RELA fusion

2. Acute Lymphoblastic Leukemia

5. Blinatumomab, a bispecific T-cell engaging molecule, is active against which CD antigen that is expressed on B-lymphoblasts?

A. CD10
B. CD15
C. CD19
D. CD20
E. CD22

6. Of the variables listed below, what is the most important factor for survival after relapse of acute lymphoblastic leukemia?

A. Time to marrow relapse since initial diagnosis
B. Sex
C. Central nervous system involvement at relapse
D. Response to induction therapy during initial diagnosis
E. Percent of marrow blasts at the time of relapse

7. An 8-year-old girl presents with National Cancer Institute (NCI) Standard Risk acute pre-B-cell acute lymphoblastic leukemia. Her family history is significant for her mother having been diagnosed with breast cancer at age 34 years and a maternal uncle who developed osteosarcoma as a teenager. What cytogenetic abnormality is most likely to be detected in this patient?

A. t(1;19)
B. *CRLF2* rearrangement with a *JAK2* mutation
C. *KMT2A* rearrangement
D. Hypodiploidy with a modal chromosome number of 34
E. Hypodiploidy with a modal chromosome number of 24

3. Stem Cell Transplantation

8. When should autologous hematopoietic stem cell transplantation be used, and what are the common cancers it is used for?

A. It should be used when high dose therapy is needed to maximize response. Most common cancers it is used for include lymphoma, late relapse of acute lymphoblastic leukemia, neuroblastoma, and Ewing sarcoma.
B. It should be used any time this approach can provide a meaningful survival benefit over chemotherapy. Most common cancers it is used for include neuroblastoma, responsive brain tumors in young children to avoid/minimize early radiation therapy, and relapsed lymphoma.
C. It should be used for tumors in which a graft-versus-tumor effect does not occur. Most common cancers include neuroblastoma, lymphoma, selected brain tumors, rhabdomyosarcoma, and Ewing sarcoma with lung metastases.
D. It should be used to avoid extensive treatment with chemotherapy and to shorten treatment. Most common cancers include neuroblastoma, relapsed Wilms' tumor, and selected brain tumors.
E. It should be used to avoid complications of graft-versus-host disease. Most common cancers include neuroblastoma, selected brain tumors, and relapsed lymphoma.

9. Which of the following statements about myeloablative, myeloablative but reduced toxicity, reduced intensity, and non-myeloablative approaches is not correct?

A. Myeloblative approaches are needed for high-risk malignancies to maximize depth of remission and decrease the likelihood of relapse.
B. Reduced intensity regimens can be successfully used for most nonmalignant disorders to minimize risk of late effects.
C. Reduced intensity regimens can markedly decrease the risk of transplant-related mortality in patients who have underlying significant comorbidities but at the cost of more relapse and possibly more graft-versus-host disease.
D. Non-myeloablative regimens are used for the very highest risk patients to minimize toxicity and for certain diseases such as aplastic anemia.
E. Myeloablative reduced toxicity approaches are often needed to decrease graft rejection and maximize chimerism in certain non-malignant disorders.

10. A 3-year-old boy with X-linked chronic granulomatosis disease is day +25 after haploidentical bone marrow transplant (father donor) using posttransplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis. He engrafted on day +16 and was preparing for discharge when cytomegalovirus (CMV) was noted to be positive on PCR, and he developed a fever and mild rash. His counts have fallen to a WBC of 0.1 and he remains transfusion dependent. What diagnostic evaluations/treatments should you pursue?

A. Rule out infection by sending blood cultures, start broad spectrum antibiotics, and obtain other diagnostic workup as appropriate. Consider skin biopsy and treat with steroids for likely acute GVHD (aGHVD).
B. Initiate an infectious workup and treat with broad-spectrum antibiotics. Consult with the PICU team because the low blood counts are likely a preseptic presentation.
C. Test for possible rejection with rapid FISH chimerism and consider withdrawal of immune suppression if donor chimerism is low.
D. Send blood cultures, start antibiotics, and treat his CMV with foscarnet. Send rapid chimerism by STR to assess for possible rejection. If donor chimerism is low or absent, work on obtaining an alternative donor for a second procedure.
E. Start steroids to treat aGVHD and give supportive care with granulocyte colony stimulating factor.

4. Myeloproliferative Myelodysplastic, and Histiocytic Disorders

11. Several gene mutations have been associated with juvenile myelomonocytic leukemia (JMML), and they may or may not have prognostic implications. A gene expression–based classification system has been found to be an independent predictor of clinical outcome in these patients. What is the disease signature that predicts a poor outcome?

A. Tyrosine kinase inhibitors
B. Acute myeloid leukemia–like
C. Chronic myeloid leukemia-like
D. BRAF pathway abnormalities

12. A female infant is diagnosed with hemophagocytic lymphohistiocytosis (HLH) not associated with an Epstein-Barr virus (EBV) infection. In taking the family history, you learn that another female infant died of HLH 2 years ago. Also, a newborn female child died of an unknown disease 4 years prior and was said have been bleeding profusely, jaundiced, and had a distended abdomen. When counseling the family about the genetics of HLH, how will you explain it?

A. It is an X-linked syndrome
B. It is an autosomal recessive syndrome
C. It is a dominant inheritance syndrome
D. It is an autosomal recessive syndrome with incomplete penetrance

13. A 2-month-old infant is brought to your clinic with an extensive scaly rash on the scalp, which has been biopsied and shown to be Langerhans cell histiocytosis (LCH). You want to determine whether this patient has skin-only LCH or involvement of any of the "high-risk" organs. The child has a normal CBC; normal liver enzymes and bilirubin; and a normal skeletal survey, skull films, and chest X ray.

What other screening test will be important for finding involvement of a high-risk organ?

A. Reticulocyte count
B. Erythrocyte sedimentation rat
C. Alkaline phosphatase
D. Serum albumin and total protein

5. Disorders of Leukocytes

14. A young child with consanguineous parents has developmental delay and a history of multiple recurrent bacterial infections and short stature. He presents to the emergency department following trauma and requires a blood transfusion. Blood work identifies leukocytosis, neutrophilia, and the Bombay blood group (absent H antigen as well as absent A and B antigens). What is this patient's diagnosis?

A. Chediak-Higashi syndrome
B. Leukocyte adhesion deficiency (LAD) Type II
C. CD18 deficiency
D. Griscelli syndrome

15. A 4-year-old male child presents to the emergency department with his fourth invasive *Staph* infection. CBC consistently identifies moderate neutropenia. Sophisticated lab testing identifies lack of Toll-like receptor responses. The patient undergoes whole exome sequencing and is found to have pathogenic variants in *IRAK4.* What does *"IRAK4"* stand for?

A. Interferon gamma receptor-associated kinase 4
B. Inducible RAS activating kinase 4
C. Interleukin-1 receptor-associated kinase 4
D. Immune response activating kinase 4

16. An avid 16-year-old triathlete was in a bike accident and developed cellulitis, which was treated with Bactrim. While still on antibiotics, he moved with his family from Houston to Denver, and during the car trip he developed fever, pharyngitis, and malaise. Upon arriving in Denver he presented to the emergency department and was noted to have significant lymphocytosis with some atypical lymphocytes. What is the most likely cause of the white blood cell abnormalities?

A. Drug reaction
B. Altitude higher than 5,000 ft above sea level
C. GATA2 mutation
D. Epstein-Barr virus infection

6. Retinoblastoma, Germ Cell Tumors, and Hepatoblastoma

17. You have been asked to see a 15-year-old girl who is being referred for evaluation of an ovarian mass. Her history is also significant for secondary amenorrhea, and physical examination shows signs of virilization. As you review her family history, what syndrome will you consider?

A. Li-Fraumeni syndrome
B. DICER-1 syndrome
C. Turner syndrome
D. Beckwith-Wiedemann syndrome
E. Lynch syndrome

18. A 3-year-old boy is referred to you for evaluation of right leukocoria. Funduscopic examination under anesthesia reveals a large amelanotic mass occupying more than two-thirds of the vitreous space in his right eye, with massive retinal detachment, consistent with group E retinoblastoma. The left eye is normal. An MRI confirms the funduscopic findings and shows no extraocular disease. What is the most appropriate next step in the management of this child's disease?

A. Enucleation
B. Systemic chemotherapy
C. Brachytherapy
D. Needle biopsy
E. Intravitreal chemotherapy

19. A 9-month-old boy has been referred to you for the evaluation of an enlarged abdomen. Imaging studies show a large liver mass (PRETEXT III). Alfa-fetoprotein is 98 ng/mL, and a CT scan of the lungs show bilateral lung metastases. A needle biopsy is performed, and you are planning to review the specimen with the pathologist. Which of the following diagnoses are you suspecting?

A. Pure fetal histology hepatoblastoma
B. Embryonal sarcoma of the liver
C. Fibrolamellar hepatocellular carcinoma
D. Small cell undifferentiated hepatoblastoma
E. Conventional hepatocellular carcinoma

7. Immunology and Immunodeficiency

20. Which statement is correct regarding lymphocyte counts in infants versus adults?

A. NK-cell numbers are lowest at birth and increase with age.
B. B-cell numbers are highest at birth and decline with age.
C. T-cell numbers in infants are higher than in adults.
D. Infants have low lymphocyte counts that increase with age.

21. A 4-year-old girl with a history of relapsed pre-B-cell acute lymphoblastic leukemia is being admitted for unrelated donor bone marrow transplantation with cyclophosphamide and total body irradiation conditioning. Pretransplant workup shows the following:

Recipient
CMV IgG: negative
CMV IgM: negative
HSV I/II antibody: negative
Varicella IgG: positive (vaccinated)
Hepatitis B surface antigen: negative
Hepatitis B surface antibody: positive (vaccinated)
Hepatitis B core antibody: negative
Hepatitis C antibody: negative

Donor
CMV IgG: negative
CMV IgM: negative
HSV I/II antibody: positive
Varicella IgG: positive
Hepatitis B surface antigen: negative
Hepatitis B core antibody: negative
Hepatitis C antibody: negative

How should the patient be managed during the admission with respect to infection prophylaxis?

A. Acyclovir IV for herpes simplex virus (HSV) suppression
B. Weekly screening by polymerase chain reaction (PCR) for cytomegalovirus (CMV) in blood
C. Antifungal prophylaxis
D. Valganciclovir PO for CMV suppression
E. Foscarnet IV for CMV suppression

22. You are asked to evaluate a 2-day-old boy in the newborn nursery with petechiae who has a platelet count of 8,000/mcL. On further questioning, you learn that he had a maternal uncle who died of intracerebral hemorrhage as a toddler. There is no eczema on physical examination. Review of the smear shows anisocytosis; poikilocytosis; normal white blood cell morphology; and small, infrequent platelets. The neonatologists have sent human platelet antigen (HPA)-1a testing from both parents, which is pending.

Which of the following is the most likely diagnosis?

A. Congenital infection
B. Neonatal alloimmune thrombocytopenia
C. Wiskott-Aldrich syndrome
D. May-Hegglin anomaly

8. Neuroblastoma and Related Tumors

23. You are seeing a 12-year-old female who presented to the emergency department with the sudden onset of severe abdominal pain. Imaging that was obtained to rule out appendicitis revealed a mass adjacent to the bladder. The mass was surgically resected, and pathology demonstrated a paraganglioma. Which of the studies below would be most useful to determine disease stage for this patient?

A. Bone Scan
B. Lumbar puncture for cerebrospinal fluid cytology
C. Bone marrow aspirate and biopsy
D. Ga 68-DOTATATE PET/CT
E. MRI of the brain

24. Your patient with relapsed high-risk neuroblastoma returns to your care after travelling to an outside institution for ^{131}I-MIBG therapy. In the weeks following ^{131}I-MIBG therapy, what adverse events directly attributable to this therapy will the patient most likely encounter?

A. Myelosuppression requiring growth factor and blood product support
B. Severe mucositis
C. Hemorrhagic cystitis
D. Symptomatic hypothyroidism
E. Renal failure

25. An otherwise healthy 18-year-old female is diagnosed with high-risk neuroblastoma after presenting with fatigue and bony pain. Imaging findings demonstrate a left adrenal mass with multiple osseous metastases. She successfully completes standard therapy for high-risk neuroblastoma, but experiences several episodes of disease recurrence and ultimately dies of her disease 10 years after her initial diagnosis. During her treatment, her tumor was sent for molecular analysis. Of the following, what molecular aberration was most likely to have been detected?

A. *ETV6-NTRK3* gene fusion
B. *PTPN11* mutation
C. *ATRX* mutation
D. *WT1* mutation
E. *MYCN* amplification

9. Wilms' Tumor and Other Renal Tumors

26. A 2-year-old girl has a diagnosis of overall stage IV favorable histology Wilms' tumor with pulmonary metastases and local stage III disease due to finding positive lymph nodes. After she completes 6 weeks of vincristine/dactinomycin/doxorubicin (DD4A) chemotherapy, restaging shows complete resolution of some but not all lung nodules. Tumor genetic testing reveals combined loss of heterozygosity for 1p and 16q.

Which of the following would be the most appropriate treatment plan?

A. Continue chemotherapy with vincristine, doxorubicin, and dactinomycin to complete 25 weeks of therapy. Administer radiation to lungs and flank.
B. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks of therapy. Radiation to flank only. No lung radiation.
C. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to flank only. No lung radiation.
D. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to lungs and flank.
E. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks. Whole abdomen radiation and lung radiation.

27. A 3-month-old female presents to the emergency room with vomiting and abdominal distension. She has a left-side abdominal mass, and an abdominal ultrasound confirms an 8-cm mass arising from the left kidney. Liver lesions are also noted. Nephrectomy is performed and reveals a histologic diagnosis of malignant rhabdoid tumor of the kidney (MRTK). Which of the following is not a true statement about the management of this patient?

A. Most patients with rhabdoid tumor of the kidney present in infancy.
B. Most patients with rhabdoid tumor of the kidney present with metastatic (stage III or IV) disease.
C. She has an excellent prognosis with surgery, chemotherapy, and radiation.
D. Germline testing for SMARCB1/INI1 mutation on chromosome 22 is recommended, with brain MRI every 3 months until she is 5 years old, if testing is germline positive for SMARCB1/INI1.
E. EZH2 methyltransferase inhibitors are under investigation as potential therapeutic agents for rhabdoid tumors because of their mechanism of action.

28. A 3-year-old nonsyndromic, well-appearing male with no significant past medical history presents with an abdominal mass palpated by his mother when giving him a bath. CT imaging reveals a 9-cm right renal mass without involvement of the inferior vena cava (IVC) and no evidence of tumor thrombus by ultrasound. The left kidney appears normal, and there is no imaging evidence of tumor rupture or adherence to surrounding organs. There are diffuse, bilateral pulmonary metastases from which he is asymptomatic with a normal respiratory rate and no supplemental oxygen requirement. Following the National Wilms Tumor Study Group (NWTS)/Children's Oncology Group (COG) approach to pediatric renal tumors, which of the following are appropriate next steps?

A. Core biopsy of the renal mass followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin
B. Nephrectomy with lymph node sampling followed by chemotherapy based on histology and stage
C. Fine-needle aspiration followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin
D. Neoadjuvant three drug chemotherapy—vincristine, actinomycin and doxorubicin—followed by nephrectomy at week 6
E. Neoadjuvant three drug chemotherapy—vincristine, actinomycin, and doxorubicin—followed by diagnostic biopsy at week 6 if primary tumor is showing good response to therapy

10. Clinical Pharmacology and Targeted Therapies

29. A 2-month-old girl is found to have a small, hard mass on her scalp. The mass increases in size over the next 4 weeks. A biopsy is performed that confirms a diagnosis of embryonal rhabdomyosarcoma. You initiate chemotherapy with vincristine, dactinomycin, and cyclophosphamide. The child presents to clinic for day 1 of cycle 3 of chemotherapy, and the mass on her scalp is smaller. She is afebrile, absolute neutrophil count is 1,405 cells/mcL, platelet count is 154,000/mcL, and total bilirubin is 0.8 mg/dL. Her mother reports she looks very tired because her eyelids have been "very droopy," and she thinks she has a sore throat because her cry is hoarse. Her last bowel movement was 2 days ago.

What is the most appropriate chemotherapy plan?

A. Continue vincristine, dactinomycin, and cyclophosphamide at full dosage.
B. Do not administer any chemotherapy; rhabdomyosarcoma is progressing and she needs different therapy.
C. Administer dactinomycin and cyclophosphamide but hold the vincristine and reevaluate weekly. If the ptosis and hoarse cry resolve, vincristine can be resumed with a dose reduction and, if tolerated, re-escalated to the full dose in the future.
D. Administer dactinomycin and cyclophosphamide but discontinue vincristine permanently.
E. Administer vincristine and cyclophosphamide but do not administer dactinomycin; the ptosis is due to dactinomycin.

30. A 12-year-old patient with localized osteosarcoma is being treated with cisplatin, doxorubicin, and high-dose methotrexate. The pain at his primary site rapidly resolves after initiation of chemotherapy. After tumor resection, pathology reveals the tumor was greater than 95% necrotic. You want to continue cisplatin, doxorubicin, and high-dose methotrexate.

Which of the following is the best answer regarding the evaluations that should be performed to monitor for toxicity in patients receiving cisplatin, doxorubicin, and high-dose methotrexate?

A. Complete blood count, creatinine, liver function tests
B. Complete blood count, serum electrolytes (sodium, potassium, BUN, chloride), and EKG to monitor for prolonged QTc
C. Complete blood count, creatinine, serum magnesium, audiogram, and echocardiogram
D. Complete blood count, creatinine, serum magnesium, chest x-ray
E. Complete blood count, creatinine, serum magnesium, audiogram

31. A 9-year-old boy is being treated for standard-risk acute lymphoblastic leukemia. His treatment protocol calls for administration of intravenous methotrexate and intramuscular L-asparaginase during interim maintenance chemotherapy.

What is the most appropriate sequence of drug administration?

A. Administer L-asparaginase during the methotrexate infusion.
B. Administer L-asparaginase immediately after the methotrexate infusion.
C. Administer both drugs at the same time to maximize synergistic activity.
D. Administer methotrexate 24 hours after the asparaginase.
E. Administer the L-asparaginase 24 hours after the methotrexate.

11. Hemoglobinopathies

32. You have a new patient consult in clinic this morning. The referral packet includes the newborn screen report, which is flagged abnormal hemoglobinopathy screen, F, A, Bart's, refer to hematology, and a complete blood count done at 4 years of age with a hemoglobin of 10 g/dL and an MCV of 68. The pediatrician has informed the parents the child has some form of alpha thalassemia. The older brother had the same newborn screen results but had a normal complete blood count when checked. The mother wants to know why her second child has an abnormal complete blood count when she and her husband do not have any blood problems. How would you respond to the child's mother?

A. The mother and father are both silent carriers and each passed a deleted alpha globin allele to their child. The child inherited a trans-deletion genotype alpha thalassemia trait.
B. The mother has cis deletion alpha thalassemia and the father has no alpha globin deletion, giving the child alpha thalassemia trait.
C. Neither parent has an alpha globin deletion; this was a new spontaneous mutation causing alpha thalassemia in the child.
D. Both parents carry cis deletions in the alpha globin gene cluster.

33. A 14-year-old Syrian male with beta thalassemia major has relocated to your community as a refugee. He has been receiving chronic transfusion therapy in Turkey for the past 3 years. On his first visit, you notice that his height is below the fifth percentile. He has skin discoloration and hepatosplenomegaly. His mother reports they have not had regular access to chelation therapy. Laboratory testing shows a serum ferritin of 6,200 ng/mL. A cardiac MRI shows grossly normal cardiac function but a T2* value of 9 ms.

What is the most likely cause of his short stature?

A. Lack of regular blood transfusion causing growth failure
B. Cirrhosis and liver failure
C. Ineffective erythropoiesis and chronic anemia
D. Growth hormone deficiency due to iron deposition in the pituitary
E. Adrenal insufficiency

34. A 7-year-old Hispanic male is referred to the hematology consult service by his pediatrician because of concern for hemoglobinopathy. In his records, you find a hemoglobin electrophoresis performed last year which shows hemoglobin A 78% and hemoglobin F 22%. His complete blood count is normal, and he has normal growth and development. Which of the following is true for this patient?

A. There is no diagnosis. These values are normal in children.
B. He has delta-beta thalassemia because he has an elevated hemoglobin F level.
C. Delta-beta thalassemia does not cause microcytosis.
D. Hereditary persistence of fetal hemoglobin results in pancellular hemoglobin F distribution.

12. Blood Coagulation Overview and Acquired Hemorrhagic Disorders

35. Which of the following is a key feature of Facto XIII?

A. Its half-life is about 10 days.
B. It is an important activator of thrombin.
C. Its levels are normal in newborns.
D. It is part of the contact activation system.
E. Low levels result in a prolonged PT and PTT.

36. Which of the following characteristics are similar with respect to Factor VIII and von Willebrand factor (vWF)?

A. Both are made in endothelial cells and megakaryocytes.
B. Both are activated by thrombin.
C. They are present in normal to high relative amounts in newborns.
D. They are stored in Weibel-Palade bodies in endothelial cells.
E. A deficiency of either one prolongs the PTT.

37. Which of the following alters the function of thrombin from a procoagulant protein to one that downregulates the formation of fibrinogen?

A. Protein C
B. Protein S
C. Antithrombin
D. Thrombomodulin (*)
E. Factor V

13. Inherited Bleeding Disorders

38. A 4-year-old girl with a history of recurrent epistaxis and easy bruising is referred to you for evaluation. She is found to have a prolonged PTT and a factor VIII level that is less than 1%. Both parents have a history of excessive bleeding. She is admitted with a severe episode of epistaxis, and your colleague orders 40 IU/kg of recombinant factor VIII. Her epistaxis resolves initially but within an hour starts again at the same severity as before.

What is the best next step?

A. Infuse a von Willebrand factor concentrate.
B. Give another dose of recombinant factor VIII concentrate.
C. Call otorhinolaryngology to pack her nose.
D. Check for a factor VIII inhibitor.
E. Administer desmopressin.

39. A 12-year-old girl presents to your clinic with significant menstrual bleeding at the onset of menarche and is noted to have a hemoglobin of 9.9, although she is not symptomatic from her anemia. Her mother reports that she has a history of epistaxis when she was a child with some episodes lasting 30 minutes and that she also has heavy menstrual bleeding. Which of the following tests will lead to the most likely diagnosis?

A. Factor XI level
B. Factor X level
C. Factor XIII level
D. Ristocetin cofactor activity
E. Fibrinogen level

40. A newborn male has severe bleeding after circumcision, resulting in the need for a blood transfusion. You are called to consult on this child, and you diagnose him with severe hemophilia A. Upon taking a family history, you note that no other family members have hemophilia, other bleeding disorders, or a bleeding diathesis. Which of the following is the most likely outcome of genotyping the Factor VIII gene?

A. No mutation will be found because there is no family history.
B. A missense mutation in the F8 gene will be identified.
C. An inversion mutation in the F8 gene will be identified.
D. A nonsense mutation in the F8 gene will be found.
E. A large deletion of the F8 gene will be found.

14. Transfusion Medicine

41. A 16-year-old female patient with severe factor XI deficiency presents with acute appendicitis and requires urgent surgery. You are called by the surgeon, who wants to know what, if any, blood products or treatments are required to reduce the risk of perioperative bleeding. The patient weighs 62 kg. What should you tell him to administer?

A. Cryoprecipitate (five units), which will likely raise her factor XI level to 20%
B. Factor XI concentrate (20 units/kg), which will raise her factor XI level to 20%
C. Fresh frozen plasma (20 mL/kg), which will raise her factor XI level to 20%
D. Prothrombin complex concentrate (40 units/kg), which will raise her factor XI level to 20%
E. Apheresis platelets at 10 mL/kg, which will raise factor XI level to 20% from the release of factor XI stored in platelet alpha granules

42. A 10-year-old patient with aplastic anemia, who is blood type B negative, is receiving a red blood cell transfusion. About 10 minutes after the transfusion starts, the patient develops anxiety and lower back pain. The transfusion continues for another 5 minutes until it is stopped when he develops a temperature of 40 °C with chills and rigors. A transfusion reaction work-up is most likely to reveal what findings?

A. Spherocytes on peripheral blood smear
B. Gram-negative *Bacillus* on gram stain of remaining RBC unit
C. Chest x-ray with bilateral pulmonary infiltrates that are new compared to an x-ray done last week
D. DAT positive for C3
E. Antibody screen positive for anti-Jk^a antibodies

43. A laboratory study is conducted to determine the optimal usage of platelets for transfusion. The blood bank inventory along with the transfusion records and medical records of subjects who were recipients of platelet transfusion are reviewed. Which of the following conclusions is most likely to be made from this study?

A. Frozen storage of platelets helps increase the units available.
B. Platelet transfusions are rarely successful in patients with autoimmune thrombocytopenia.
C. Platelet units carry no risk for transmission of hepatitis C infection.
D. Pooled donor platelets are preferred over single-donor platelets.
E. Platelet transfusion is not indicated above a level of 10,000/mcL.

44. A 14-year-old male patient is diagnosed with very high risk acute lymphoblastic leukemia and is likely going to require an allogeneic hematopoietic stem cell transplant to cure his leukemia. Prior to going to transplant, he is likely to require multiple blood transfusions. Which of the following products or component modifications is the best way to prevent him from developing alloimmunization due to anti-HLA antibodies prior to transplant?

A. Frozen RBCs
B. Volume-reduced blood products
C. Irradiation of all blood products
D. Monthly IVIg infusions
E. Leukoreduced blood products

15. Thrombotic Disorders

45. You receive a phone call that a 3-year-old patient on long-term warfarin therapy for congenital heart disease has an international normalized ratio (INR) of 5.8. On further history, you learn the patient and several family members have had recent gastrointestinal illnesses, but the patient is recovering. His mother reports he is not experiencing bleeding symptoms.

Which of the following interventions would be most reasonable in this clinical scenario?

A. Hold 1 to 2 doses of warfarin and recheck INR
B. Administer oral vitamin K therapy
C. Administer fresh frozen plasma (FFP)
D. Administer recombinant factor VIIa
E. Administer prothrombin complex concentrates (PCCs)

46. A healthy 17-year-old African American male presents with a thrombosis of the right upper extremity. His past medical history is remarkable only for sickle cell trait. The history is negative for recent risk factors for thrombosis (illness, surgery, immobility). He is the pitcher for his high school baseball team. Imaging confirms anatomical compression/narrowing of the right subclavian vein.

Which of the following interventions is most likely to decrease this patient's long-term risk of recurrent thrombosis?

A. Systemic thrombolysis
B. Catheter-directed thrombolysis
C. Extended 12-month course of anticoagulation with low-molecular-weight heparin (LMWH)
D. Resection of right first rib
E. Use of compression sleeve during baseball practices and games

47. A 16-year-old female presents to the emergency room with a new complaint of chest pain. When performing a review of systems and physical examination, which of the following would substantially decrease your suspicion for a diagnosis of pulmonary embolism?

A. Cough
B. Fever
C. Rib tenderness
D. Shortness of breath
E. Normal pulse oximetry

48. The pathophysiology of venous thrombosis is often explained by Virchow's triad, which includes hypercoagulability, endothelial injury, and venous stasis. Based on Virchow's triad and your knowledge of risk factors for thrombosis, which of the following pediatric patients has the greatest risk of hospital-acquired venous thromboembolism?

A. 3-day-old full-term infant admitted to hospital pediatrics for hyperbilirubinemia
B. 6-month-old male admitted to the infectious disease unit for respiratory syncytial virus
C. Ex-28 week premature infant, requiring NICU-level care for necrotizing enterocolitis
D. 7-year-old male with acute lymphoblastic leukemia receiving maintenance chemotherapy admitted to hematology/oncology unit for fever and neutropenia
E. 17-year-old male admitted to the ENT unit for postoperative bleeding and dehydration after recent tonsillectomy

16. Nutritional Anemias

49. Which of the following best characterizes the function of ferroportin in iron metabolism?

A. A form of storage iron in intestinal mucosal cells
B. A transport protein in the plasma
C. A receptor protein on the surface of erythroid progenitors
D. Transmembrane iron exporter
E. A form of storage iron in hepatic cells

50. A 20-month-old otherwise healthy male presents late for his 18-month well child check. During his first year of life, he took iron-fortified formula and had a point-of-care hemoglobin (Hgb) of 12 g/dL at his 1-year well child check. His mother reports that he is a picky eater but loves milk and has recently become obsessive about chewing the corners of his cardboard books. Physical examination is normal except for a flow murmur. Which combination of laboratory test results listed below would most likely characterize this patient?

A. Hgb 8.7 g/dL, mean corpuscular volume (MCV) 60 fL, serum ferritin 2 ng/mL
B. Hgb 12.0 g/dL, MCV 80 fL, serum ferritin 30 ng/mL
C. Hgb 9.2 g/dL, MCV 60 fL, serum ferritin 30 ng/mL
D. Hgb 11.2 g/dL, MCV 90 fL, serum ferritin 7 ng/mL
E. Hgb 9.8 g/dL, MCV 68 fL, serum ferritin 50 ng/mL

51. Assuming that adherence has been excellent, which of the following should have returned to normal 6 weeks following appropriate oral iron treatment for a child with severe dietary iron deficiency (hemoglobin [Hgb] 5.0 g/dL and mean corpuscular volume [MCV] 48 fL at the beginning of therapy)?

A. Hgb concentration
B. MCV
C. Red cell distribution width
D. Peripheral blood smear
E. Serum ferritin

52. Iron-refractory iron deficiency anemia (IRIDA) is a rare inherited condition characterized by congenital iron deficiency anemia, poor response to oral iron, and partial but incomplete response to intravenous iron therapy. Which is the genetic mutation associated with IRIDA?

A. *TFR2*
B. *H63D*
C. *TMPRSS6*
D. *EPOR*
E. *C282Y*

17. Sarcomas

53. You are caring for a patient with a large localized Ewing sarcoma of the soft tissues of the arm. The surgeon believes that the tumor can be resected without amputation but asks whether you can give some chemotherapy to shrink the tumor before surgery.

Which of the following would you tell the surgeon?

A. If the tumor can be resected without amputation, then the best time to do the resection is before any chemotherapy to improve the prognosis.
B. You agree with waiting to do the resection until week 12 of therapy and will begin chemotherapy; you recognize that radiotherapy will not be necessary if the tumor is completely resected at week 12 of therapy.
C. You agree with waiting to do the resection until week 12 of therapy and will begin chemotherapy; you recognize that radiotherapy will be necessary even if the tumor is completely resected at week 12 of therapy.
D. If the tumor can be resected without amputation, then the best time to do the resection is before any chemotherapy; you recognize that this is the only way to avoid radiotherapy.

54. You are treating a patient with localized osteosarcoma of the distal femur with methotrexate, doxorubicin, and cisplatin (MAP) chemotherapy. At week 10 of treatment, the patient undergoes complete resection of the tumor. Pathology demonstrates 40% necrosis.

Which of the following represents the most appropriate further therapy?

A. Ifosfamide and etoposide (IE)
B. MAP plus ifosfamide and etoposide (MAPIE)
C. Gemcitabine docetaxel
D. MAP
E. Sorafenib

55. You are discussing prognosis with the mother of a patient with stage 3, group III rhabdomyosarcoma.

Which of the following is the most unfavorable primary site?

A. Extremity
B. Prostate
C. Infratemporal fossa
D. Neck
E. Biliary tree

56. A 12-year-old patient has been referred to you following complete resection with clean margins of a high-grade malignant peripheral nerve sheath tumor of the shoulder region. The tumor measured approximately 4 cm in greatest dimension. A CT scan of the chest and a bone scan were within normal limits. The patient does not have evidence of neurofibromatosis type 1 (NF1).

Which of the following treatment approaches would you recommend?

A. Chemotherapy with doxorubicin and ifosfamide
B. Radiotherapy
C. Chemotherapy with doxorubicin and ifosfamide plus radiotherapy
D. Observation

18. Acute and Chronic Myelogenous Leukemia

57. You have a new 7-year-old female patient with a WBC count of 6,000/mm3, hemoglobin of 7.2 g/dL, and platelet count of 30,000/mm3. A bone marrow aspirate reveals 14% blasts with a monocytic morphologic appearance that are surface marker positive for CD33. You receive a call from the fluorescence in situ hybridization (FISH) lab that the bone marrow is positive for KMT2A rearrangement in 68% of cells. Your staff asks whether this represents a diagnosis of acute leukemia in the current classification scheme for this type of hematologic malignancy.

What would you say?

A. No, because for a diagnosis of acute leukemia you must have 30% or more blasts in the marrow.
B. No, because for a diagnosis of acute leukemia you must have 20% or more blasts in the marrow.
C. No, because the cytogenetics do not include +21, monosomy 7, or trisomy 8.
D. Yes, because the morphology is monocytic.
E. Yes, because the FISH is positive for KMT2A rearrangement.

58. A 13-year-old Hispanic girl is found to have a WBC count of 6,500/mm3 with 40% Auer rod–containing granular blasts that, by flow cytometry, express very bright CD33 but are negative for human leukocyte antigen–DR isotype (HLA-DR). She is oozing blood around her peripheral IV site. Coagulation studies reveal an international normalized ratio (INR) of 3.4, a fibrinogen of 170, and a markedly elevated D-dimer. Marrow aspirate shows nearly 90% blasts with a similar morphology. You send the marrow to the fluorescence in situ hybridization (FISH) lab and request STAT testing for the most likely recurrent genetic abnormality based on the clinical presentation.

How do you plan to initiate therapy?

A. Perform a lumbar puncture to determine leukemic involvement, then proceed with induction chemotherapy.
B. Begin therapy with all-trans retinoic acid (ATRA) immediately while aggressively managing coagulopathy with blood product support.
C. Start dexamethasone and hydroxyurea immediately while aggressively managing coagulopathy with blood product support.
D. Start induction chemotherapy, obtain HLA typing, and start a donor search because of the poor prognosis associated with this leukemic phenotype.
E. Refer the patient immediately for leukapheresis because of her severe coagulopathy.

59. A 13-year-old girl presents with acute myeloid leukemia (AML) and a WBC count of 120,000/mm3. Cytogenetics reveals a normal karyotype, and fluorescence in situ hybridization (FISH) tests for inv(16), t(8;21), t(15;17); 11q23 abnormalities; monosomy 7; and 5q deletion are negative. Molecular testing is negative for mutations in FLT3, NPM1, and CEBPA. She is treated with 10 days of daunorubicin, AraC, and gemtuzumab for induction therapy. On day 30, she recovers counts, and a bone marrow aspiration shows 2.2% leukemic blasts by flow cytometry. She receives a second course of treatment with daunorubicin and AraC, and her marrow is now in morphologic remission and is MRD-negative by flow cytometry. She has no HLA-matched siblings, but an unrelated donor search reveals a large number of potential matches.

Which course of treatment is most likely to result in the best outcome?

A. Give two more courses of intensification chemotherapy.
B. Perform an autologous hematopoietic stem cell transplant (HSCT).
C. Give one more course of intensification chemotherapy and then perform a matched unrelated donor HSCT.
D. Give one more course of intensification chemotherapy and then 1 year of maintenance chemotherapy.

60. An 18-year old male patient presents with bruising, fatigue, and diffuse extremity pain. He is noted to be tachypneic and hypoxic and has a diffuse interstitial infiltrate on chest x-ray. CBC reveals a WBC count of 285,000/mm3 (85% myeloblasts, with monocytic morphology), hemoglobin of 7.9 g/dL, and platelet count of 36,000/mm3.

What is the most likely cause of the infiltrate and respiratory symptoms and the most appropriate initial treatment?

A. Hyperleukocytosis; initiation of induction chemotherapy
B. Hyperleukocytosis; leukapheresis or manual exchange transfusion and initiation of induction chemotherapy
C. COVID-19 infection; convalescent plasma and prednisone
D. Pneumococcal pneumonia; vancomycin
E. Reactive airway disease; prednisone and albuterol

19. Biostatistics and Epidemiology

61. In a study to investigate the rates of central line–acquired bacterial infections, it is discovered that patient length of stay (LOS) is not normally distributed but is highly right-skewed.

What is the correct relationship between the mean, median, and mode of LOS?

A. The mean is less than the median but greater than the mode.
B. The mean is equal to the median and the mode.
C. The mean is greater than the median and mode.
D. The mean and median will both be less than the mode.
E. The mean is greater than the median but less than the mode.

62. A study is designed to investigate the rates of central line–associated blood stream infections among pediatric hematology/oncology patients. Three common central line types (totally implanted catheter [port], peripherally inserted central catheter [PICC], and tunneled externalized catheter [TEC]) were included in the study.

What data structure is central line type?

A. Continuous
B. Dichotomous
C. Nominal
D. Ordinal
E. Survival

63. A study is designed to investigate the rates of central line–associated blood stream infections (CLABSI) among pediatric hematology/oncology patients. Investigators wish to compare the length of stay (LOS) between subjects receiving three common central line types (totally implanted catheter [port], peripherally inserted central catheter [PICC], and tunneled externalized catheter [TEC]). It is discovered that LOS is not normally distributed.

What is the appropriate test for comparing the LOS between patients receiving the three central line types?

A. Student's *t* test
B. ANOVA
C. Wilcoxon-Mann-Whitney test
D. Kruskal-Wallis test
E. Chi-square test

20. Bone Marrow Failure

64. You examine a 10-year-old boy with severe aplastic anemia. He has no dysmorphic features and is at the 50th percentile for height and weight. Family history includes a sister with aplastic anemia unresponsive to anti-human thymocyte globulin (ATG) and cyclosporine who died early in the course of an unrelated donor hematopoietic stem cell transplant complicated by severe mucositis and transplant-related organ toxicities. There are no other siblings. A cousin died of acute myeloid leukemia at age 5 years. A peripheral blood sample test for Fanconi anemia is negative with no increased chromosomal breaks in response to diepoxybutane or mitomycin C.

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

A. Administer ATG and cyclosporine.
B. Search for a donor for matched unrelated transplant.
C. Send a bone marrow aspirate for Fanconi anemia testing.
D. Send a skin fibroblast culture for Fanconi anemia testing.
E. Start oral therapy with oxymetholone.

65. A 5-year-old girl with a previously normal CBC now presents in your office with a hemoglobin of 8.5 g/dL, corrected reticulocyte count of 0.1%, and mean corpuscular volume of 80 fl. White cells and platelets are normal in number and morphology. Bilirubin, LDH, BUN, creatinine, and urinalysis are normal. Direct and indirect antiglobulin tests are negative. Workup for infection, including parvovirus, is negative. Occult blood in her stools is negative. Physical examination is unremarkable. She has had no restriction in her energy or activities and the family agrees she is "fine."

What is the most appropriate next step in management?

A. Administer erythropoietin.
B. Initiate a red cell transfusion.
C. Observe serial hemoglobin values closely.
D. Prescribe oral iron supplement.
E. Send red cell adenosine deaminase (eADA).

66. You are consulting on a 10-year-old male with severe persistent neutropenia, a history of recurrent infections, and warts. The rest of the peripheral blood count is normal. His mother also has neutropenia. Bone marrow examination shows a hypercellular marrow and retained myeloid cells with vacuolated cytoplasm. There are no abnormalities in the red cells or platelet precursors. Cytogenetics are 46XY. You start granulocyte colony stimulating factor therapy and the neutrophil count increases.

A mutation in which of the following genes is most likely to have caused this familial inherited bone marrow failure syndrome?

A. *CXCR4*
B. *ELANE*
C. *GATA 2*
D. Mitochondrial DNA
E. *SBDS*

21. Cancer Predispositions

67. You are consulted on a 4-year-old girl who is newly diagnosed with standard-risk pre-B acute lymphoblastic leukemia. After reviewing her previous complete blood examinations, you note she has had a platelet count ranging from 80,000 to 100,000 cells/mcL over the past 2 years. Her father mentions that he has also been told he has mild thrombocytopenia. You suspect the child may have a cancer predisposition syndrome.

Which sample should you send for analysis, and which gene is most likely implicated?

A. Skin fibroblasts to evaluate the *RUNX1* gene
B. Skin fibroblasts to evaluate the *ETV6* gene
C. Buccal swab to evaluate the *RUNX1* gene
D. Buccal swab to evaluate the *ETV6* gene
E. Skin fibroblasts to evaluate the *TP53* gene

68. You receive a phone call from a community pediatrician who is caring for a 2-year-old toddler with a cancer predisposition syndrome. The pediatrician describes a child at the 95th percentile for height and weight with a history of corrective oral surgery to reduce a large tongue and a history of an omphalocele in infancy. The pediatrician is currently performing ultrasound of the abdomen and laboratory evaluation for this patient every 3 months.

Which tumor is this patient most at risk of developing?

A. Pleuropulmonary blastoma
B. Hepatocellular carcinoma
C. Cystic nephroma
D. Nephroblastoma
E. Pheochromocytoma

69. You are seeing a 12-year-old boy in the survivorship program who presented at 2 years old with a desmoplastic nodular medulloblastoma. You note the child recently underwent germline genetic testing and was found to have nevoid basal cell carcinoma syndrome.

In which gene is the child most likely to have a pathogenic variant?

A. *PTEN*
B. *CDKN2A*
C. *SUFU*
D. *SMARCB1*
E. *TP53*

70. A 10-year-old girl is a long-term survivor of type II pleuropulmonary blastoma (PPB). You suspect she has a cancer predisposition syndrome and perform genetic testing, which confirms she has DICER1 syndrome.

Which other cancer is she predisposed to?

A. Papillary thyroid cancer
B. Medullary thyroid cancer
C. Pheochromocytoma
D. Renal cell carcinoma
E. Osteosarcoma

22. Congenital and Acquired Hemolytic Anemias

71. A newborn infant develops jaundice on day of life 2. Labs are drawn, and she has a hemoglobin of 7.4 g/dL with a reticulocyte count of 8%. Upon peripheral blood smear review, she is found to have bizarre red cell forms with significant poikilocytosis. Although her parents have normal blood counts, on review of their peripheral blood smears, they both have a moderate number of ovalocytes. Which of the following is the most likely cause of the infant's red cell findings?

A. She has an autosomal dominant ankyrin mutation from one of her parents causing hereditary spherocytosis.
B. She has inherited band 3 variants from each parent and will likely need a splenectomy after she turns 5 years old.
C. She has inherited an alpha-spectrin mutation from both of her parents and may experience an improvement in her anemia over time.
D. She has inherited a *PKLR* variant from each parent, and enzyme testing will be consistent with her diagnosis of pyruvate kinase deficiency.

72. A 10-year-old girl has had transfusion-dependent anemia since age 6 months. She is found to have an unstable hemoglobin by sequence analysis (Hb Indianapolis). She has jaundice, obvious bony deformity from extramedullary hematopoiesis, and hepatosplenomegaly.

Which of the following statements is correct?

A. Her diagnosis should have been picked up on newborn screen by electrophoresis, isoelectric focusing, or high-performance liquid chromatography similar to other beta-hemoglobinopathies.
B. Since her spleen is intact, her peripheral blood smear cannot have nucleated red cells or Howell Jolly bodies.
C. If she undergoes splenectomy, her anemia should be entirely ameliorated.
D. Since she is transfused, she will not be at risk for gallstones.
E. If she undergoes splenectomy, she will be at long-term risk for both infections and thrombosis.

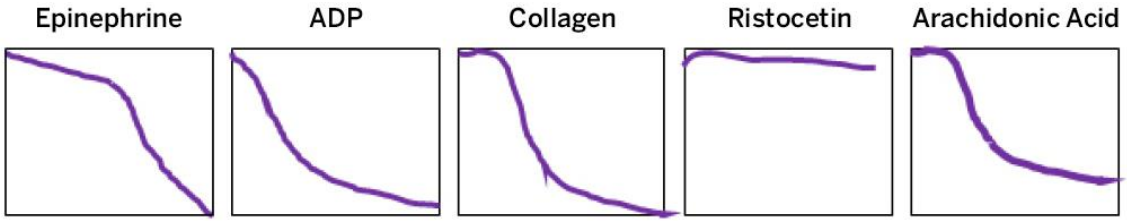
73. A 5-year-old boy is evaluated for apparent ongoing hemolysis. His hemoglobin is 9.5 g/dL, with 8% reticulocytes and MCV 87 fL. Platelets and leukocytes are normal. His direct antiglobulin test (DAT) is negative. No cold agglutinin is detectable. His family history is negative for blood disorders. Peripheral smear reveals basophilic stippling in 10% of the red blood cells.

Given these findings, which of the following blood disorders is most likely?

A. Rh-null disease
B. Hereditary pyropoikilocytosis
C. Glucose phosphate isomerase deficiency
D. Unstable hemoglobin
E. Pyrimidine 5'-nucleotidase deficiency

23. Disorders of Platelets

74. An 18-month-old boy, whose parents are first cousins, is referred to you because of a significant episode of epistaxis. The parents report that the child had bleeding after circumcision and large hematomas with immunizations. Platelet aggregation studies show the following:



This child's platelets are unable to interact with which of the following?

A. ADP
B. Fibrinogen
C. von Willebrand factor
D. Platelet factor 4
E. ADAMTS13
F. Collagen

75. A patient is scheduled for upcoming surgery. He is on nonsteroidal anti-inflammatory drugs (NSAIDs) for rheumatoid arthritis. You are being asked what to do with his medications for the surgery.

What is the mechanism of action of NSAIDS?

A. Irreversible inhibition of cyclooxygenase 1
B. Irreversible inhibition of cyclooxygenase 2
C. Reversible inhibition of cyclooxygenase 1
D. Reversible inhibition of cyclooxygenase 2
E. Direct inhibition of ADP

76. A 17-year-old patient is referred to you for a platelet count of 1,200,000/mm3. On history, she notes that she often has numbness and tingling in her hands and feet and has frequent epistaxis. She is otherwise well-appearing and has no recent infections. On her exam, you note splenomegaly.

What do you expect to see on further evaluation?

A. Elevated C-reactive protein
B. Low ferritin
C. A hypocellular bone marrow
D. Low von Willebrand factor activity
E. Low thrombopoietin levels

24. Lymphoma

77. A 15-year-old female presents with 1 month of fatigue and 3 days of chest pain and shortness of breath. Her physical exam is unremarkable. A chest x-ray shows a large mediastinal mass that is greater than 33% of the diameter of her chest cavity. A biopsy shows nodular sclerosing, classic Hodgkin lymphoma (cHL). Metastatic workup at diagnosis, including CT scan of neck, chest, abdomen, and pelvis and PET scan, shows no other site of disease. According to the Ann Arbor staging system, the patient has which stage of cHL?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV

78. A 15-year-old female presents with 1-month history of fatigue and a 3-day history of chest pain and shortness of breath. Her chest x-ray shows a large mediastinal mass that is greater than 33% of the thoracic diameter at the level of the diaphragm. A biopsy shows diffuse large B-cell lymphoma. Metastatic work-up, including a CT scan of neck, chest, abdomen, and pelvis; bone marrow biopsy; lumbar puncture; and PET scan show no other site of disease. According to the St. Jude (Murphy) staging system, what is the stage of this patient's non-Hodgkin lymphoma (NHL)?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV

79. A 19-year-old freshman in college presents with "lumps" on the right side of his neck and in the right axilla. He had a fever to 39 °C 1 day in the past week. On physical exam, there are firm anterior cervical and axillary nodes, all greater than 2 cm in diameter. A chest x-ray shows a large mediastinal mass. A biopsy of the axillary node reveals classic Hodgkin lymphoma. Which of the following symptoms revealed during the history is a B symptom?

A. Fever to 39 °C
B. 10% weight loss in past 6 months
C. Fatigue
D. Alcohol-induced pain
E. Pruritis
F. A and B

80. A 17-year-old female presents with cervical adenopathy and a history of daily fevers and drenching night sweats. A biopsy is performed and reveals classic Hodgkin lymphoma. Which of the following is least appropriate as part of the staging workup?

A. Chest x-ray
B. CT scan of chest, abdomen, and pelvis
C. Functional imaging (PET scan)
D. Lumbar puncture and cerebrospinal fluid (CSF) analysis
E. All of the above are indicated

25. Oncologic Emergencies

81. A 14-year-old boy presents with cough, shortness of breath, and difficulty lying down. His face and neck swell when his arms are raised. Chest x-ray reveals a large mediastinal mass. A tissue diagnosis is desired. A biopsy is performed with local anesthesia because the anesthesiologist thinks that the patient has a very high general anesthesia risk.

Which of the following findings does not make general anesthesia unsafe?

A. Tumor diameter greater than 45% of transthoracic diameter
B. Tracheal cross-sectional area less than 50% of predicted
C. Peak expiratory flow rate less than 50% of predicted
D. A malignancy of hematopoietic origin
E. A large pericardial effusion

82. A 13-year-old boy presents to the emergency department with complaints of headache and visual changes. History reveals progressive dyspnea on exertion, generalized fatigue, and increased bruising. His labs are significant for a WBC of 350,000/mcL, of which 80% are reported to be blasts and appear to be myeloblasts without the presence of Auer rods. His hemoglobin is 7.2 g/dL, and his platelets are 18,000/mcL. A CT scan of the head shows a small intracerebral hemorrhage. His coags are normal.

Which of the following is the most appropriate therapy?

A. Start induction chemotherapy.
B. Perform emergent leukapheresis followed the next day by induction chemotherapy.
C. Perform emergent leukapheresis plus hydroxyurea.
D. Provide emergent cranial radiation plus hydroxyurea followed the next day by induction chemotherapy.
E. Provide emergent cranial radiation plus emergent leukapheresis and hydroxyurea followed the next day by induction chemotherapy.

83. When reviewing the chemistry panel of a newly diagnosed patient with acute lymphoblastic leukemia who is lethargic, complaining of flank pain, and experiencing nausea and vomiting, which of the following would you expect to see?

A. Potassium 4.5 mmol/L, phosphorus 8 mg/dL, uric acid 7 mg/dL, calcium 9.0 mg/dL, BUN 12 mg/dL, BUN 12 mg/dL
B. Potassium 6.5 mmol/L, phosphorus 8 mg/dL, uric acid 9 mg/dL, calcium 10 mg/dL, BUN 14 mg/dL
C. Potassium 4 mmol/L, phosphorus 9 mg/dL, uric acid 10 mg/dL, calcium 10 mg/dL, BUN 10 mg/dL
D. Potassium 7 mmol/L, phosphorus 12 mg/dL, uric acid 10 mg/dL, calcium 7 mg/dL, BUN 25 mg/dL

26. Palliative and Supportive Care

84. A 9-year-old child with osteosarcoma is being admitted for cisplatin therapy. What is the best regimen for prevention of chemotherapy-induced nausea and vomiting (CINV)?

A. Palonosetron and olanzapine
B. Dexamethasone and aprepitant
C. Granisetron, dexamethasone at 50% dosing, and aprepitant
D. Granisetron, dexamethasone at 100% dosing, and aprepitant
E. Lorazepam, diphenhydramine, and scopolamine patch

85. A 4-year-old child with acute lymphoblastic leukemia is receiving high-dose methotrexate during interim maintenance. He receives ondansetron and aprepitant during his stay, which control his nausea and vomiting well. These medications work by inhibiting signaling in which part of the brain?

A. Vestibular system
B. Cerebral cortex
C. Hypothalamus
D. Vomiting center
E. Chemoreceptor trigger zone

86. A 16-year-old patient with a left-side pelvic osteosarcoma is taking extended release oxycodone twice daily as well as immediate release oxycodone for breakthrough pain approximately 2 or 3 times per day. She describes her pain as burning, tingling, and shooting in her left leg. Her pain worsens with hot showers. Her most recent EKG has a QTc of 495. What would be the best strategy to manage her pain?

A. Switch from long-acting oxycodone to methadone.
B. Recommend more frequent use of her immediate release oxycodone.
C. Add amitriptyline daily. Start low and titrate upward on dosage.
D. Add gabapentin three times daily. Start low and titrate upward on dose.
E. Add sertraline daily. Start low and titrate upward on dose.

27. Research Ethics and Quality Improvement

87. A leukemia investigator plans to obtain bone marrow under general anesthesia to measure minimal residual disease (MRD) and to see if this time point can predict early relapse. The specimen will be obtained at a time point when otherwise no bone marrow would be sampled. The results are not shared with the treating oncologist, and no therapeutic interventions are decided or based on the results. Which of the following statements is most accurate about this intervention?

A. It constitutes a minimal-risk procedure because bone marrow assessments are considered routine for patients diagnosed with acute lymphoblastic leukemia.
B. It constitutes a minimal-risk procedure because it is a single additional procedure being performed during the course of treatment.
C. It constitutes a greater than minimal-risk procedure because it is being done under general anesthesia.
D. It is justifiable because future patients may benefit from knowledge gained by the research.

88. What are the six dimensions of quality care according to the Institute of Medicine?

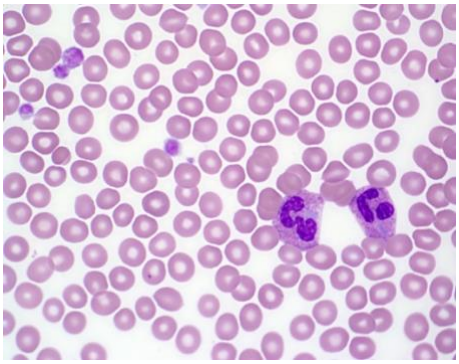
A. Safe, timely, effective, efficient, equitable, and person-centered
B. Safe, transparent, effective, efficient, equitable, and person-centered
C. Safe, timely, effective, low-cost, equitable, and person-centered
D. Safe, timely, effective, efficient, cutting-edge, and person-centered

89. A pediatric fellow is planning a project intended to decrease the incidence of acute chest syndrome among patients with sickle cell disease who are already admitted to the hospital for other reasons. The fellow discussed with her mentor whether the project proposal should be submitted for review by the Institutional Review Board (IRB). The mentor explains that, at their intuition, quality improvement activities do not require IRB review but research projects must be submitted to the IRB. Which of the following is NOT a relevant consideration in determining whether the project is research or quality improvement?

A. The aim to create new knowledge for the individual institution versus discovering new and generalizable knowledge
B. The chosen methodology which will include repeated Plan-Do-Study-Act cycles
C. The intent to publish the results in a peer reviewed hematology journal
D. The efforts to hold biases/confounders stable over time, rather than control for them with, for example, randomization

28. Review of Peripheral Blood and Bone Marrow Morphology: Non-Malignant Hematology

90. The patient is a 6-year-old boy referred to a hematologist for thrombocytopenia. He has no bleeding history or family history of bleeding. His only other past medical history is mild high-frequency hearing loss. What gene is responsible for these findings?

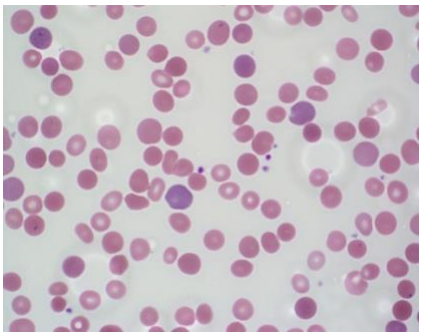


A. *NBEAL2*
B. *GP-1Ba*
C. *MYH9*
D. Deletions of long arm of chromosome 11
E. *GATA1*

91. A 4-year-old boy is pale with intermittent jaundice and splenomegaly.

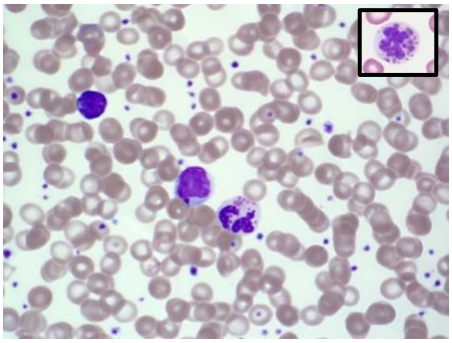
Laboratory results are as follows: RBC 4.85 M/mcL (N); Hgb 8.6 g/dL (L); Hct 25.8% (L); MCV 81.6 (N); MCHC 38% (H); RDW 20% (H); Retic 7% (H).

What are the two best tests to distinguish autoimmune hemolytic anemia from hereditary spherocytosis?



A. Free erythrocyte protoporphyrin and IgG levels
B. Hemoglobin electrophoresis and direct antiglobulin test (DAT)
C. Lactate dehydrogenase (LDH) and modified Russell viper venom test
D. Red cell distribution width (RDW) and mean corpuscular hemoglobin concentration (MCHC)
E. DAT and osmotic fragility testing

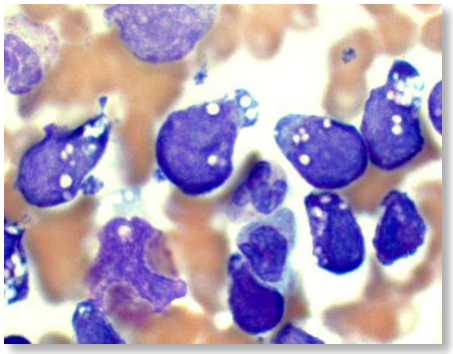
92. The patient is a 2-month-old boy who presented with a skin abscess and is febrile. On exam, he is noted to have silvery hair and hypopigmented skin. A CBC shows a leukocyte count of 3.4 K/mcL with 10% neutrophils. What does the abnormality on the peripheral smear suggest?



A. Abnormal lysosomal biogenesis
B. Abnormal ribosome function
C. Abnormal phagocytosis of opsonized particles
D. Abnormal mitochondrial activity
E. Impaired DNA repair activity

29. Review of Peripheral Blood and Bone Marrow Morphology: Malignant Diseases

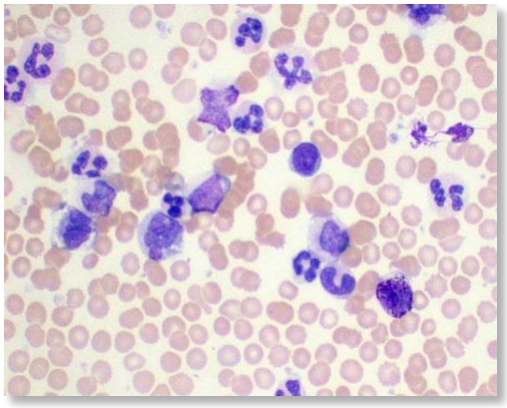
93. A 7-year-old boy presents with recent onset of vomiting and lethargy. Blood smear shows increased neutrophils with a left shift and 8% abnormal cells. Bone marrow contains 60% of the same cells. Flow cytometry shows that the cells are TdT–, CD10+, CD19+, CD20+, sIg+.



What is the most likely diagnosis?

A. Burkitt leukemia/lymphoma
B. B-cell acute lymphoblastic leukemia (ALL)
C. T-cell ALL
D. Hematogones
E. Diffuse large B-cell lymphoma (DLBCL)

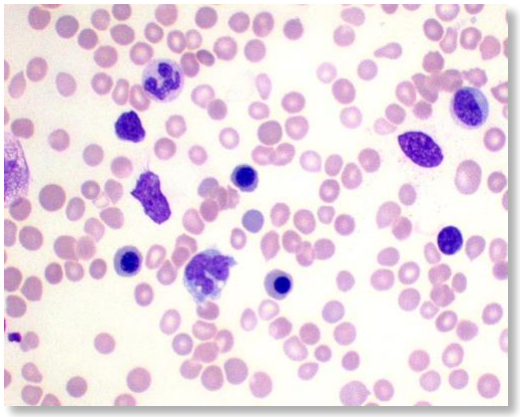
94. You are seeing a 13-year-old boy with fatigue, weight loss, night sweats, and splenomegaly. Peripheral blood shows anemia, thrombocytosis, and leukocytosis (300,000/mm3).



What is this patient's most likely diagnosis?

A. Leukemoid reaction
B. Acute lymphoblastic leukemia (ALL)
C. Chronic myeloid leukemia (CML)
D. Juvenile myelomonocytic leukemia (JMML)
E. Acute myeloid leukemia (AML)

95. You are seeing a 2-year-old girl with new onset of fever and bronchitis. She has maculopapular rash and hepatosplenomegaly. Blood smear shows leukocytosis (100,000/mm3), anemia, and thrombocytopenia. Ancillary tests include fetal hemoglobin of 80% and normal blood karyotype.



What is the most likely diagnosis?

A. Leukemoid Reaction
B. Acute lymphoblastic leukemia (ALL)
C. Chronic myeloid leukemia (CML)
D. Juvenile myelomonocytic leukemia (JMML)
E. Acute myeloid leukemia (AML)

30. Survivorship

96. A 15-year-old girl with a history of osteosarcoma presents to survivor clinic for her first evaluation. Her mother complains that she does not listen well and is wondering if she may have trouble hearing. Which of the follow is true regarding platinum-associated hearing loss?

A. Platinum chemotherapy is most often associated with conductive hearing loss.
B. Low-frequency volumes are affected first.
C. Older age at exposure increases risk.
D. Platinum-associated hearing loss is due to destruction of the cochlear hair cells.
E. Carboplatin is more ototoxic than cisplatin.

97. An 18-year old male patient with acute lymphoblastic leukemia recently started maintenance therapy and is complaining of increased hip pain. The pain increases during weight-bearing activity; however, it occasionally hurts at night as well. His CBCd is normal. Which of the following risk factors is most commonly associated with this process?

A. Younger age at diagnosis
B. Non-White race
C. Low body-mass index
D. Dexamethasone exposure
E. Male sex

98. A 19-year old male patient with a history of acute lymphoblastic leukemia, currently 13 years from completion of therapy, presents for a fertility consultation. He is interested in his risk for infertility. Which of the following statements is true?

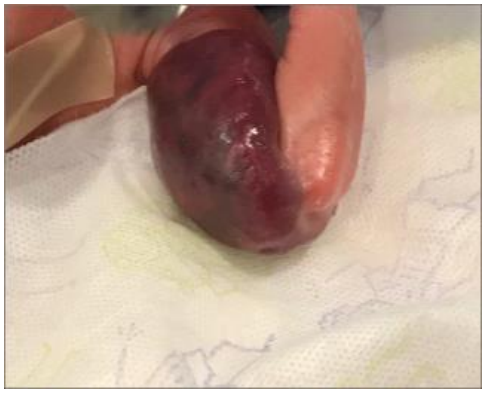
A. A semen analysis at this point would provide accurate information about future fertility.
B. Males can maintain gonadal function at higher cumulative alkylator dosages compared with females.
C. He should have been offered sperm cryopreservation at diagnosis.
D. His risk for testosterone deficiency is greater than his risk for infertility.
E. Prepubertal status at diagnosis is protective from gonadal injury in males.

31. Vascular Anomalies

99. An infant is born with a firm mass over the chest with a central area of purpura and a "halo" around it. An ultrasound reveals a high-flow lesion. What is the most likely diagnosis?

A. Fibrosarcoma
B. Infantile hemangioma
C. Congenital hemangioma
D. Capillary malformation

100. An infant is born with a 7 cm × 6 cm lesion over the upper extremity from the elbow to the shoulder. The lesion is indurated and purpuric, with some petechiae around the edges. No other areas of petechiae are noted on the skin. The infant is doing well without other systemic problems. i were 9 and 9. You are called by the pediatric nurse practitioner to the NICU.



What is the most appropriate next step?

A. Do nothing because the infant is doing well and had good Apgars.
B. Obtain an ultrasound for more information about the lesion.
C. Obtain an MRI to assess the extent of the lesion.
D. Obtain labs, including a CBC with platelet count and fibrinogen.

100 Self-assessment Questions With Answers and Explanations

aspho

Questions With Answers and Explanations

1. Brain Tumors

1. A 9-year-old boy presents to the emergency department with emesis and headache of 3 weeks' duration. MRI reveals a large heterogeneous mass in the cerebellum. He undergoes a resection, and the pathology is most consistent with a classic medulloblastoma.

Which of the following findings would classify the patient as a high-risk medulloblastoma?

A. Elevated serum and CSF AFP and beta-HCG tumor markers
B. WNT subgrouping on molecular classification
C. A presurgical spine MRI that reveals bulky tumor in the spine
D. A postoperative brain MRI with no signs of residual tumor

Answer: C
Explanation

Although molecular classification is slowly becoming part of prognostication and treatment paradigms for medulloblastoma, the most accepted and studied risk groups are standard- and high-risk medulloblastoma. WNT subgrouping seems to portend an improved survival, and by itself does not make a patient high-risk. In addition to histology (classic, desmoplastic, extremely nodular, and anaplastic/large cell), the other characteristics that define risk groups are age, amount of residual disease, and metastases. Both lumbar CSF cytology and a full spine MRI are necessary to evaluate for metastatic disease. Spinal MRI should be done preoperatively or 10 to 14 days postoperatively to avoid postoperative changes that can make interpretation difficult. Lumbar CSF cytology also should be done 10 to 14 days postoperatively. Metastatic disease in the spine would increase the patient's risk level to high and change treatment. Medulloblastoma metastases typically are confined to the brain and spine. Medulloblastoma does not secrete tumor markers.

2. A 6-year-old boy is noted to have worsening visual acuity on serial eye exams. Recent MRI of his brain and orbits reveals an optic chiasm mass, most consistent with an optic pathway glioma. Upon further examination, the physician notes axillary freckling and numerous "spots" on the patient's skin.

This patient most likely has a which of the following genetic disorders?

A. Neurofibromatosis type-1 (NF1)
B. Li Fraumeni syndrome
C. Tuberous sclerosis
D. Cystic Fibrosis

Answer: A
Explanation
Children with neurofibromatosis type-1 (NF-1) have about a 15% to 20% risk of developing low-grade gliomas (LGG), most commonly in the optic pathway. They also have a variety of other abnormalities such as axillary freckling and café-au-lait spots. Li Fraumeni syndrome is associated with p53 mutations and high-grade tumors, like high-grade gliomas and sarcomas. The characteristic brain tumor in tuberous sclerosis is a subependymal giant cell astrocytoma (SEGA). Patients with cystic fibrosis are not at increased risk of CNS tumors. LGGs in patients with NF1 are often indolent and do not necessitate any therapy at all. However, most would agree that when visual acuity is affected by the tumor, treatment is indicated to prevent further vision decline and possibly improve vision in some patients. The best known current therapy is LGG chemotherapy. Common first-line LGG chemotherapies are combinations of carboplatin/vincristine, vinblastine alone, or a combination of thioguanine, procarbazine, lomustine (CCNU), and vincristine (TPCV). TPCV often is avoided for patients with NF-1 because of the risks of secondary malignancy with alkylator use. Radiotherapy is avoided for children with NF-1 because of the high risk of secondary malignancy.

3. An 8-year-old boy undergoes a resection of a tumor in the right cerebrum next to the lateral ventricle (supratentorial). The pathologist feels the histology is most consistent with an ependymoma. The tumor is sent for advanced molecular and genetic testing. Which of the following findings would further support a diagnosis of ependymoma?

A. BRAFKIAA1549 fusion
B. BRAFV600E mutation
C. RELA fusion
D. H3K27M mutation

Answer: C
Explanation
Both A and B (the BRAF abnormalities) are most commonly seen in glial tumors, specifically in low-grade glioma. BRAFKIAA1549 fusion is seen in 60% to 80% of classic pilocytic astrocytoma, the most common pediatric low-grade glioma. The BRAFV600E mutation is most commonly seen in low-grade glioma but has also been described in about 8% to 10% of high-grade glioma. Supratentorial ependymomas seemingly are divided by two major molecular aberrations, including the C11orf95-RELA fusion and the YAP1 fusion. The RELA fusion is much more common and seems to portend a worse prognosis, whereas the YAP1 fusion is quite rare and most often seen in infants with an improved survival outcome. The H3K27M mutation is a defining characteristic of diffuse midline gliomas, such as diffuse intrinsic pontine glioma (DIPG).

4. A 5-year-old boy presents with a 3-week history of his right eye "not moving to the right side." The remainder of his neurologic exam is normal with the exception of a weak gag. MRI of the brain reveals a diffusely infiltrative mass in the pons.

If this patient were to undergo a stereotactic biopsy, what would be the most likely molecular finding?

A. BRAFKIAA1549 fusion
B. Trisomy 21
C. H3 K27M mutation
D. RELA fusion

Answer: C
Explanation
Advances over the last decade have revealed a characteristic histone mutation in DIPG and other midline high-grade gliomas in H3 K27M. The World Health Organization now classifies midline tumors harboring this abnormality as diffuse midline gliomas (DMG), which portend a worse prognosis than other high-grade gliomas. BRAFKIAA1549 fusion is commonly seen in low-grade glioma. Trisomy 21 is not commonly seen in brain tumors. RELA fusion is a common finding in supratentorial ependymoma.

2. Acute Lymphoblastic Leukemia

5. Blinatumomab, a bispecific T-cell engaging molecule, is active against which CD antigen that is expressed on B-lymphoblasts?

A. CD10
B. CD15
C. CD19
D. CD20
E. CD22

Answer: C
Explanation
There are currently no targeted agents available for CD10 or CD15. Rituximab is a monoclonal antibody against CD20. Inotuzumab is a calicheamicin-conjugated monoclonal antibody against CD22. Blinatumomab is a bispecific T-cell engaging molecule that brings together a patient's CD3-positive cells to the patient's CD19-positive lymphoblasts.

6. Of the variables listed below, what is the most important factor for survival after relapse of acute lymphoblastic leukemia?

A. Time to marrow relapse since initial diagnosis
B. Sex
C. Central nervous system involvement at relapse
D. Response to induction therapy during initial diagnosis
E. Percent of marrow blasts at the time of relapse

Answer: A
Explanation
The most important prognostic factor for survival after relapse is the time to relapse after initial diagnosis, especially for those with marrow involvement. Although outcomes after relapse may be shifting with new therapies that have become available for children and adolescents and young adults who experience relapse, historic outcomes for relapse prior to the introduction of these newer therapies (blinatumomab, inotuzumab, and CAR-T cells) were remarkably constant across multiple consortia. For example, survival for patients who relapse less than 18 months from initial diagnosis is the worst, with most 3-year survival rates less than 20%. Neither sex nor central nervous system involvement worsen the prognosis for marrow relapse. In addition, percent marrow blasts at the time of relapse has no significance, nor does the response rate of the patient at initial diagnosis, although measurable residual disease at end induction for B-acute lymphoblastic leukemia (ALL) and end consolidation for T-ALL is generally considered to be the most important prognostic variable for ultimate relapse.

7. An 8-year-old girl presents with National Cancer Institute (NCI) Standard Risk acute pre-B-cell acute lymphoblastic leukemia. Her family history is significant for her mother having been diagnosed with breast cancer at age 34 years and a maternal uncle who developed osteosarcoma as a teenager. What cytogenetic abnormality is most likely to be detected in this patient?

A. t(1;19)
B. *CRLF2* rearrangement with a *JAK2* mutation
C. *KMT2A* rearrangement
D. Hypodiploidy with a modal chromosome number of 34
E. Hypodiploidy with a modal chromosome number of 24

Answer: D
Explanation
For this patient, her strong family history is notable for a number of solid tumors that are present in the Li-Fraumeni cancer predisposition syndrome. Defined by germline mutations in *TP53*, this particular cancer predisposition syndrome has data to support regular screening for early cancer detection through regular blood tests and MRI/ultrasound screening, so it will be important to institute cancer screening for this patient and any siblings. Next generation sequencing has revealed that hypodiploid acute lymphoblastic leukemia (ALL) with a modal chromosome number of 32-29 demonstrates a high percentage of *TP53* mutations; up to 90% of such patients have *TP53* mutations with 40% to 50% of these being germline mutations. Haploid ALL, which

is a subtype of hypodiploid ALL and displays fewer than 32 chromosomes, does not usually harbor *TP53* mutations.

3. Stem Cell Transplantation

8. When should autologous hematopoietic stem cell transplantation be used, and what are the common cancers it is used for?

A. It should be used when high dose therapy is needed to maximize response. Most common cancers it is used for include lymphoma, late relapse of acute lymphoblastic leukemia, neuroblastoma, and Ewing sarcoma.
B. It should be used any time this approach can provide a meaningful survival benefit over chemotherapy. Most common cancers it is used for include neuroblastoma, responsive brain tumors in young children to avoid/minimize early radiation therapy, and relapsed lymphoma.
C. It should be used for tumors in which a graft-versus-tumor effect does not occur. Most common cancers include neuroblastoma, lymphoma, selected brain tumors, rhabdomyosarcoma, and Ewing sarcoma with lung metastases.
D. It should be used to avoid extensive treatment with chemotherapy and to shorten treatment. Most common cancers include neuroblastoma, relapsed Wilms' tumor, and selected brain tumors.
E. It should be used to avoid complications of graft-versus-host disease. Most common cancers include neuroblastoma, selected brain tumors, and relapsed lymphoma.

Answer: B
Explanation
Autologous transplantation, often called high-dose chemotherapy with stem cell rescue, is an approach that is limited to tumors with a dose-response curve that allows cure to be achieved after receiving one or more rounds of intensive therapy. It should not be limited to tumors in which a graft-versus-tumor effect (GVT) from an allogeneic donor does not occur, but for any disease for which it can be shown to have a beneficial effect on survival above standard chemotherapy. There are rare situations in which a patient with a disease like acute myeloid leukemia (AML), which has a great GVT effect and usually requires an allogeneic hematopoietic stem cell transplant (HSCT), can benefit from autologous bone marrow transplant (BMT) (eg, lower risk disease that relapses late, has a molecular marker, and patients achieve a very deep remission—acute promyelocytic leukemia and t(8:21) AML). Some tumors have a great response to high-dose chemotherapy but can be cured equally well with intensive chemotherapy (eg, relapsed Wilms' tumor). Whether autologous HSCT should be used in this setting for Wilms' tumor is controversial, and patient/center preference is used. Use of this approach to avoid graft-versus-host disease is highly desirable; however, in many cancer types, GVT is vital and needed for success (high risk acute lymphoblastic leukemia and AML). The most common tumor types benefitting from autologous HSCT include neuroblastoma, responsive brain tumors (several tumor types in children younger than 3 years to avoid, postpone, or minimize radiation therapy, relapsed responsive medulloblastoma), and relapsed lymphoma that is responsive to chemotherapy. There has been benefit shown in other diseases, as well (eg, relapsed germ cell

tumors, disseminated retinoblastoma). With this explanation in mind, option B is the correct answer.

9. Which of the following statements about myeloablative, myeloablative but reduced toxicity, reduced intensity, and non-myeloablative approaches is not correct?

A. Myeloblative approaches are needed for high-risk malignancies to maximize depth of remission and decrease the likelihood of relapse.
B. Reduced intensity regimens can be successfully used for most nonmalignant disorders to minimize risk of late effects.
C. Reduced intensity regimens can markedly decrease the risk of transplant-related mortality in patients who have underlying significant comorbidities but at the cost of more relapse and possibly more graft-versus-host disease.
D. Non-myeloablative regimens are used for the very highest risk patients to minimize toxicity and for certain diseases such as aplastic anemia.
E. Myeloablative reduced toxicity approaches are often needed to decrease graft rejection and maximize chimerism in certain non-malignant disorders.

Answer: B
Explanation
Myeloablative regimens are used to both maximize depth of remission and to minimize the risk of rejection. This has been shown to reduce relapse in disorders such as high-risk acute myeloid leukemia and acute lymphoblastic leukemia, where these approaches are standard; hence, answer A is true. Although reduced intensity regimens can be successfully used in some nonmalignant disorders, many disorders cannot be treated as effectively with these approaches because of higher risks of partial chimerism or rejection. In these disorders, reduced-toxicity approaches are best. With this in mind, answer B is the correct answer (the only statement that is incorrect) and answer E is true. A very important use of reduced intensity conditioning (RI or RIC) regimens is in patients who have major comorbidities, such as decreased lung or heart function, or partially controlled fungal infections. Although transplant-related mortality (TRM) decreases with these approaches, relapse increases, and the need to use peripheral blood stem cells for the success of these approaches results in more graft-versus-host disease. The trade-off of sacrificing intensity for graft-versus-leukemia effect can cure many patients who do not have good alternatives; however, they need to be in a good remission (minimal residual disease–negative, preferably) to have a reasonable chance of success. For the sickest patients, non-myeloablative approaches offer an alternative and can cure a number of patients with little toxicity (although with higher relapse). Severe aplastic anemia treatment regimens are non-myeloablative and generally result in few if any late effects and normal fertility. With this in mind, C and D are true.

10. A 3-year-old boy with X-linked chronic granulomatosis disease is day +25 after haploidentical bone marrow transplant (father donor) using posttransplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis. He engrafted on day +16 and was preparing for discharge when cytomegalovirus (CMV) was noted to be positive on PCR, and he developed a fever and mild rash. His counts have fallen to a WBC of 0.1 and he remains transfusion dependent. What diagnostic evaluations/treatments should you pursue?

A. Rule out infection by sending blood cultures, start broad spectrum antibiotics, and obtain other diagnostic workup as appropriate. Consider skin biopsy and treat with steroids for likely acute GVHD (aGHVD).
B. Initiate an infectious workup and treat with broad-spectrum antibiotics. Consult with the PICU team because the low blood counts are likely a preseptic presentation.
C. Test for possible rejection with rapid FISH chimerism and consider withdrawal of immune suppression if donor chimerism is low.
D. Send blood cultures, start antibiotics, and treat his CMV with foscarnet. Send rapid chimerism by STR to assess for possible rejection. If donor chimerism is low or absent, work on obtaining an alternative donor for a second procedure.
E. Start steroids to treat aGVHD and give supportive care with granulocyte colony stimulating factor.

Answer: D
Explanation
This patient is at high risk for rejection because he is undergoing bone marrow transplantation (BMT) for a nonmalignant condition that is often associated with excessive inflammation, and he has received a haploidentical procedure. Suspicion for rejection should be high. This patient also initially showed count recovery but later developed a fever, rash, and low counts, a classic presentation of acute rejection. Of note, however, infection or graft-versus-host disease (GVHD) could also cause a picture similar to this, so this must be approached carefully. Option A includes many things that should be done, but with counts falling to nearly 0, GVHD is less likely, and there is no mention of assessing for graft failure. Option B focuses on infection and possible sepsis. Although overwhelming sepsis could present like this, other signs such as hypotension would likely be present. Option C is not correct because this boy received a transplant from his father, so FISH chimerism, which relies on sex differences between donor and recipient, cannot be performed. Option D is correct—a rule-out for bacteria must be performed with initiation of antibiotics even though all of these symptoms (fever, rash, low counts) can be explained by acute rejection. The fever could also be associated with the cytomegalovirus (CMV) reactivation, and if this proves to be acute rejection, the rejection was likely triggered by the CMV reactivation. When rejection is proven by noting absent donor chimerism, full control of the infection followed by a salvage hematopoietic stem cell transplant (HSCT) procedure to restore engraftment should be done as soon as possible. Option E focuses only on acute GVHD, which is not likely, and growth factors such as granulocyte colony stimulating factor (G-CSF) do not improve counts in the face of acute rejection.

4. Myeloproliferative Myelodysplastic, and Histiocytic Disorders

11. Several gene mutations have been associated with juvenile myelomonocytic leukemia (JMML), and they may or may not have prognostic implications. A gene expression–based classification system has been found to be an independent predictor of clinical outcome in these patients. What is the disease signature that predicts a poor outcome?

A. Tyrosine kinase inhibitors
B. Acute myeloid leukemia–like
C. Chronic myeloid leukemia-like
D. BRAF pathway abnormalities

Answer: B
Explanation
The diagnostic category of leukemia and myelodysplastic syndrome (MDS) gene expression profiling in a large cohort of patients can identify 16 classes of acute and chronic leukemias. When this gene profiling algorithm was applied to JMML, patients with the worst prognosis (older than 1 year, more than 9% monocytes, more than 2% peripheral blasts, platelets less than 50,000/mcl, more likely to have elevated hemoglobin for age, and monosomy 7 at presentation) had an "acute myeloid leukemia–like" gene expression profile.

12. A female infant is diagnosed with hemophagocytic lymphohistiocytosis (HLH) not associated with an Epstein-Barr virus (EBV) infection. In taking the family history, you learn that another female infant died of HLH 2 years ago. Also, a newborn female child died of an unknown disease 4 years prior and was said have been bleeding profusely, jaundiced, and had a distended abdomen. When counseling the family about the genetics of HLH, how will you explain it?

A. It is an X-linked syndrome
B. It is an autosomal recessive syndrome
C. It is a dominant inheritance syndrome
D. It is an autosomal recessive syndrome with incomplete penetrance

Answer: B
Explanation
There are five genes associated with hemophagocytic lymphohistiocytosis (HLH): *MUNC13-4, STXBP2, RAB27A, STX11,* and *PRF1.* Familial HLH is associated with homozygous defects in these genes, although the specific mutations carried by each parent may be different. It is rare that there will be compound heterozygous mutations in two of the associated genes, although this has been reported. The question specifically avoided EBV-associated HLH to make the likelihood of *SH2D1a (XLP-1)* or the *BIRC4 (XLP-2)* gene defects likely. In the case of *XLP-1,* the gene is X-linked.

13. A 2-month-old infant is brought to your clinic with an extensive scaly rash on the scalp, which has been biopsied and shown to be Langerhans cell histiocytosis (LCH). You want to determine whether this patient has skin-only LCH or involvement of any of the "high-risk" organs. The child has a normal CBC; normal liver enzymes and bilirubin; and a normal skeletal survey, skull films, and chest X ray.

What other screening test will be important for finding involvement of a high-risk organ?

A. Reticulocyte count
B. Erythrocyte sedimentation rat
C. Alkaline phosphatase
D. Serum albumin and total protein

Answer: D
Explanation
Serum albumin and total protein are very sensitive for detecting decreased synthetic capacity of the liver and are often abnormal before liver enzymes and bilirubin are elevated. Of course, the albumin and protein could be low if the child has chronic diarrhea from intestinal involvement. If that symptom is present, one should do endoscopy with biopsies to prove intestinal involvement. Liver involvement can be proven by biopsy, which may show CD1a+ cells infiltrating the liver or just lymphocytic infiltrates. A CT or ultrasound of the abdomen will demonstrate a hypodense signal along the biliary tracts.

5. Disorders of Leukocytes

14. A young child with consanguineous parents has developmental delay and a history of multiple recurrent bacterial infections and short stature. He presents to the emergency department following trauma and requires a blood transfusion. Blood work identifies leukocytosis, neutrophilia, and the Bombay blood group (absent H antigen as well as absent A and B antigens). What is this patient's diagnosis?

A. Chediak-Higashi syndrome
B. Leukocyte adhesion deficiency (LAD) Type II
C. CD18 deficiency
D. Griscelli syndrome

Answer: B
Explanation
This scenario is consistent with leukocyte adhesion deficiency (LAD) Type II, caused by pathogenic biallelic variants in *SLC35C1*. As a result, fucosylation of macromolecules is defective, resulting in no SLeX (CD15) on myeloid cells and the red blood cell phenotype (Bombay) described above. Infections typically are not as severe as they are in LAD-I, though patients have associated severe mental deficits, short stature, and distinctive facial appearance. XLP and Griscelli syndrome are associated with defects in vesicle trafficking with risk of hemophagocytic lymphohistiocytosis (HLH). CD18 deficiency is associated with LAD-I.

15. A 4-year-old male child presents to the emergency department with his fourth invasive *Staph* infection. CBC consistently identifies moderate neutropenia. Sophisticated lab testing identifies lack of Toll-like receptor responses. The patient undergoes whole exome sequencing and is found to have pathogenic variants in *IRAK4.* What does *"IRAK4"* stand for?

A. Interferon gamma receptor-associated kinase 4
B. Inducible RAS activating kinase 4
C. Interleukin-1 receptor-associated kinase 4
D. Immune response activating kinase 4

Answer: C
Explanation
IRAK4 is interleukin-1 (IL1) receptor-associated kinase 4 and plays critical roles in initiating innate immune responses against pathogens. Patients with *IRAK4* dysfunction have frequent bacterial infections but rarely experience abnormal viral or parasitic infections. This is due to the role of IL1 and Toll-like receptors (TLR) in inducing innate immune responses to bacteria. Deficiency of MyD88 has a clinically identical phenotype. TLR signaling (except TLR3) and most IL1R require functional *IRAK4* and MyD88.

16. An avid 16-year-old triathlete was in a bike accident and developed cellulitis, which was treated with Bactrim. While still on antibiotics, he moved with his family from Houston to Denver, and during the car trip he developed fever, pharyngitis, and malaise. Upon arriving in Denver he presented to the emergency department and was noted to have significant lymphocytosis with some atypical lymphocytes. What is the most likely cause of the white blood cell abnormalities?

A. Drug reaction
B. Altitude higher than 5,000 ft above sea level
C. GATA2 mutation
D. Epstein-Barr virus infection

Answer: D
Explanation
This patient most likely has acute primary Epstein-Barr virus infection (mononucleosis), which frequently is associated with elevated lymphocyte count as well as atypical lymphocytes. Many drugs, including sulfonamides, and living at high elevations can be associated with neutropenia. GATA2 can be associated with loss of monocytic populations with risk of infections and myeloid malignancies.

6. Retinoblastoma, Germ Cell Tumors, and Hepatoblastoma

17. You have been asked to see a 15-year-old girl who is being referred for evaluation of an ovarian mass. Her history is also significant for secondary amenorrhea, and physical examination shows signs of virilization. As you review her family history, what syndrome will you consider?

A. Li-Fraumeni syndrome
B. DICER-1 syndrome
C. Turner syndrome
D. Beckwith-Wiedemann syndrome
E. Lynch syndrome

Answer: B
Explanation
This girl has a virilizing ovarian mass, consistent with a testosterone-secreting stromal sex-cord tumor—either a Sertoli-Leydig cell tumor or a gynandroblastoma, which is extremely rare in children. Approximately 50% of patients with these tumors have a germline mutation of *DICER-1*. Other malignancies occurring in DICER-1 families include pleuropulmonary blastoma, cystic nephroma, Wilms' tumor, medulloblastoma, ciliary body medulloepithelioma, and uterine cervix embryonal rhabdomyosarcoma.

18. A 3-year-old boy is referred to you for evaluation of right leukocoria. Funduscopic examination under anesthesia reveals a large amelanotic mass occupying more than two-thirds of the vitreous space in his right eye, with massive retinal detachment, consistent with group E retinoblastoma. The left eye is normal. An MRI confirms the funduscopic findings and shows no extraocular disease. What is the most appropriate next step in the management of this child's disease?

A. Enucleation
B. Systemic chemotherapy
C. Brachytherapy
D. Needle biopsy
E. Intravitreal chemotherapy

Answer: A
Explanation
This boy has unilateral group E retinoblastoma. The standard of care for advanced intraocular disease is enucleation, followed by risk-adapted chemotherapy based on pathology. In some cases, systemic or intra-arterial chemotherapy together with intensive focal treatments may be offered for unilateral group E retinoblastoma, but the risks and benefits of this conservative approach need to be discussed in detail with the family. Brachytherapy may be used for small tumors that are not amenable to laser or cryotherapy but not for large tumors occupying the cavity. Intravitreal chemotherapy is used for the treatment of vitreous seeds. Finally, a biopsy is not recommended in the management of retinoblastoma because of the risk of orbital

contamination. Retinoblastoma is one of the few malignancies in which treatment decisions are made without histologic confirmation.

19. A 9-month-old boy has been referred to you for the evaluation of an enlarged abdomen. Imaging studies show a large liver mass (PRETEXT III). Alfa-fetoprotein is 98 ng/mL, and a CT scan of the lungs show bilateral lung metastases. A needle biopsy is performed, and you are planning to review the specimen with the pathologist. Which of the following diagnoses are you suspecting?

A. Pure fetal histology hepatoblastoma
B. Embryonal sarcoma of the liver
C. Fibrolamellar hepatocellular carcinoma
D. Small cell undifferentiated hepatoblastoma
E. Conventional hepatocellular carcinoma

Answer: D
Explanation
This is a typical presentation of a small cell undifferentiated hepatoblastoma: infant with a very aggressive primary liver tumor and low alfa-fetoprotein. Small cell undifferentiated hepatoblastomas share molecular alterations with rhabdoid tumors (*hSNF5* alterations), and on standard pathology they have absent INI staining. Pure fetal histology hepatoblastoma usually presents with localized disease and has an excellent prognosis. Fibrolamellar and conventional hepatocellular carcinomas, while also having a very aggressive clinical behavior, present in the second decade of life. Embryonal sarcoma of the liver is a less aggressive malignancy that usually presents after 3 years of age.

7. Immunology and Immunodeficiency

20. Which statement is correct regarding lymphocyte counts in infants versus adults?

A. NK-cell numbers are lowest at birth and increase with age.
B. B-cell numbers are highest at birth and decline with age.
C. T-cell numbers in infants are higher than in adults.
D. Infants have low lymphocyte counts that increase with age.

Answer: C
Explanation
T-cell counts are highest in infancy and decline with age. Option A is incorrect because NK-cell counts are high at birth and thereafter do not vary much with age. B-cell numbers increase in toddlers and young children and then go back down in adults; therefore, they are not highest at birth and option B is incorrect. The absolute lymphocyte count is higher in infants, averaging around 6,000/mcL compared with 2,000/mcL in adults (largely because of higher T-cell counts); therefore, option D is incorrect.

21. A 4-year-old girl with a history of relapsed pre-B-cell acute lymphoblastic leukemia is being admitted for unrelated donor bone marrow transplantation with cyclophosphamide and total body irradiation conditioning. Pretransplant workup shows the following:

Recipient
CMV IgG: negative
CMV IgM: negative
HSV I/II antibody: negative
Varicella IgG: positive (vaccinated)
Hepatitis B surface antigen: negative
Hepatitis B surface antibody: positive (vaccinated)
Hepatitis B core antibody: negative
Hepatitis C antibody: negative

Donor
CMV IgG: negative
CMV IgM: negative
HSV I/II antibody: positive
Varicella IgG: positive
Hepatitis B surface antigen: negative
Hepatitis B core antibody: negative
Hepatitis C antibody: negative

How should the patient be managed during the admission with respect to infection prophylaxis?

A. Acyclovir IV for herpes simplex virus (HSV) suppression
B. Weekly screening by polymerase chain reaction (PCR) for cytomegalovirus (CMV) in blood
C. Antifungal prophylaxis
D. Valganciclovir PO for CMV suppression
E. Foscarnet IV for CMV suppression

Answer: C
Explanation
The profound and prolonged neutropenia induced by myeloablative conditioning for allogeneic transplantation puts the patient at high risk of invasive fungal infection, and prophylaxis is routine. Option A is incorrect because the patient is herpes simplex virus (HSV) seronegative. Although the donor is seropositive, HSV is not transmitted by donor cells. Options B, D, and E are incorrect because neither the donor nor the recipient are cytomegalovirus (CMV) seropositive, so screening and prophylaxis are not required.

22. You are asked to evaluate a 2-day-old boy in the newborn nursery with petechiae who has a platelet count of 8,000/mcL. On further questioning, you learn that he had a maternal uncle who died of intracerebral hemorrhage as a toddler. There is no eczema on physical examination. Review of the smear shows anisocytosis; poikilocytosis; normal white blood cell morphology; and small, infrequent platelets. The neonatologists have sent human platelet antigen (HPA)-1a testing from both parents, which is pending.

Which of the following is the most likely diagnosis?

A. Congenital infection
B. Neonatal alloimmune thrombocytopenia
C. Wiskott-Aldrich syndrome
D. May-Hegglin anomaly

Answer: C
Explanation
Wiskott-Aldrich syndrome is characterized by a classic triad of microthrombocytopenia, eczema, and immunodeficiency; the latter two manifestations are commonly absent in neonates. In addition, the maternal male relative having any manifestation of Wiskott-Aldrich syndrome (including lymphoma) is a tip-off. The presentation is not suggestive of congenital infection, so option A is incorrect. The finding of small platelets is inconsistent with immune thrombocytopenia, so option B is incorrect. May-Hegglin anomaly caused by autosomal dominant mutations in the *MYH9* gene typically manifests as mild macrothrombocytopenia; therefore, option D is incorrect.

8. Neuroblastoma and Related Tumors

23. You are seeing a 12-year-old female who presented to the emergency department with the sudden onset of severe abdominal pain. Imaging that was obtained to rule out appendicitis revealed a mass adjacent to the bladder. The mass was surgically resected, and pathology demonstrated a paraganglioma. Which of the studies below would be most useful to determine disease stage for this patient?

A. Bone Scan
B. Lumbar puncture for cerebrospinal fluid cytology
C. Bone marrow aspirate and biopsy
D. Ga 68-DOTATATE PET/CT
E. MRI of the brain

Answer: D
Explanation
Ga 68 dotatate is a radioisotope that binds to the somatostatin receptor. Based on the intensity of signals detected, PET images obtained using Ga 68 dotatate indicate the presence and density of somatostatin receptors in tissues. In 2016 the FDA approved Ga 68-DOTATATE PET for adult and pediatric patients with somatostatin positive neuroendocrine tumors (NETs), including

pheochromocytoma and paraganglioma. Ga 68-DOTATATE PET is now the gold standard imaging modality for NETs. ^{123}I-MIBG scans can also be used for the staging of pheochromocytoma and paraganglioma. Lumbar puncture, bone marrow aspirate and biopsy, and MRI of the brain are not indicated in the routine staging of these diseases. Although bone scan can detect bony metastases in pheochromocytoma and paraganglioma, Ga 68-DOTATATE PET is both more sensitive and specific.

24. Your patient with relapsed high-risk neuroblastoma returns to your care after travelling to an outside institution for ^{131}I-MIBG therapy. In the weeks following ^{131}I-MIBG therapy, what adverse events directly attributable to this therapy will the patient most likely encounter?

A. Myelosuppression requiring growth factor and blood product support
B. Severe mucositis
C. Hemorrhagic cystitis
D. Symptomatic hypothyroidism
E. Renal failure

Answer: A
Explanation
The need for blood product support (both packed red blood cells [PRBC] and platelets) and growth factor support in the weeks following ^{131}I-MIBG therapy is very common and expected. Many heavily pretreated patients require autologous stem cell infusion following ^{131}I-MIBG therapy. Severe mucositis and hemorrhagic cystitis are not commonly associated with ^{131}I-MIBG therapy. Although renal failure could be attributed to ^{131}I-MIBG therapy, it is rare. Hypothyroidism is a very common finding but typically does not occur acutely. Evidence of effects on the thyroid is often based on laboratory studies, and many patients are asymptomatic.

25. An otherwise healthy 18-year-old female is diagnosed with high-risk neuroblastoma after presenting with fatigue and bony pain. Imaging findings demonstrate a left adrenal mass with multiple osseous metastases. She successfully completes standard therapy for high-risk neuroblastoma, but experiences several episodes of disease recurrence and ultimately dies of her disease 10 years after her initial diagnosis. During her treatment, her tumor was sent for molecular analysis. Of the following, what molecular aberration was most likely to have been detected?

A. *ETV6-NTRK3* gene fusion
B. *PTPN11* mutation
C. *ATRX* mutation
D. *WT1* mutation
E. *MYCN* amplification

Answer: C
Explanation
Inactivating mutations in the *ATRX* chromatin remodeling gene are found in 14% of patients with high-risk neuroblastoma and in 44% of adolescent and adult patients with metastatic neuroblastoma. In addition to the association with older age at diagnosis, this mutation is

associated with an indolent disease course and poor overall survival, as is seen in this patient's case. *ETV6-NTRK3* gene fusions are characteristic of infantile fibrosarcoma and cellular congenital mesoblastic nephroma. Although *NTRK* aberrations can be seen in neuroblastoma, this specific fusion product is not. *PTPN11* mutations are seen in neuroblastoma, particularly in patients with a germline mutation and phenotypic evidence of Noonan's syndrome. These mutations are also not associated with older age or an indolent disease course. *WT1* mutations are not associated with neuroblastoma. *MYCN* amplification is incorrect because the incidence of *MYCN* amplification is low in older patients with neuroblastoma (approximately 3%), whereas the incidence of *ATRX* mutations is higher. Of note, *ATRX* mutations are mutually exclusive of *MYCN* amplification in neuroblastoma.

9. Wilms' Tumor and Other Renal Tumors

26. A 2-year-old girl has a diagnosis of overall stage IV favorable histology Wilms' tumor with pulmonary metastases and local stage III disease due to finding positive lymph nodes. After she completes 6 weeks of vincristine/dactinomycin/doxorubicin (DD4A) chemotherapy, restaging shows complete resolution of some but not all lung nodules. Tumor genetic testing reveals combined loss of heterozygosity for 1p and 16q.

Which of the following would be the most appropriate treatment plan?

A. Continue chemotherapy with vincristine, doxorubicin, and dactinomycin to complete 25 weeks of therapy. Administer radiation to lungs and flank.
B. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks of therapy. Radiation to flank only. No lung radiation.
C. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to flank only. No lung radiation.
D. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to lungs and flank.
E. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks. Whole abdomen radiation and lung radiation.

Answer: D
Explanation
Choices A, and B are incorrect as treatment with 5 drugs is superior to 3 drugs with lung radiation in patients with stage IV FHWT with either slow incomplete response, or pulmonary metastases, and/or in patients with combined loss of heterozygosity (LOH; 1p and 16q). Option C is incorrect because lung radiation therapy (RT) is indicated both for patients with LOH of 1p and 16q and for patients with slow incomplete response of pulmonary lesions.

Option D is correct because the use of vincristine/dactinomycin/doxorubicin (DD4A) with the addition of cyclophosphamide and etoposide (Regimen M), along with lung radiation, was shown to improved event-free survival (EFS) and overall survival (OS) from treatment with

DD4A and radiation therapy for patients with stage IV FHWT with slow incomplete response of pulmonary nodules, as well as for the group of patients with combined LOH of 1p and 16q. As this patient has both risk factors, Regimen M chemotherapy and appropriate radiotherapy fields would be the recommended therapy.

Option E is incorrect as whole abdomen radiation is not indicated for stage III local disease due to positive lymph nodes and as noted above, the addition of cyclophosphamide and etoposide improves clinical outcomes in patients with stage III and IV disease with combined LOH of 1p and 16q.

27. A 3-month-old female presents to the emergency room with vomiting and abdominal distension. She has a left-side abdominal mass, and an abdominal ultrasound confirms an 8-cm mass arising from the left kidney. Liver lesions are also noted. Nephrectomy is performed and reveals a histologic diagnosis of malignant rhabdoid tumor of the kidney (MRTK). Which of the following is not a true statement about the management of this patient?

A. Most patients with rhabdoid tumor of the kidney present in infancy.
B. Most patients with rhabdoid tumor of the kidney present with metastatic (stage III or IV) disease.
C. She has an excellent prognosis with surgery, chemotherapy, and radiation.
D. Germline testing for SMARCB1/INI1 mutation on chromosome 22 is recommended, with brain MRI every 3 months until she is 5 years old, if testing is germline positive for SMARCB1/INI1.
E. EZH2 methyltransferase inhibitors are under investigation as potential therapeutic agents for rhabdoid tumors because of their mechanism of action.

Answer: C
Explanation
Options A and B are both true statements, so they are incorrect.

Option C is the correct answer because this is *not* a true statement. Prognosis is poor for patients with renal rhabdoid tumor despite intensive chemotherapy, surgery, and radiation; it is especially poor for young infants with metastatic disease.

Option D is a true statement. Patients with rhabdoid tumor should be offered germline testing for SMARCB1 (also known as INI1) on chromosome 22 because patients with germline mutations have an increased risk to develop rhabdoid tumors in the brain.

Answer E is also a true statement, as EZH2 inhibition blocks the oncogenic proliferation in some tumors INI1 mutations, and is under investigation in therapeutic trials for MRTK.

28. A 3-year-old nonsyndromic, well-appearing male with no significant past medical history presents with an abdominal mass palpated by his mother when giving him a bath. CT imaging reveals a 9-cm right renal mass without involvement of the inferior vena cava (IVC) and no evidence of tumor thrombus by ultrasound. The left kidney appears normal, and there is no imaging evidence of tumor rupture or adherence to surrounding organs. There are diffuse, bilateral pulmonary metastases from which he is asymptomatic with a normal respiratory rate and no supplemental oxygen requirement. Following the National Wilms Tumor Study Group (NWTS)/Children's Oncology Group (COG) approach to pediatric renal tumors, which of the following are appropriate next steps?

A. Core biopsy of the renal mass followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin
B. Nephrectomy with lymph node sampling followed by chemotherapy based on histology and stage
C. Fine-needle aspiration followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin
D. Neoadjuvant three drug chemotherapy—vincristine, actinomycin and doxorubicin—followed by nephrectomy at week 6
E. Neoadjuvant three drug chemotherapy—vincristine, actinomycin, and doxorubicin—followed by diagnostic biopsy at week 6 if primary tumor is showing good response to therapy

Answer: B
Explanation
By age and presentation, this patient most likely has favorable-histology Wilms' tumor (FHWT) with pulmonary metastases; however, this can only be confirmed by histologic diagnosis. With this presentation, other pediatric renal tumors remain in the differential, including diffuse anaplastic Wilms' tumor, clear cell sarcoma of the kidney, or malignant rhabdoid tumor.

The National Wilms Tumor Study Group (NWTS)/Children's Oncology Group (COG) recommends upfront nephrectomy over biopsy for all patients (except bilateral or bilaterally predisposed) when feasible. Although the patient has pulmonary metastases, and her disease is therefore designated as overall stage IV, the local stage (kidney) may still be stage I or II. There is no evidence of tumor thrombus (extending to above the level of the hepatic veins), and the tumor is below the size at which risk of intraoperative rupture is increased (12-14 cm). If the diagnosis of this patient is FHWT, with upfront nephrectomy, depending upon intraoperative findings and lymph node status, this patient may be spared flank radiation if stage I or II for nephrectomy.

Option A is incorrect. Although option A can be an appropriate approach in some presentations of renal tumors, following the NWTS/COG approach, upfront biopsy is not recommended when nephrectomy is possible. Option C is incorrect. Fine-needle aspirations are always discouraged for tissue diagnosis in renal tumors because they are inadequate for obtaining important tumor biology and often inadequate for histologic diagnosis. Option D is incorrect. This approach could be appropriate according to treatment guidelines of The International Society of Paediatric Oncology (SIOP), which would recommend initiation of chemotherapy with vincristine,

actinomycin, and doxorubicin; however, these drugs would only be appropriate if the diagnosis is FHWT. This is not the recommended NWTS/COG approach. Option E is incorrect because this management approach is not recommended from either group.

10. Clinical Pharmacology and Targeted Therapies

29. A 2-month-old girl is found to have a small, hard mass on her scalp. The mass increases in size over the next 4 weeks. A biopsy is performed that confirms a diagnosis of embryonal rhabdomyosarcoma. You initiate chemotherapy with vincristine, dactinomycin, and cyclophosphamide. The child presents to clinic for day 1 of cycle 3 of chemotherapy, and the mass on her scalp is smaller. She is afebrile, absolute neutrophil count is 1,405 cells/mcL, platelet count is 154,000/mcL, and total bilirubin is 0.8 mg/dL. Her mother reports she looks very tired because her eyelids have been "very droopy," and she thinks she has a sore throat because her cry is hoarse. Her last bowel movement was 2 days ago.

What is the most appropriate chemotherapy plan?

A. Continue vincristine, dactinomycin, and cyclophosphamide at full dosage.
B. Do not administer any chemotherapy; rhabdomyosarcoma is progressing and she needs different therapy.
C. Administer dactinomycin and cyclophosphamide but hold the vincristine and reevaluate weekly. If the ptosis and hoarse cry resolve, vincristine can be resumed with a dose reduction and, if tolerated, re-escalated to the full dose in the future.
D. Administer dactinomycin and cyclophosphamide but discontinue vincristine permanently.
E. Administer vincristine and cyclophosphamide but do not administer dactinomycin; the ptosis is due to dactinomycin.

Answer: C
Explanation
Vincristine causes peripheral neuropathy, which in infants presents as bilateral ptosis, hoarse cry, los of deep tendon reflexes, and constipation. In older children and adults, foot drop and paresthesia occur. If vincristine is temporarily held until symptoms resolve, it then can be resumed at partial or full dose. Dactinomycin causes myelosuppression and liver dysfunction. Cyclophosphamide causes myelosuppression.

30. A 12-year-old patient with localized osteosarcoma is being treated with cisplatin, doxorubicin, and high-dose methotrexate. The pain at his primary site rapidly resolves after initiation of chemotherapy. After tumor resection, pathology reveals the tumor was greater than 95% necrotic. You want to continue cisplatin, doxorubicin, and high-dose methotrexate.

Which of the following is the best answer regarding the evaluations that should be performed to monitor for toxicity in patients receiving cisplatin, doxorubicin, and high-dose methotrexate?

A. Complete blood count, creatinine, liver function tests
B. Complete blood count, serum electrolytes (sodium, potassium, BUN, chloride), and EKG to monitor for prolonged QTc
C. Complete blood count, creatinine, serum magnesium, audiogram, and echocardiogram
D. Complete blood count, creatinine, serum magnesium, chest x-ray
E. Complete blood count, creatinine, serum magnesium, audiogram

Answer: C
Explanation
Cisplatin is associated with high-frequency hearing loss, which can be symptomatic with tinnitus and requires periodic monitoring with audiogram. Cisplatin also causes decreases in glomerular filtration rate and cation wasting frequently resulting in hypomagnesemia. Although hypomagnesemia can predispose a patient to prolonged QTc, that is a secondary effect. Doxorubicin causes myelosuppression as well as a late effect of decreased left ventricular ejection fraction measured by echocardiogram. High-dose methotrexate is contraindicated in patients with significant acute or chronic kidney disease. Elevated serum creatinine should prompt further evaluation of renal function prior to administration of high-dose methotrexate.

31. A 9-year-old boy is being treated for standard-risk acute lymphoblastic leukemia. His treatment protocol calls for administration of intravenous methotrexate and intramuscular L-asparaginase during interim maintenance chemotherapy.

What is the most appropriate sequence of drug administration?

A. Administer L-asparaginase during the methotrexate infusion.
B. Administer L-asparaginase immediately after the methotrexate infusion.
C. Administer both drugs at the same time to maximize synergistic activity.
D. Administer methotrexate 24 hours after the asparaginase.
E. Administer the L-asparaginase 24 hours after the methotrexate.

Answer: E
Explanation
L-asparaginase can prevent methotrexate toxicity, probably by interfering with the formation of methotrexate polyglutamates intracellularly. Therefore, L-asparaginase is administered 24 hours after methotrexate and is the rationale behind the Capizzi I regimen. The reverse sequence (L-asparaginase followed by methotrexate) or concomitant administration of both drugs can abrogate the anticancer effect of methotrexate.

11. Hemoglobinopathies

32. You have a new patient consult in clinic this morning. The referral packet includes the newborn screen report, which is flagged abnormal hemoglobinopathy screen, F, A, Bart's, refer to hematology, and a complete blood count done at 4 years of age with a hemoglobin of 10 g/dL and an MCV of 68. The pediatrician has informed the parents the child has some form of alpha thalassemia. The older brother had the same newborn screen results but had a normal complete blood count when checked. The mother wants to know why her second child has an abnormal complete blood count when she and her husband do not have any blood problems. How would you respond to the child's mother?

A. The mother and father are both silent carriers and each passed a deleted alpha globin allele to their child. The child inherited a trans-deletion genotype alpha thalassemia trait.
B. The mother has cis deletion alpha thalassemia and the father has no alpha globin deletion, giving the child alpha thalassemia trait.
C. Neither parent has an alpha globin deletion; this was a new spontaneous mutation causing alpha thalassemia in the child.
D. Both parents carry cis deletions in the alpha globin gene cluster.

Answer: A
Explanation
Alpha globin deletions causing alpha thalassemia minor may be inherited in the cis (deletion on the same allele) or trans (deletion on both the maternal and paternal allelles). Option A is the correct answer because individuals with one deleted alpha globin are called *silent carriers* and will have no hematologic abnormalities on complete blood count. Hemoglobin Bart's is only detected at or near birth. If the offspring inherits both parental alleles with one missing alpha globin gene, the child will still inherit two functioning alpha globin, which is consistent with alpha thalassemia trait. Option B is incorrect because if the mother has a cis deletion, then she only has two functioning alpha globin, which would cause changes to her complete blood count, and she would have alpha thalassemia trait and not be a silent carrier. Option C is incorrect because the spontaneous loss of two alpha globin genes, one from each parental gamete, would be statistically unlikely, or the loss of two alpha globin on the same allele for one parental gamete. Option D is incorrect because (a) the parents would have abnormal blood counts, and (b) they have one child who had hemoglobin Bart's but now has a normal complete blood count.

33. A 14-year-old Syrian male with beta thalassemia major has relocated to your community as a refugee. He has been receiving chronic transfusion therapy in Turkey for the past 3 years. On his first visit, you notice that his height is below the fifth percentile. He has skin discoloration and hepatosplenomegaly. His mother reports they have not had regular access to chelation therapy. Laboratory testing shows a serum ferritin of 6,200 ng/mL. A cardiac MRI shows grossly normal cardiac function but a T2* value of 9 ms.

What is the most likely cause of his short stature?

A. Lack of regular blood transfusion causing growth failure
B. Cirrhosis and liver failure
C. Ineffective erythropoiesis and chronic anemia
D. Growth hormone deficiency due to iron deposition in the pituitary
E. Adrenal insufficiency

Answer: D
Explanation
Iron overload damages a number of tissues, including the liver, heart, and endocrine glands. Hepatic toxicity includes fibrosis, cirrhosis, and liver failure. Endocrinopathies include diabetes mellitus, growth hormone deficiency, hypogonadism, hypothyroidism, and adrenal insufficiency. Recommended routine care of thalassemia includes monitoring of thyroid hormone, parathyroid, and vitamin D starting at age 6 years and to add sex hormones such as testosterone, estradiol, LH, and FSH from age 10 years through puberty.

34. A 7-year-old Hispanic male is referred to the hematology consult service by his pediatrician because of concern for hemoglobinopathy. In his records, you find a hemoglobin electrophoresis performed last year which shows hemoglobin A 78% and hemoglobin F 22%. His complete blood count is normal, and he has normal growth and development. Which of the following is true for this patient?

A. There is no diagnosis. These values are normal in children.
B. He has delta-beta thalassemia because he has an elevated hemoglobin F level.
C. Delta-beta thalassemia does not cause microcytosis.
D. Hereditary persistence of fetal hemoglobin results in pancellular hemoglobin F distribution.

Answer: D
Explanation
Fetal hemoglobin (hemoglobin F [alpha^2 gamma^2]) is the major hemoglobin present during gestation and constitutes approximately 60% to 80% of total hemoglobin in the full-term newborn. After birth, a hemoglobin switch occurs, and gamma globin production decreases while beta globin increases, leading to increasing levels of adult hemoglobin, or hemoglobin A. Most people have less than 2% hemoglobin F by the time they are 2 years old. Hereditary persistence of fetal hemoglobin (HPFH) is a benign condition with a wide range of hemoglobin F production from a few percentage in nondeletional HPFH, which produces heterocellular hemoglobin F, to up to 30% in deletional HPFH with pancellular hemoglobin F production.

12. Blood Coagulation Overview and Acquired Hemorrhagic Disorders

35. Which of the following is a key feature of Facto XIII?

A. Its half-life is about 10 days.
B. It is an important activator of thrombin.
C. Its levels are normal in newborns.
D. It is part of the contact activation system.
E. Low levels result in a prolonged PT and PTT.

Answer: A
Explanation
Factor XIII has some unique properties that differentiate it from the other clotting factors, and a key feature is its very long half-life, making A the correct answer. This is important when considering the management of Factor XIII deficiency. In addition, a deficiency of Factor XIII does not prolong the PT and PTT, making it the only factor deficiency that results in a normal PT and PTT, thus E is incorrect. It is not part of the contact activation system (Factor XI and Factor XII are), and it is activated by thrombin and not vice versa, making D and B incorrect. Lastly, similar to most of the clotting factors, its levels are low in the newborn period, making C incorrect as well.

36. Which of the following characteristics are similar with respect to Factor VIII and von Willebrand factor (vWF)?

A. Both are made in endothelial cells and megakaryocytes.
B. Both are activated by thrombin.
C. They are present in normal to high relative amounts in newborns.
D. They are stored in Weibel-Palade bodies in endothelial cells.
E. A deficiency of either one prolongs the PTT.

Answer: C
Explanation
Factor VIII and vWF circulate as a complex in the blood, and both are present in normal to high amounts in newborns, making C the correct answer. Option A is incorrect because Factor VIII is not made in megakaryocytes, and B is incorrect because vWF is not activated by thrombin. Thrombin cleaves Factor VIII from vWF and activates, but vWF circulates as an active protein, although it stays in a dormant form until it binds to subendothelial collagen. vWF is stored in Weibel-Palade bodies but not Factor VIII, so D is incorrect, and a deficiency of vWF without a concomitant reduction in Factor VIII does not prolong the PTT. A severe enough deficiency, however, will result in low circulating Factor VIII levels because Factor VIII is required to be bound to vWF, so a prolonged PTT can result from the low Factor VIII. The majority of patients with type 1 von Willebrand disease, however, can have a quite low vWF level but a normal Factor VIII level, and therefore their PTT is normal.

37. Which of the following alters the function of thrombin from a procoagulant protein to one that downregulates the formation of fibrinogen?

A. Protein C
B. Protein S
C. Antithrombin
D. Thrombomodulin (*)
E. Factor V

Answer: D
Explanation
Thrombin is the key enzyme in the coagulation system. Its activation results in numerous prothrombotic steps (activation of Factor VIII to Factor VIIIa, cleaving fibrinogen to fibrin, activating Factor XIII and thrombin activatable fibrinolysis inhibitor); however, thrombin also plays a key role in limiting the coagulation reaction to the site of endothelial disruption. It does so by binding to thrombomodulin, which is a surface protein that is present on intact endothelial cells (ie, ones from whom bleeding is not occurring). This makes option D the correct answer. Although proteins C and S are key regulators of more thrombin generation, their activation is driven by the binding of thrombin to thrombomodulin—they do not in and of themselves alter the function of thrombin, although their activity ultimately does reduce further thrombin generation. Antithrombin does inhibit thrombin by directly binding to it and forming thrombin-antithrombin complexes, which nullify the activity of each, but antithrombin does not alter thrombin's function, so option C is also incorrect. Factor V serves to activate thrombin and does the opposite of what the question is asking, making option E incorrect.

13. Inherited Bleeding Disorders

38. A 4-year-old girl with a history of recurrent epistaxis and easy bruising is referred to you for evaluation. She is found to have a prolonged PTT and a factor VIII level that is less than 1%. Both parents have a history of excessive bleeding. She is admitted with a severe episode of epistaxis, and your colleague orders 40 IU/kg of recombinant factor VIII. Her epistaxis resolves initially but within an hour starts again at the same severity as before.

What is the best next step?

A. Infuse a von Willebrand factor concentrate.
B. Give another dose of recombinant factor VIII concentrate.
C. Call otorhinolaryngology to pack her nose.
D. Check for a factor VIII inhibitor.
E. Administer desmopressin.

Answer: A
Explanation
There are two key points in this scenario. First, the patient is a girl, which makes it highly unlikely she would have severe hemophilia because of the X-linked inheritance pattern. Second,

both parents have a history of excessive bleeding, suggesting an autosomal recessive pattern of inheritance. Finally, she does not respond appropriately to a recombinant factor VIII concentrate. Such a patient probably has type 3 von Willebrand disease because they have exceedingly low, even unmeasurable factor VIII levels, but it is inherited in autosomal recessive pattern, meaning boys and girls are affected equally. Therefore, the next best step is to infuse a von Willebrand factor concentrate. More factor VIII an hour after the first dose will not help because in the absence of von Willebrand factor, the half-life of infused factor VIII is extremely low. Asking otorhinolaryngology to help is not out of the question, but it will not solve the underlying problem, which is absence of von Willebrand factor. She is unlikely to have an inhibitor, because she had some response to the infused factor VIII, and desmopressin, although helpful in type 1 von Willebrand disease, will not help in type 3 because it works by releasing von Willebrand factor from its storage area, and this patient does not have any von Willebrand factor to release.

39. A 12-year-old girl presents to your clinic with significant menstrual bleeding at the onset of menarche and is noted to have a hemoglobin of 9.9, although she is not symptomatic from her anemia. Her mother reports that she has a history of epistaxis when she was a child with some episodes lasting 30 minutes and that she also has heavy menstrual bleeding. Which of the following tests will lead to the most likely diagnosis?

A. Factor XI level
B. Factor X level
C. Factor XIII level
D. Ristocetin cofactor activity
E. Fibrinogen level

Answer: D
Explanation
Heavy menstrual bleeding at the onset of menarche is a common presentation for bleeding disorders in adolescent girls, and the most common bleeding disorder that results in such symptoms is von Willebrand disease (VWD). The diagnosis of VWD can be made with the ristocetin cofactor activity assay, making D the correct answer. While the other answers can all lead to a diagnosis of a bleeding disorder, deficiencies of Factor X and Factor XIII and fibrinogen are very rare. Factor XI deficiency is more common, especially among Ashkenazi Jews, but does not usually lead to bleeding symptoms in the absence of surgery or trauma.

40. A newborn male has severe bleeding after circumcision, resulting in the need for a blood transfusion. You are called to consult on this child, and you diagnose him with severe hemophilia A. Upon taking a family history, you note that no other family members have hemophilia, other bleeding disorders, or a bleeding diathesis. Which of the following is the most likely outcome of genotyping the Factor VIII gene?

A. No mutation will be found because there is no family history.
B. A missense mutation in the F8 gene will be identified.
C. An inversion mutation in the F8 gene will be identified.
D. A nonsense mutation in the F8 gene will be found.
E. A large deletion of the F8 gene will be found.

Answer: C
Explanation
By far the most common mutations in severe hemophilia A are inversion mutations, with an inversion of intron 22 being the most common, accounting for approximately 45% of the mutations in severe hemophilia, making C the correct answer. The other mutations in options B, D, and E all do occur but are much less common individually. Option A is incorrect because the lack of a family history does not mean this patient won't have a mutation. On very rare occasions, no mutation in the F8 gene is found upon genotyping, but this is most likely technique-related, and with improved sequencing techniques, such instances are becoming even less common.

14. Transfusion Medicine

41. A 16-year-old female patient with severe factor XI deficiency presents with acute appendicitis and requires urgent surgery. You are called by the surgeon, who wants to know what, if any, blood products or treatments are required to reduce the risk of perioperative bleeding. The patient weighs 62 kg. What should you tell him to administer?

A. Cryoprecipitate (five units), which will likely raise her factor XI level to 20%
B. Factor XI concentrate (20 units/kg), which will raise her factor XI level to 20%
C. Fresh frozen plasma (20 mL/kg), which will raise her factor XI level to 20%
D. Prothrombin complex concentrate (40 units/kg), which will raise her factor XI level to 20%
E. Apheresis platelets at 10 mL/kg, which will raise factor XI level to 20% from the release of factor XI stored in platelet alpha granules

Answer: C
Explanation
Fresh frozen plasma is the only blood product that contains factor XI. Typically, 1 mL/kg of fresh frozen plasma will raise the factor level by 1%. Therefore, 20 mL/kg will increase factor XI level to 20%.

Cryoprecipitate contains fibrinogen and factors VIII and XIII, but not factor XI. Prothrombin complex concentrates contain factors II, IX, and X ± VII. Factor XI is neither produced by nor stored in platelets. There is no commercially available factor XI concentrate.

42. A 10-year-old patient with aplastic anemia, who is blood type B negative, is receiving a red blood cell transfusion. About 10 minutes after the transfusion starts, the patient develops anxiety and lower back pain. The transfusion continues for another 5 minutes until it is stopped when he develops a temperature of 40 °C with chills and rigors. A transfusion reaction work-up is most likely to reveal what findings?

A. Spherocytes on peripheral blood smear
B. Gram-negative *Bacillus* on gram stain of remaining RBC unit
C. Chest x-ray with bilateral pulmonary infiltrates that are new compared to an x-ray done last week
D. DAT positive for C3
E. Antibody screen positive for anti-Jk^{a} antibodies

Answer: D
Explanation
The combination of fever, anxiety, and back pain within the first 10 to 15 minutes of a red blood cell transfusion is most consistent with an acute hemolytic transfusion reaction due to ABO incompatibility. Patients who have type B blood will have anti-A antibodies that will fix complement, leading to rapid intravascular hemolysis. Therefore, he will have a DAT positive for C3 (complement). Answer A describes IgG-mediated extravascular hemolysis that can either be due to autoimmune hemolytic anemia or delayed hemolytic transfusion reaction, which is typically 1 to 28 days after transfusion. Spherocytes are seen with a DHTR, not an ABO-incompatible AHTR. Answer B describes a septic transfusion reaction, which can present with fever but is more likely to also present with hypotension rather than anxiety or flank pain. Answer C describes the x-ray findings of a patient with transfusion-related acute lung injury (TRALI), which can present with fever but also respiratory symptoms. Answer E describes what may be found in a patient with delayed transfusion reaction due to evanescent anti-Jk^{a} antibodies that were not detected on the initial screening test.

43. A laboratory study is conducted to determine the optimal usage of platelets for transfusion. The blood bank inventory along with the transfusion records and medical records of subjects who were recipients of platelet transfusion are reviewed. Which of the following conclusions is most likely to be made from this study?

A. Frozen storage of platelets helps increase the units available.
B. Platelet transfusions are rarely successful in patients with autoimmune thrombocytopenia.
C. Platelet units carry no risk for transmission of hepatitis C infection.
D. Pooled donor platelets are preferred over single-donor platelets.
E. Platelet transfusion is not indicated above a level of 10,000/mcL.

Answer: B
Explanation
Autoimmune thrombocytopenia is typically caused by antibodies against ubiquitous platelet antigens; therefore, transfused platelets are likely to be destroyed via the same mechanism as the patient's own platelets. Platelets are stored at room temperature, not frozen. Platelet units can transmit all bloodborne pathogens, including hepatitis C. There is no significant advantage

between whole blood–derived and apheresis platelets; each has advantages and disadvantages compared with the other. In most patients with hypoproliferative thrombocytopenia, a platelet transfusion threshold of 10,000/mcL is appropriate; however, many clinical situations may alter this threshold, including planned surgical or invasive procedures, medications such as anticoagulation, recent history, or current bleeding complications.

44. A 14-year-old male patient is diagnosed with very high risk acute lymphoblastic leukemia and is likely going to require an allogeneic hematopoietic stem cell transplant to cure his leukemia. Prior to going to transplant, he is likely to require multiple blood transfusions. Which of the following products or component modifications is the best way to prevent him from developing alloimmunization due to anti-HLA antibodies prior to transplant?

A. Frozen RBCs
B. Volume-reduced blood products
C. Irradiation of all blood products
D. Monthly IVIg infusions
E. Leukoreduced blood products

Answer: E
Explanation
Avoidance of transfusions is the most effective way to reduce risk of alloimmunization; however, it may not be practical in patients receiving intensive chemotherapy regimens for hematologic malignancies. Leukoreduction of all blood products is effective in reducing contaminating WBCs, which have the highest density of HLA antigens on their surfaces. Frozen RBCs, while effective in reducing contaminating WBCs, are not a practical approach for transfusing patients unless they have hard-to-match RBC transfusion needs. Monthly IVIg infusions will neither prevent nor treat HLA alloimmunization. Irradiation is effective in preventing transfusion-associated graft-versus-host disease (TA-GVHD), but does not affect incidence of HLA alloimmunization.

15. Thrombotic Disorders

45. You receive a phone call that a 3-year-old patient on long-term warfarin therapy for congenital heart disease has an international normalized ratio (INR) of 5.8. On further history, you learn the patient and several family members have had recent gastrointestinal illnesses, but the patient is recovering. His mother reports he is not experiencing bleeding symptoms.

Which of the following interventions would be most reasonable in this clinical scenario?

A. Hold 1 to 2 doses of warfarin and recheck INR
B. Administer oral vitamin K therapy
C. Administer fresh frozen plasma (FFP)
D. Administer recombinant factor VIIa
E. Administer prothrombin complex concentrates (PCCs)

Answer: A
Explanation
Holding warfarin is a reasonable approach for this patient who is not bleeding, is at low risk of subsequent bleeding, and is recovering from his gastrointestinal illness. Vitamin K reverses the action of warfarin but can lead to over-correction. Fresh frozen plasma (FFP) and prothrombin complex concentrates (PCCs) contain vitamin K–dependent proteins but are only indicated in patients with active bleeding or when urgent reversal is required (eg, need for emergency surgery). Evidence does not indicate that recombinant factor VIIa is an effective antidote for warfarin, and this intervention is also associated with a high risk of thrombosis.

46. A healthy 17-year-old African American male presents with a thrombosis of the right upper extremity. His past medical history is remarkable only for sickle cell trait. The history is negative for recent risk factors for thrombosis (illness, surgery, immobility). He is the pitcher for his high school baseball team. Imaging confirms anatomical compression/narrowing of the right subclavian vein.

Which of the following interventions is most likely to decrease this patient's long-term risk of recurrent thrombosis?

A. Systemic thrombolysis
B. Catheter-directed thrombolysis
C. Extended 12-month course of anticoagulation with low-molecular-weight heparin (LMWH)
D. Resection of right first rib
E. Use of compression sleeve during baseball practices and games

Answer: D
Explanation
Although thrombolysis may reduce the risk of post-thrombotic syndrome, there is not evidence that it decreases the risk of recurrent venous thromboembolism (VTE). Likewise, there is also not evidence that 12 versus 3 to 6 months of anticoagulation would reduce risk of long-term recurrence. This patient has an anatomic abnormality (thoracic outlet syndrome) and will continue to be at risk of VTE recurrence unless the abnormality is surgically corrected. Use of a compression sleeve can help alleviate symptoms of post-thrombotic syndrome and improve circulation during activity but will not reduce risk of VTE.

47. A 16-year-old female presents to the emergency room with a new complaint of chest pain. When performing a review of systems and physical examination, which of the following would substantially decrease your suspicion for a diagnosis of pulmonary embolism?

A. Cough
B. Fever
C. Rib tenderness
D. Shortness of breath
E. Normal pulse oximetry

Answer: C
Explanation
Shortness of breath and chest pain are the most common symptoms of pulmonary embolism. Cough and/or fever would make you suspect infection more but are also seen in pulmonary embolism, so the diagnosis would still need to be considered in the differential. Hypoxia can be seen in patients with pulmonary embolism, but most patients will have normal oxygen saturations. Point tenderness of the costal cartilages is highly suggestive of costochondritis, which is one of the most common causes of chest pain in teenagers.

48. The pathophysiology of venous thrombosis is often explained by Virchow's triad, which includes hypercoagulability, endothelial injury, and venous stasis. Based on Virchow's triad and your knowledge of risk factors for thrombosis, which of the following pediatric patients has the greatest risk of hospital-acquired venous thromboembolism?

A. 3-day-old full-term infant admitted to hospital pediatrics for hyperbilirubinemia
B. 6-month-old male admitted to the infectious disease unit for respiratory syncytial virus
C. Ex-28 week premature infant, requiring NICU-level care for necrotizing enterocolitis
D. 7-year-old male with acute lymphoblastic leukemia receiving maintenance chemotherapy admitted to hematology/oncology unit for fever and neutropenia
E. 17-year-old male admitted to the ENT unit for postoperative bleeding and dehydration after recent tonsillectomy

Answer: C
Explanation
Premature infants have among the highest rates of venous thromboembolism (VTE). This patient requires intensive care and would have a central line in place as well as inflammation. The other patients do not requiring critical care, and the patients described in options A, B, and E would not have a central line in place, which is the most important risk factor for VTE in pediatrics. The patient described in option D does likely have a central line, but cancer would be in remission at this point, he is not critically ill, and he would not be receiving asparaginase while in maintenance phases of chemotherapy.

16. Nutritional Anemias

49. Which of the following best characterizes the function of ferroportin in iron metabolism?

A. A form of storage iron in intestinal mucosal cells
B. A transport protein in the plasma
C. A receptor protein on the surface of erythroid progenitors
D. Transmembrane iron exporter
E. A form of storage iron in hepatic cells

Answer: D

Explanation
Ferroportin is the only known iron exporter and is found predominantly, though not exclusively, on enterocytes and reticuloendothelial macrophages. Iron is stored in the tissues as ferritin or hemosiderin, so options A and E are incorrect. Transferrin (option B) binds and transports two atoms of ferric iron (Fe^{+++}) from the intestinal mucosal cell or other sites to erythroid marrow, where it binds to membrane-bound transferrin receptors (option C).

50. A 20-month-old otherwise healthy male presents late for his 18-month well child check. During his first year of life, he took iron-fortified formula and had a point-of-care hemoglobin (Hgb) of 12 g/dL at his 1-year well child check. His mother reports that he is a picky eater but loves milk and has recently become obsessive about chewing the corners of his cardboard books. Physical examination is normal except for a flow murmur. Which combination of laboratory test results listed below would most likely characterize this patient?

A. Hgb 8.7 g/dL, mean corpuscular volume (MCV) 60 fL, serum ferritin 2 ng/mL
B. Hgb 12.0 g/dL, MCV 80 fL, serum ferritin 30 ng/mL
C. Hgb 9.2 g/dL, MCV 60 fL, serum ferritin 30 ng/mL
D. Hgb 11.2 g/dL, MCV 90 fL, serum ferritin 7 ng/mL
E. Hgb 9.8 g/dL, MCV 68 fL, serum ferritin 50 ng/mL

Answer: A
Explanation
Young children who drink excessive cow's milk are at risk for nutritional iron deficiency anemia. In children who previously received iron-fortified formula, the risk is highest during the second year of life after transition to cow's milk. Iron stores initially become depleted, followed by iron-deficient erythropoiesis and finally frank anemia. Children with iron-deficiency anemia have low serum ferritin, therefore options B, C, and E are incorrect. Iron-deficiency anemia results in a microcytic anemia (low mean corpuscular volume), so answer D is incorrect.

51. Assuming that adherence has been excellent, which of the following should have returned to normal 6 weeks following appropriate oral iron treatment for a child with severe dietary iron deficiency (hemoglobin [Hgb] 5.0 g/dL and mean corpuscular volume [MCV] 48 fL at the beginning of therapy)?

A. Hgb concentration
B. MCV
C. Red cell distribution width
D. Peripheral blood smear
E. Serum ferritin

Answer: A
Explanation
In uncomplicated nutritional iron deficiency, the hemoglobin (Hgb) concentration (option A) virtually always returns to the normal range within 6 weeks. The rate of Hgb rise often is quite dramatic. The mean corpuscular volume (MCV; option B) takes 3 months or so to return to

normal. The red cell distribution width (RDW; option C) actually increases for the first 8 weeks following iron treatment as a result of a young population of large, well-hemoglobinized erythrocytes accompanying the older hypochromic microcytic cells from the iron-deficient state. The peripheral blood film (option D), like the RDW and MCV, does not return to normal for 2 to 3 months. Serum ferritin (option E) is the last parameter to normalize.

52. Iron-refractory iron deficiency anemia (IRIDA) is a rare inherited condition characterized by congenital iron deficiency anemia, poor response to oral iron, and partial but incomplete response to intravenous iron therapy. Which is the genetic mutation associated with IRIDA?

A. *TFR2*
B. *H63D*
C. *TMPRSS6*
D. *EPOR*
E. *C282Y*

Answer: C
Explanation
In patients with IRIDA, mutations in *TMPRSS6* (option C) disrupt the "iron sensor" and result in inappropriately high levels of hepcidin, even in iron deficiency. The constitutively elevated hepcidin results in iron-restricted erythropoiesis by impaired release of iron into the plasma from both duodenal enterocytes and RE macrophages. Hepcidin exerts its effect on these cells by binding and degrading ferroportin, the only known cellular iron exporter; therefore, there is no "pump" to bring iron into the plasma, where it is then bound to transferrin. *TFR2, H63D,* and *C282Y* (options A, B, and E) are all mutations that result in hereditary hemochromatosis. *EPOR* (option D) is a mutation of the erythropoietin receptor that results in primary erythrocytosis.

17. Sarcomas

53. You are caring for a patient with a large localized Ewing sarcoma of the soft tissues of the arm. The surgeon believes that the tumor can be resected without amputation but asks whether you can give some chemotherapy to shrink the tumor before surgery.

Which of the following would you tell the surgeon?

A. If the tumor can be resected without amputation, then the best time to do the resection is before any chemotherapy to improve the prognosis.
B. You agree with waiting to do the resection until week 12 of therapy and will begin chemotherapy; you recognize that radiotherapy will not be necessary if the tumor is completely resected at week 12 of therapy.
C. You agree with waiting to do the resection until week 12 of therapy and will begin chemotherapy; you recognize that radiotherapy will be necessary even if the tumor is completely resected at week 12 of therapy.
D. If the tumor can be resected without amputation, then the best time to do the resection is before any chemotherapy; you recognize that this is the only way to avoid radiotherapy.

Answer: B
Explanation
Local control of Ewing sarcoma is generally done after chemotherapy has started. Radiotherapy is not necessary if a complete resection is done after the initiation of chemotherapy. This contrasts with rhabdomyosarcoma therapy, in which radiotherapy is recommended for most patients following delayed primary resection.

54. You are treating a patient with localized osteosarcoma of the distal femur with methotrexate, doxorubicin, and cisplatin (MAP) chemotherapy. At week 10 of treatment, the patient undergoes complete resection of the tumor. Pathology demonstrates 40% necrosis.

Which of the following represents the most appropriate further therapy?

A. Ifosfamide and etoposide (IE)
B. MAP plus ifosfamide and etoposide (MAPIE)
C. Gemcitabine docetaxel
D. MAP
E. Sorafenib

Answer: D
Explanation
Percent necrosis at the time of resection of osteosarcoma has prognostic importance with less than 90% necrosis considered unfavorable. However, a large randomized trial did not show benefit of intensifying MAP therapy with IE (MAPIE). In fact, patients treated with MAPIE had more toxicity, including some evidence for more secondary malignancies. Although all of the regimens listed on the question have activity in osteosarcoma, there is not evidence at this time that switching from MAP to any of them after resection benefits the patient. The failure-free survival for patients with poor necrosis treated with MAP is approximately 50%. It is generally recommended to continue therapy with MAP.

55. You are discussing prognosis with the mother of a patient with stage 3, group III rhabdomyosarcoma.

Which of the following is the most unfavorable primary site?

A. Extremity
B. Prostate
C. Infratemporal fossa
D. Neck
E. Biliary tree

Answer: A
Explanation
The biliary tree and neck are favorable primary sites. The extremity, prostate, and infratemporal fossa are unfavorable primary sites. The least favorable of these sites is consistently the extremity.

56. A 12-year-old patient has been referred to you following complete resection with clean margins of a high-grade malignant peripheral nerve sheath tumor of the shoulder region. The tumor measured approximately 4 cm in greatest dimension. A CT scan of the chest and a bone scan were within normal limits. The patient does not have evidence of neurofibromatosis type 1 (NF1).

Which of the following treatment approaches would you recommend?

A. Chemotherapy with doxorubicin and ifosfamide
B. Radiotherapy
C. Chemotherapy with doxorubicin and ifosfamide plus radiotherapy
D. Observation

Answer: D
Explanation
Optimal therapy for non-rhabdomyosarcoma soft tissue sarcomas remains controversial. The benefit of chemotherapy has been difficult to show. Important prognostic factors include size (≤ or > 5 cm), grade, and resectability (Group). Generally, patients with small tumors (≤ 5 cm) that are completely resected are observed without further therapy. Radiotherapy is used in the setting of either microscopic or gross residual disease. Chemotherapy, usually with doxorubicin and ifosfamide, is given to patients with large (> 5 cm), high grade, unresectable tumors of some histologic subtypes. Malignant peripheral nerve sheath tumor is not considered very chemotherapy sensitive.

18. Acute and Chronic Myelogenous Leukemia

57. You have a new 7-year-old female patient with a WBC count of 6,000/mm3, hemoglobin of 7.2 g/dL, and platelet count of 30,000/mm3. A bone marrow aspirate reveals 14% blasts with a monocytic morphologic appearance that are surface marker positive for CD33. You receive a call from the fluorescence in situ hybridization (FISH) lab that the bone marrow is positive for KMT2A rearrangement in 68% of cells. Your staff asks whether this represents a diagnosis of acute leukemia in the current classification scheme for this type of hematologic malignancy.

What would you say?

A. No, because for a diagnosis of acute leukemia you must have 30% or more blasts in the marrow.
B. No, because for a diagnosis of acute leukemia you must have 20% or more blasts in the marrow.
C. No, because the cytogenetics do not include +21, monosomy 7, or trisomy 8.
D. Yes, because the morphology is monocytic.
E. Yes, because the FISH is positive for KMT2A rearrangement.

Answer: E

Explanation
The patient has a myeloid neoplasm by virtue of the presenting histochemical findings and cell surface markers. The current classification (ie, World Health Organization [WHO]) uses a minimum of 20% blasts in the marrow for a designation of acute myeloid leukemia (AML) versus myelodysplastic syndrome if there are fewer than 20% blasts. In the old French-American-British classification scheme, this cutoff had been 30% or more for a diagnosis of AML. A crucial feature of the WHO classification is that a patient need not have 20% blasts in the marrow for a diagnosis of AML if they have one of a growing list of AML-defining recurrent genetic abnormalities detected by conventional karyotype, fluorescence *in situ* hybridization (FISH), or molecular profiling. These include translocations involving the *KMT2A* gene at chromosome 11q23, formerly known as *MLL*. The most common translocation in AML is the t(9;11)(p21.3;q23.3), which results in the *MLLT3-KMT2A* fusion protein.

58. A 13-year-old Hispanic girl is found to have a WBC count of 6,500/mm3 with 40% Auer rod–containing granular blasts that, by flow cytometry, express very bright CD33 but are negative for human leukocyte antigen–DR isotype (HLA-DR). She is oozing blood around her peripheral IV site. Coagulation studies reveal an international normalized ratio (INR) of 3.4, a fibrinogen of 170, and a markedly elevated D-dimer. Marrow aspirate shows nearly 90% blasts with a similar morphology. You send the marrow to the fluorescence in situ hybridization (FISH) lab and request STAT testing for the most likely recurrent genetic abnormality based on the clinical presentation.

How do you plan to initiate therapy?

A. Perform a lumbar puncture to determine leukemic involvement, then proceed with induction chemotherapy.
B. Begin therapy with all-trans retinoic acid (ATRA) immediately while aggressively managing coagulopathy with blood product support.
C. Start dexamethasone and hydroxyurea immediately while aggressively managing coagulopathy with blood product support.
D. Start induction chemotherapy, obtain HLA typing, and start a donor search because of the poor prognosis associated with this leukemic phenotype.
E. Refer the patient immediately for leukapheresis because of her severe coagulopathy.

Answer: B
Explanation
This case represents a likely diagnosis of acute promyelocytic leukemia (APL; M3 in the French-American-British classification; characterized in most cases by t(15;17) PML-RARA fusion), which has an overall favorable prognosis because of its high event-free survival rates with all-trans retinoic acid (ATRA); arsenic trioxide; and, in high-risk cases, chemotherapy. Thus, stem cell transplant is not indicated in first remission. If the white blood cell count had been greater than 10,000/mm^3 at diagnosis, this would define a higher-risk APL rather than lower risk, in which case cytotoxic therapy with either idarubicin or gemtuzumab would be indicated in addition to ATRA and arsenic trioxide to reduce the risk of differentiation syndrome. Recent data have indicated that prolonged remissions may be possible in lower-risk cases with ATRA and arsenic trioxide alone. Coagulopathy due to disseminated intravascular coagulation is present

in a high percentage of patients with APL, and therefore this should be evaluated before performing a lumbar puncture to avoid the risk of bleeding. Also, central nervous system disease is rare in APL.

59. A 13-year-old girl presents with acute myeloid leukemia (AML) and a WBC count of 120,000/mm3. Cytogenetics reveals a normal karyotype, and fluorescence in situ hybridization (FISH) tests for inv(16), t(8;21), t(15;17); 11q23 abnormalities; monosomy 7; and 5q deletion are negative. Molecular testing is negative for mutations in FLT3, NPM1, and CEBPA. She is treated with 10 days of daunorubicin, AraC, and gemtuzumab for induction therapy. On day 30, she recovers counts, and a bone marrow aspiration shows 2.2% leukemic blasts by flow cytometry. She receives a second course of treatment with daunorubicin and AraC, and her marrow is now in morphologic remission and is MRD-negative by flow cytometry. She has no HLA-matched siblings, but an unrelated donor search reveals a large number of potential matches.

Which course of treatment is most likely to result in the best outcome?

A. Give two more courses of intensification chemotherapy.
B. Perform an autologous hematopoietic stem cell transplant (HSCT).
C. Give one more course of intensification chemotherapy and then perform a matched unrelated donor HSCT.
D. Give one more course of intensification chemotherapy and then 1 year of maintenance chemotherapy.

Answer: C
Explanation
Patients with neither favorable nor unfavorable genetics who have residual leukemia after the first induction course have been shown to have a high risk of relapse with chemotherapy alone. Allogeneic hematopoietic stem cell transplant (HSCT) is likely the optimal therapy in this setting. Continuing chemotherapy alone will be very unlikely to result in cure, and maintenance chemotherapy is not a component of most AML treatment protocols. Similarly, autologous HSCT is also unlikely to provide a curative approach to therapy because of the potential for contaminating leukemia cells in the graft and the lack of a graft versus leukemia effect. Because it will take time to arrange an unrelated allogeneic donor, giving another course of chemotherapy to maintain remission followed by HSCT would be the best of the available treatments.

60. An 18-year old male patient presents with bruising, fatigue, and diffuse extremity pain. He is noted to be tachypneic and hypoxic and has a diffuse interstitial infiltrate on chest x-ray. CBC reveals a WBC count of 285,000/mm3 (85% myeloblasts, with monocytic morphology), hemoglobin of 7.9 g/dL, and platelet count of 36,000/mm3.

What is the most likely cause of the infiltrate and respiratory symptoms and the most appropriate initial treatment?

A. Hyperleukocytosis; initiation of induction chemotherapy
B. Hyperleukocytosis; leukapheresis or manual exchange transfusion and initiation of induction chemotherapy
C. COVID-19 infection; convalescent plasma and prednisone
D. Pneumococcal pneumonia; vancomycin
E. Reactive airway disease; prednisone and albuterol

Answer: B
Explanation
WBC counts greater than 100,000/mm^3 are associated with the clinical syndrome of hyperleukocytosis, especially when the cause of the elevated WBC count is acute myeloid leukemia. Clinical features of hyperleukocytosis can include central nervous system (CNS) findings (eg, lethargy, focal neurological deficits, intracranial bleeding, hemorrhagic stroke), respiratory findings (tachypnea, dyspnea, hypoxia, and diffuse interstitial infiltrates), and renal dysfunction (often complicated by concomitant tumor lysis syndrome). The pathophysiology of hyperleukocytosis includes increased viscosity of blood and resultant congestion within the capillary beds of the affected organs. Hyperleukocytosis is an acute medical emergency that requires immediate "debulking" of the circulating tumor burden, which is best accomplished by manual exchange transfusion or by leukapheresis. Initiation of chemotherapy should proceed as soon as possible but should not be the first step in management. The other choices are less likely in the clinical scenario presented.

19. Biostatistics and Epidemiology

61. In a study to investigate the rates of central line–acquired bacterial infections, it is discovered that patient length of stay (LOS) is not normally distributed but is highly right-skewed.

What is the correct relationship between the mean, median, and mode of LOS?

A. The mean is less than the median but greater than the mode.
B. The mean is equal to the median and the mode.
C. The mean is greater than the median and mode.
D. The mean and median will both be less than the mode.
E. The mean is greater than the median but less than the mode.

Answer: C

Explanation
When data are normally distributed, the mean, median, and mode will all be about the same. This will look like a symmetric distribution of the data. In such cases, "typical" measures can be described by the mean or median or even the mode, for that matter. When the data are skewed right (ie, has a long tail to the right), however, the mean is easily influenced by the extreme values and will be greater than the median and mode. This suggests that the mean is not a very good measure of what is "typical" when the data are right-skewed. When the data are left-skewed, the mean will be less than the median and also will not be ideal for describing "typical" results. When the data are skewed (right or left), the median will be preferable to the mean.

62. A study is designed to investigate the rates of central line–associated blood stream infections among pediatric hematology/oncology patients. Three common central line types (totally implanted catheter [port], peripherally inserted central catheter [PICC], and tunneled externalized catheter [TEC]) were included in the study.

What data structure is central line type?

A. Continuous
B. Dichotomous
C. Nominal
D. Ordinal
E. Survival

Answer: C
Explanation
Because the central line type consists of three finite categories—port, PICC, and TEC—which have no inherent ordering, the correct answer is C, nominal. Continuous measures can take on any value within a specified interval. Survival data record the time to a specific event and, depending on the unit of time, are often treated as continuous data. Nominal data can assume only finite categories that do not have an inherent numerical ordering. Central line type in this question is this type of data because there are three categories that have no numerical relationship. Dichotomous data are a special case of nominal data in which the data have only two categories. Ordinal data also are categorical, but the levels of the categories enjoy some numerical association such as education level or income level.

63. A study is designed to investigate the rates of central line–associated blood stream infections (CLABSI) among pediatric hematology/oncology patients. Investigators wish to compare the length of stay (LOS) between subjects receiving three common central line types (totally implanted catheter [port], peripherally inserted central catheter [PICC], and tunneled externalized catheter [TEC]). It is discovered that LOS is not normally distributed.

What is the appropriate test for comparing the LOS between patients receiving the three central line types?

A. Student's *t* test
B. ANOVA
C. Wilcoxon-Mann-Whitney test
D. Kruskal-Wallis test
E. Chi-square test

Answer: D
Explanation
Length of stay (LOS) is typically a continuous variable, indicating that the type of test must be appropriate for that type of data. This rules out the chi-square test, which is specific for categorical data comparisons. We further learn the investigators wish to compare LOS between three groups of patients. This would suggest that the appropriate test is either ANOVA, if the data are normally distributed, or Kruskal-Wallis, if not. This is because Student's *t* test and the Wilcoxon-Mann-Whitney test are indicated for comparisons of two groups. Because we additionally learn the data are not normally distributed, the appropriate test will be the Kruskal-Walli test.

20. Bone Marrow Failure

64. You examine a 10-year-old boy with severe aplastic anemia. He has no dysmorphic features and is at the 50th percentile for height and weight. Family history includes a sister with aplastic anemia unresponsive to anti-human thymocyte globulin (ATG) and cyclosporine who died early in the course of an unrelated donor hematopoietic stem cell transplant complicated by severe mucositis and transplant-related organ toxicities. There are no other siblings. A cousin died of acute myeloid leukemia at age 5 years. A peripheral blood sample test for Fanconi anemia is negative with no increased chromosomal breaks in response to diepoxybutane or mitomycin C.

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

A. Administer ATG and cyclosporine.
B. Search for a donor for matched unrelated transplant.
C. Send a bone marrow aspirate for Fanconi anemia testing.
D. Send a skin fibroblast culture for Fanconi anemia testing.
E. Start oral therapy with oxymetholone.

Answer: D
Explanation
A family history of a sibling with aplastic anemia and a cousin with pediatric acute myeloid leukemia raises the possibility of an inherited bone marrow failure syndrome (IBMFS) even in the absence of other clinical stigmata such as congenital anomalies. The significant transplant-related toxicity experienced by the sibling is suggestive of an IBMFS such as Fanconi anemia. A reduced-intensity transplant conditioning regimen would be indicated for a patient with Fanconi anemia. Peripheral blood tests for Fanconi anemia may be negative if the lymphocytes have reverted to wild type (somatic mosaicism). The gold standard to establish the diagnosis of Fanconi anemia or conclusively exclude it in this situation is to test skin fibroblasts. There is no advantage to testing the bone marrow aspirate for chromosomal breakage because somatic mosaicism also has been reported in the hematopoietic cells, and chromosomal breakage assays have not been standardized for marrow samples. Patients with Fanconi anemia typically fail to respond to anti-human thymocyte globulin and cyclosporine therapy for aplastic anemia. Oxymetholone is commonly used to support blood counts in Fanconi anemia patients but should not be considered until a diagnosis is confirmed and transplant options considered.

65. A 5-year-old girl with a previously normal CBC now presents in your office with a hemoglobin of 8.5 g/dL, corrected reticulocyte count of 0.1%, and mean corpuscular volume of 80 fl. White cells and platelets are normal in number and morphology. Bilirubin, LDH, BUN, creatinine, and urinalysis are normal. Direct and indirect antiglobulin tests are negative. Workup for infection, including parvovirus, is negative. Occult blood in her stools is negative. Physical examination is unremarkable. She has had no restriction in her energy or activities and the family agrees she is "fine."

What is the most appropriate next step in management?

A. Administer erythropoietin.
B. Initiate a red cell transfusion.
C. Observe serial hemoglobin values closely.
D. Prescribe oral iron supplement.
E. Send red cell adenosine deaminase (eADA).

Answer: C
Explanation
This patient has normocytic red cell aplasia, the most common causes of which are Diamond-Blackfan anemia (DBA) and transient erythroblastopenia of childhood (TEC). DBA, which is often associated with an elevated erythrocyte adenosine deaminase level, typically presents in infancy with macrocytic red cell aplasia but may present in adulthood with normalization of the mean corpuscular volume (MCV) for age. TEC typically presents at an older age than DBA, and the MCV is typically normal. In an asymptomatic patient, transfusion may be deferred at this hemoglobin level. Thus, this patient is most likely to have TEC, and close clinical observation of her blood counts (and clinical status) for the need for a transfusion is the indicated management. An eADA may help to clarify your thinking that this is TEC, but likely, by the time you have the result, blood counts will have recovered and it will be unnecessary. Close observation will still be required. Erythropoietin levels are typically already high with red cell aplasia, and additional

exogenous dosing is not beneficial. Although she is anemic, the MCV does not demonstrate microcytosis, which should predate the anemia if the cause were iron insufficient hematopoiesis.

66. You are consulting on a 10-year-old male with severe persistent neutropenia, a history of recurrent infections, and warts. The rest of the peripheral blood count is normal. His mother also has neutropenia. Bone marrow examination shows a hypercellular marrow and retained myeloid cells with vacuolated cytoplasm. There are no abnormalities in the red cells or platelet precursors. Cytogenetics are 46XY. You start granulocyte colony stimulating factor therapy and the neutrophil count increases.

A mutation in which of the following genes is most likely to have caused this familial inherited bone marrow failure syndrome?

A. *CXCR4*
B. *ELANE*
C. *GATA 2*
D. Mitochondrial DNA
E. *SBDS*

Answer: A
Explanation
This patient has isolated neutropenia, with associated infections, and warts. While all of the genes listed are associated with an inherited bone marrow failure syndrome (IBMFS) with neutropenia, the one associated with myeloid hyperplasia of the marrow is *CXCR4,* which is mutated in myelokathexis/WHIM syndrome. In WHIM syndrome (neutropenia with warts, hypogammaglobulinemia, infections, and myelokathexis), autosomal dominant mutations in *CXCR4* cause a gain of function defect that results in a limitation of down regulation after stimulation. Granulocyte colony stimulating factor (G-CSF) ameliorates the neutropenia and apoptosis as well as the hypogammaglobulinemia that accentuates the infections seen in the disorder. While *ELANE,* which is mutated in many of the congenital neutropenia syndromes and *SBDS* in Shwachman-Diamond syndrome, cause neutropenia and will respond to G-CSF, they are not associated with warts or a hypercellular marrow unless malignant transformation has occurred. Mitochondrial DNA mutations are seen in Pearson syndrome in association with vacuolated marrow precursors and ringed sideroblasts (the later are absent here), usually in a patient with a history of metabolic disturbances, exocrine pancreatic dysfunction, and thrombocytopenia. The neutropenia of Pearson syndrome is not usually severe enough to require G-CSF when the patient is otherwise well. *GATA 2* mutations are associated with MonoMAC syndrome (among others) whose hallmarks are monocytopenia, recurrent mycobacterial infection, and warts).

21. Cancer Predispositions

67. You are consulted on a 4-year-old girl who is newly diagnosed with standard-risk pre-B acute lymphoblastic leukemia. After reviewing her previous complete blood examinations, you note she has had a platelet count ranging from 80,000 to 100,000 cells/mcL over the past 2 years. Her father mentions that he has also been told he has mild thrombocytopenia. You suspect the child may have a cancer predisposition syndrome.

Which sample should you send for analysis, and which gene is most likely implicated?

A. Skin fibroblasts to evaluate the *RUNX1* gene
B. Skin fibroblasts to evaluate the *ETV6* gene
C. Buccal swab to evaluate the *RUNX1* gene
D. Buccal swab to evaluate the *ETV6* gene
E. Skin fibroblasts to evaluate the *TP53* gene

Answer: B
Explanation
The correct sample to analyze for a leukemia predisposition syndrome is cultured skin fibroblasts, making answer choices C and D incorrect. Buccal swabs may contain peripheral blood mononuclear cells, which circulate throughout the mucosa and are also found in saliva. These blood mononuclear cells may provide false positive results, particularly in a patient who is newly diagnosed with leukemia and may have circulating blasts. The correct gene to explain this patient's phenotype is *ETV6*, making answer B correct. Thrombocytopenia 5, which is caused by germline pathogenic variants in *ETV6*, is the most common leukemia predisposition syndrome linked to pre-B acute lymphoblastic leukemia (ALL) with a preceding history of mild thrombocytopenia. Li-Fraumeni syndrome, caused by pathogenic variants in *TP53*, is associated with development of low hypodiploid pre-B ALL, and typically the family history is positive for solid tumors, not thrombocytopenia. Pathogenic variants in *RUNX1* cause familial platelet disorder with associated myeloid malignancy and are much more commonly associated with the development of acute myeloid leukemia (AML) than ALL.

68. You receive a phone call from a community pediatrician who is caring for a 2-year-old toddler with a cancer predisposition syndrome. The pediatrician describes a child at the 95th percentile for height and weight with a history of corrective oral surgery to reduce a large tongue and a history of an omphalocele in infancy. The pediatrician is currently performing ultrasound of the abdomen and laboratory evaluation for this patient every 3 months.

Which tumor is this patient most at risk of developing?

A. Pleuropulmonary blastoma
B. Hepatocellular carcinoma
C. Cystic nephroma
D. Nephroblastoma
E. Pheochromocytoma

Answer: D
Explanation
The pediatrician has described a child with Beckwith-Wiedemann syndrome (BWS), which carries an increased risk for hepatoblastoma and nephroblastoma (Wilms' tumor), making answer choice D the correct answer. Pleuropulmonary blastoma occurs in patients with *DICER1* syndrome, making option A incorrect. Patients with BWS do not develop hepatocellular carcinoma, making option B incorrect. Cystic nephromas develop in patients with *DICER1* syndrome, making choice C incorrect. Pheochromocytomas occur in patients with BWS exceedingly rarely, therefore the child is most at risk for developing Wilms' tumor, making option E incorrect.

69. You are seeing a 12-year-old boy in the survivorship program who presented at 2 years old with a desmoplastic nodular medulloblastoma. You note the child recently underwent germline genetic testing and was found to have nevoid basal cell carcinoma syndrome.

In which gene is the child most likely to have a pathogenic variant?

A. *PTEN*
B. *CDKN2A*
C. *SUFU*
D. *SMARCB1*
E. *TP53*

Answer: C
Explanation
Nevoid basal cell carcinoma syndrome, also known as Gorlin syndrome, is caused by a pathogenic variant in either the *PTCH1* or *SUFU* gene. Pathogenic variants in *SUFU* are more commonly linked to the development of desmoplastic nodular medulloblastoma in early childhood, making answer choice C correct. Option A is incorrect because pathogenic variants in *PTEN* are not linked to the development of desmoplastic nodular medulloblastoma. Option B is incorrect because *CDKN2A* is linked to familial melanoma and is unrelated to development of medulloblastoma. Option D is incorrect because pathogenic variants in *SMARCB1* are linked to the development of atypical teratoid/rhabdoid tumor. Option E is incorrect because patients with pathogenic variants in *TP53* are more likely to develop low- or high-grade gliomas.

70. A 10-year-old girl is a long-term survivor of type II pleuropulmonary blastoma (PPB). You suspect she has a cancer predisposition syndrome and perform genetic testing, which confirms she has DICER1 syndrome.

Which other cancer is she predisposed to?

A. Papillary thyroid cancer
B. Medullary thyroid cancer
C. Pheochromocytoma
D. Renal cell carcinoma
E. Osteosarcoma

Answer: A
Explanation
Pleuropulmonary blastoma (PPB) is highly associated with *DICER1* syndrome. Other tumors in this cancer predisposition syndrome include papillary thyroid carcinoma, making A the correct answer. Medullary thyroid cancer is associated with multiple endocrine neoplasia (MEN2), therefore option B is incorrect. Pheochromocytomas are linked to pathogenic variants in the *SHDx* gene family and not associated with *DICER1,* making option C incorrect. Renal cell carcinoma is linked to hereditary leiomyosarcoma and renal cell carcinoma predisposition or Von Hippel-Lindau, making option D incorrect. Osteosarcoma is linked to Li-Fraumeni syndrome, making option E incorrect.

22. Congenital and Acquired Hemolytic Anemias

71. A newborn infant develops jaundice on day of life 2. Labs are drawn, and she has a hemoglobin of 7.4 g/dL with a reticulocyte count of 8%. Upon peripheral blood smear review, she is found to have bizarre red cell forms with significant poikilocytosis. Although her parents have normal blood counts, on review of their peripheral blood smears, they both have a moderate number of ovalocytes. Which of the following is the most likely cause of the infant's red cell findings?

A. She has an autosomal dominant ankyrin mutation from one of her parents causing hereditary spherocytosis.
B. She has inherited band 3 variants from each parent and will likely need a splenectomy after she turns 5 years old.
C. She has inherited an alpha-spectrin mutation from both of her parents and may experience an improvement in her anemia over time.
D. She has inherited a *PKLR* variant from each parent, and enzyme testing will be consistent with her diagnosis of pyruvate kinase deficiency.

Answer: C
Explanation
The parents of this patient have normal blood counts and peripheral blood smear findings consistent with hereditary elliptocytosis, and this newborn has findings consistent with hereditary pyropoikilocytosis. Hereditary pyropoikilocytosis has an autosomal recessive pattern with a family history of hereditary elliptocytosis and is most often caused by alpha-spectrin mutations inherited in trans. The hemolysis can be severe but, in some patients, improves with age.

Answer A is incorrect because ankyrin mutations typically cause hereditary spherocytosis (HS; associated with approximately 50% of cases). The parents' normal labs and their peripheral blood smears are not consistent with autosomal dominant HS in this family. Answer B is incorrect because, like answer A, band 3 mutations cause autosomal dominant HS. Answer D is less likely because carriers of one copy of a *PKLR* variant typically have no clinical findings by blood counts or peripheral blood smear and affected non-splenectomized infants often have a relatively bland peripheral blood smear.

72. A 10-year-old girl has had transfusion-dependent anemia since age 6 months. She is found to have an unstable hemoglobin by sequence analysis (Hb Indianapolis). She has jaundice, obvious bony deformity from extramedullary hematopoiesis, and hepatosplenomegaly.

Which of the following statements is correct?

A. Her diagnosis should have been picked up on newborn screen by electrophoresis, isoelectric focusing, or high-performance liquid chromatography similar to other beta-hemoglobinopathies.
B. Since her spleen is intact, her peripheral blood smear cannot have nucleated red cells or Howell Jolly bodies.
C. If she undergoes splenectomy, her anemia should be entirely ameliorated.
D. Since she is transfused, she will not be at risk for gallstones.
E. If she undergoes splenectomy, she will be at long-term risk for both infections and thrombosis.

Answer: E
Explanation
Splenectomy is associated with risk of infections, including encapsulated organism bacteremia as well as more severe infections with other organisms including babesia and malaria. In addition, splenectomy for nonmalignant hematologic conditions is associated with an increased risk of thrombosis. Hereditary xerocytosis, which this patient does not have, appears to be associated with the highest risk of thrombosis after splenectomy.

Answer A is incorrect because unstable hemoglobins, like Hb Indianapolis, are hard to detect in the periphery, particularly when beta-globin is at a lower quantity in the newborn period. Answer B is incorrect because nucleated red cells and Howell Jolly bodies can both be seen in patients with intact spleens and increased marrow stress from ineffective or increased erythropoiesis and/or hyposplenism. Answer C is incorrect for unstable hemoglobins and for most hemolytic states except hereditary spherocytosis. However, transfusion requirements may be partially ameliorated by splenectomy. Answer D is incorrect because this patient has ineffective erythropoiesis associated with indirect hyperbilirubinemia and this will continue, albeit likely at a more suppressed rate, even in the setting of transfusions.

73. A 5-year-old boy is evaluated for apparent ongoing hemolysis. His hemoglobin is 9.5 g/dL, with 8% reticulocytes and MCV 87 fL. Platelets and leukocytes are normal. His direct antiglobulin test (DAT) is negative. No cold agglutinin is detectable. His family history is negative for blood disorders. Peripheral smear reveals basophilic stippling in 10% of the red blood cells.

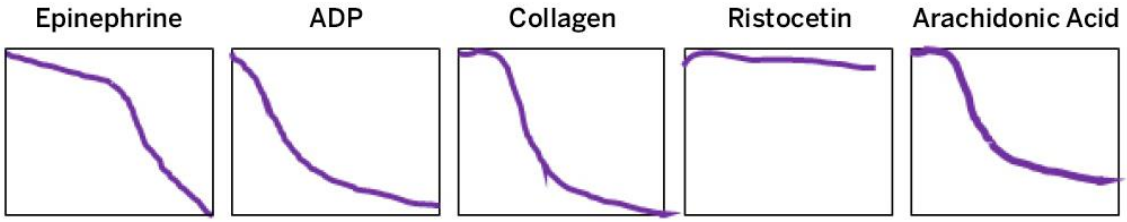
Given these findings, which of the following blood disorders is most likely?

A. Rh-null disease
B. Hereditary pyropoikilocytosis
C. Glucose phosphate isomerase deficiency
D. Unstable hemoglobin
E. Pyrimidine 5'-nucleotidase deficiency

Answer: E
Explanation
Pyrimidine 5'-nucleotidase (P5'-N) deficiency is the third most common enzyme disorder after G6PD deficiency and pyruvate kinase deficiency. P5'-N is autosomal recessive and is associated with pronounced basophilic stippling due to accumulation of pyrimidine nucleotides in erythrocytes. Answer A is incorrect because Rh-null disease is associated with stomatocytosis. Answer B is incorrect because pyropoikilocytosis is associated with a diagnosis of hereditary elliptocytosis (HE) in family members and bizarre forms and significant poikilocytosis on peripheral blood smear. Answer C is incorrect because glucose phosphate isomerase (GPI) deficiency typically has a relatively bland peripheral blood smear and is not associated with basophilic stippling. Answer D is incorrect because unstable hemoglobins are not associated with basophilic stippling but are often associated with Heinz bodies.

23. Disorders of Platelets

74. An 18-month-old boy, whose parents are first cousins, is referred to you because of a significant episode of epistaxis. The parents report that the child had bleeding after circumcision and large hematomas with immunizations. Platelet aggregation studies show the following:



This child's platelets are unable to interact with which of the following?

A. ADP
B. Fibrinogen
C. von Willebrand factor
D. Platelet factor 4
E. ADAMTS13
F. Collagen

Answer: C
Explanation
The platelet aggregation study results here are consistent with those seen in Bernard-Soulier syndrome. This is an autosomal recessive condition due to an absence of glycoprotein Ib-IX, which results in macrothrombocytopenia and poor platelet function. Glycoprotein Ib-IX causes platelet adhesion to the vascular endothelium via von Willebrand factor (vWF).

Glycoprotein VI binds collagen. Glycoprotein IIb-IIIa binds to fibrinogen and is absent in Glanzmann thrombasthenia. Absence of dense granules would result in a lack of second-wave aggregation to adenosine diphosphate (ADP) and epinephrine, and this pattern is seen in dense granule disorders like Hermansky-Pudlak syndrome. ADMATS-13 is the metalloprotease that breaks down ultralarge vWF multimers. If this is blocked by an antibody or reduced, then the patient would develop thrombotic thrombocytopenic purpura.

75. A patient is scheduled for upcoming surgery. He is on nonsteroidal anti-inflammatory drugs (NSAIDs) for rheumatoid arthritis. You are being asked what to do with his medications for the surgery.

What is the mechanism of action of NSAIDS?

A. Irreversible inhibition of cyclooxygenase 1
B. Irreversible inhibition of cyclooxygenase 2
C. Reversible inhibition of cyclooxygenase 1
D. Reversible inhibition of cyclooxygenase 2
E. Direct inhibition of ADP

Answer: C
Explanation
Both acetylsalicylic acid (ASA; Aspirin) and nonsteroidal antiinflammatory drugs (NSAIDs) have their platelet effect through inactivation of cyclooxygenase (COX), and therefore cause platelet dysfunction by inhibiting the formation of thromboxane A2. NSAIDs reversibly block COX, so the effect on platelet function is related to the half-life of the drug. Aspirin, on the other hand, irreversibly inactivates cyclooxygenase (COX), and so will have an effect for the duration of the platelet lifespan, approximately 7 to 9 days. Both of these drugs have an antiplatelet effect through COX-1 inhibition. COX-2 inhibition is shown by NSAIDs and results in anti-inflammatory effects. Direct inhibition of adenosine diphosphate (ADP) is the mechanism of action of newer antiplatelet agents, such as dipyridamole and clopidogrel, by blocking of the GPIIb/IIIa complex.

76. A 17-year-old patient is referred to you for a platelet count of 1,200,000/mm3. On history, she notes that she often has numbness and tingling in her hands and feet and has frequent epistaxis. She is otherwise well-appearing and has no recent infections. On her exam, you note splenomegaly.

What do you expect to see on further evaluation?

A. Elevated C-reactive protein
B. Low ferritin
C. A hypocellular bone marrow
D. Low von Willebrand factor activity
E. Low thrombopoietin levels

Answer: D
Explanation
The teenager described here likely has essential thrombocytosis. She currently is having paradoxical bleeding in the form of epistaxis despite having thrombocytosis. Patients with essential thrombocytosis can develop acquired von Willebrand disease (VWD), and all patients with essential thrombocytosis should have screening for acquired VWD even in the absence of bleeding because this may impact decisions about treatment with antiplatelet therapy. She does not have any clinical symptoms that would indicate that she has thrombocytosis in reaction to inflammation. In addition, she is symptomatic from her thrombocytosis, which usually is not seen in patients with reactive thrombocytosis. Therefore, her C-reactive protein (CRP) would be expected to be normal. Although iron deficiency can cause thrombocytosis, it is usually not this significant and also would not be associated with clinical symptoms. In essential thrombocytosis, the thrombopoietin level will be elevated and the bone marrow is hypercellular with increase in megakaryocytes.

24. Lymphoma

77. A 15-year-old female presents with 1 month of fatigue and 3 days of chest pain and shortness of breath. Her physical exam is unremarkable. A chest x-ray shows a large mediastinal mass that is greater than 33% of the diameter of her chest cavity. A biopsy shows nodular sclerosing, classic Hodgkin lymphoma (cHL). Metastatic workup at diagnosis, including CT scan of neck, chest, abdomen, and pelvis and PET scan, shows no other site of disease. According to the Ann Arbor staging system, the patient has which stage of cHL?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV

Answer: A
Explanation
The Ann Arbor staging system takes into account that Hodgkin lymphoma typically spreads along contiguous lymph nodes, and extranodal involvement usually results from direct extension of nodal disease. Hematogenous spread does not usually occur until disease is very advanced.

The Ann Arbor Staging System

Stage I: A single node region (I) or single extranodal organ or site (IE)
Stage II: Two or more node regions on the same side of the diaphragm (II) or one node region and localized extranodal site on the same side of the diaphragm (IIE)
Stage III: Node regions involved on both sides of the diaphragm (III) or with localized extranodal site involved (IIIE) or spleen involvement (IIIS)
Stage IV: Diffuse or disseminated involvement of more than one extranodal site

Extranodal structures contiguous with sites of lymph node involvement are considered E-lesions and include lung, pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion. Pleural and pericardial effusions alone are not considered E-lesions. Liver and bone marrow are not E-lesions but are considered stage IV.

Substage classifications are based on defined clinical features and are used in risk stratification. Substage A indicates asymptomatic disease. Substage B indicates the presence of B symptoms, which include fever greater than 38 °C for 3 consecutive days, drenching night sweats, and unexplained weight loss of at least 10% body weight over a 6-month period.

Bulk disease is not part of the Ann Arbor classification but has been used by some groups in risk stratification. Bulk disease includes large mediastinal mass with tumor diameter greater than one-third of the thoracic diameter on an upright posterioranterior chest x-ray, large extramediastinal nodal aggregate measuring greater than 6 cm in the longest transverse diameter, and macroscopic splenic nodules seen on CT, PET, or MRI imaging.

78. A 15-year-old female presents with 1-month history of fatigue and a 3-day history of chest pain and shortness of breath. Her chest x-ray shows a large mediastinal mass that is greater than 33% of the thoracic diameter at the level of the diaphragm. A biopsy shows diffuse large B-cell lymphoma. Metastatic work-up, including a CT scan of neck, chest, abdomen, and pelvis; bone marrow biopsy; lumbar puncture; and PET scan show no other site of disease. According to the St. Jude (Murphy) staging system, what is the stage of this patient's non-Hodgkin lymphoma (NHL)?

A. Stage I
B. Stage II
C. Stage III
D. Stage IV

Answer: C
Explanation
The St. Jude (Murphy) staging system frequently is used for non-Hodgkin lymphoma (NHL) in children because the Ann Arbor staging system does not adequately reflect prognosis. Childhood NHL does not progress in the orderly and predictable lymphatic pattern that Hodgkin lymphoma does, and extensive extranodal disease is common.

The St. Jude (Murphy) Staging System for NHL

Stage I: Single nodal or extranodal tumor excluding the mediastinum and abdomen
Stage II:
a) Single tumor (extranodal) with regional node involvement, or
b) Two or more nodal areas on the same side of the diaphragm, or
c) Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm, or
d) Primary gastrointestinal tract tumor that is resectable, usually in the ileocecal area with or without involvement of associated mesenteric nodes

Stage III:
a) Two single tumors (extranodal) on opposite sides of the diaphragm, or
b) Two or more nodal areas above and below the diaphragm, or
c) Any intrathoracic disease (lung, pleura, mediastinum, and thymic) or
d) All extensive, primary intraabdominal disease, or
e) All paraspinal or epidural disease regardless of other tumor sites

Stage IV: Bone marrow and/or central nervous system involvement

Patients with NHL can present with B symptoms, and these symptoms are more common in anaplastic large-cell lymphoma than other NHL. However, unlike in Hodgkin lymphoma, the presence of B symptoms is not used for risk stratification.

79. A 19-year-old freshman in college presents with "lumps" on the right side of his neck and in the right axilla. He had a fever to 39 °C 1 day in the past week. On physical exam, there are firm anterior cervical and axillary nodes, all greater than 2 cm in diameter. A chest x-ray shows a large mediastinal mass. A biopsy of the axillary node reveals classic Hodgkin lymphoma. Which of the following symptoms revealed during the history is a B symptom?

A. Fever to 39 °C
B. 10% weight loss in past 6 months
C. Fatigue
D. Alcohol-induced pain
E. Pruritis
F. A and B

Answer: B
Explanation
In Hodgkin lymphoma, substage classifications are based on defined clinical features and are used in risk stratification. B symptoms include (a) fever higher than 38 °C for at least 3 consecutive days, (b) greater than 10% unexplained weight loss over the preceding 6 months, and (c) drenching night sweats (usually requiring changing of clothing and/or bedding).

Systemic symptoms are common in patients with Hodgkin lymphoma; however, many of these symptoms, such as anorexia and fatigue, are not B symptoms. Alcohol-induced pain of involved nodal areas can occur within minutes after alcohol consumption and resolves with treatment of Hodgkin lymphoma. In addition, pruritis is common at diagnosis, can be mild or severe, and resolves with treatment. The mechanism of neither alcohol-induced pain nor pruritis is known.

80. A 17-year-old female presents with cervical adenopathy and a history of daily fevers and drenching night sweats. A biopsy is performed and reveals classic Hodgkin lymphoma. Which of the following is least appropriate as part of the staging workup?

A. Chest x-ray
B. CT scan of chest, abdomen, and pelvis
C. Functional imaging (PET scan)
D. Lumbar puncture and cerebrospinal fluid (CSF) analysis
E. All of the above are indicated

Answer: D
Explanation
Central nervous system (CNS) involvement by Hodgkin lymphoma is exceedingly rare. Evaluation of the CNS is not routine practice, and CNS prophylaxis is not part of therapy for Hodgkin lymphoma. In contrast, the common pediatric non-Hodgkin lymphoma (NHL) can be widely disseminated at presentation even when the patients appear to present with localized disease on physical examination. Evaluation of CNS with lumbar puncture and CSF cytology is important in the staging workup for pediatric NHL, and CNS prophylaxis is part of treatment for most pediatric NHL.

25. Oncologic Emergencies

81. A 14-year-old boy presents with cough, shortness of breath, and difficulty lying down. His face and neck swell when his arms are raised. Chest x-ray reveals a large mediastinal mass. A tissue diagnosis is desired. A biopsy is performed with local anesthesia because the anesthesiologist thinks that the patient has a very high general anesthesia risk.

Which of the following findings does not make general anesthesia unsafe?

A. Tumor diameter greater than 45% of transthoracic diameter
B. Tracheal cross-sectional area less than 50% of predicted
C. Peak expiratory flow rate less than 50% of predicted
D. A malignancy of hematopoietic origin
E. A large pericardial effusion

Answer: D
Explanation
There are no standard criteria to predict the severity of superior vena cava syndrome (SVCS). Several studies have evaluated anesthesia complication risks. Great vessel and tracheal compression with increasing respiratory symptoms and signs are predictive of anesthesia complications. SVCS results most often from an anterior mediastinal mass that can be caused by Hodgkin or non-Hodgkin lymphoma, T-cell lymphoblastic leukemia, sarcomas, and germ cell tumors. It is usually not caused by neuroblastoma, which can present as a posterior mediastinal mass.

82. A 13-year-old boy presents to the emergency department with complaints of headache and visual changes. History reveals progressive dyspnea on exertion, generalized fatigue, and increased bruising. His labs are significant for a WBC of 350,000/mcL, of which 80% are reported to be blasts and appear to be myeloblasts without the presence of Auer rods. His hemoglobin is 7.2 g/dL, and his platelets are 18,000/mcL. A CT scan of the head shows a small intracerebral hemorrhage. His coags are normal.

Which of the following is the most appropriate therapy?

A. Start induction chemotherapy.
B. Perform emergent leukapheresis followed the next day by induction chemotherapy.
C. Perform emergent leukapheresis plus hydroxyurea.
D. Provide emergent cranial radiation plus hydroxyurea followed the next day by induction chemotherapy.
E. Provide emergent cranial radiation plus emergent leukapheresis and hydroxyurea followed the next day by induction chemotherapy.

Answer: C
Explanation

Patients with acute myeloid leukemia who present with hyperleukocytosis have a life-threatening illness. The primary risk of hyperleukocytosis is leukostasis associated with leukocyte thrombi and aggregates within the vasculature. The immediate objective is to reduce peripheral blast count rapidly to prevent infarction and hemorrhage. This is most quickly done with leukapheresis and should especially be considered in patients with clinical signs and symptoms of leukostasis. Hydroxyurea is often also included as treatment for leukocytosis until it is safe to initiate systemic chemotherapy with the hope that it will decrease the rate of rise in blast percentage. Cranial radiation is not warranted in this setting and may increase risk of cerebral hemorrhage.

83. When reviewing the chemistry panel of a newly diagnosed patient with acute lymphoblastic leukemia who is lethargic, complaining of flank pain, and experiencing nausea and vomiting, which of the following would you expect to see?

A. Potassium 4.5 mmol/L, phosphorus 8 mg/dL, uric acid 7 mg/dL, calcium 9.0 mg/dL, BUN 12 mg/dL, BUN 12 mg/dL
B. Potassium 6.5 mmol/L, phosphorus 8 mg/dL, uric acid 9 mg/dL, calcium 10 mg/dL, BUN 14 mg/dL
C. Potassium 4 mmol/L, phosphorus 9 mg/dL, uric acid 10 mg/dL, calcium 10 mg/dL, BUN 10 mg/dL
D. Potassium 7 mmol/L, phosphorus 12 mg/dL, uric acid 10 mg/dL, calcium 7 mg/dL, BUN 25 mg/dL

Answer: D
Explanation
Tumor lysis syndrome (TLS) is common in newly diagnosed leukemia patients after initiation of therapy. Laboratory results consistent with TLS include hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. These patients may also have kidney injury evidenced by elevated BUN and/or creatinine.

26. Palliative and Supportive Care

84. A 9-year-old child with osteosarcoma is being admitted for cisplatin therapy. What is the best regimen for prevention of chemotherapy-induced nausea and vomiting (CINV)?

A. Palonosetron and olanzapine
B. Dexamethasone and aprepitant
C. Granisetron, dexamethasone at 50% dosing, and aprepitant
D. Granisetron, dexamethasone at 100% dosing, and aprepitant
E. Lorazepam, diphenhydramine, and scopolamine patch

Answer: C
Explanation
Children aged 6 months and older receiving highly emetogenic chemotherapy (HEC) that is *not* known or suspected to interact with aprepitant receive granisetron or ondansetron or palonosetron plus dexamethasone plus aprepitant. When giving aprepitant, dexamethasone

should be given at 50% dosing because both are CYP3A4 substrates. Olanzapine is not currently part of the guidelines for prevention of CINV. All regimens for low, moderate, and highly emetogenic chemotherapy include a $5HT_3$ inhibitor such as ondansetron, granisetron, or palonosetron. Lorazepam is useful for anticipatory nausea and vomiting, although a regimen containing lorazepam, diphendydramine, and scopolamine has multiple antihistamine and anticholinergic agents without any serotonin ($5HT_3$) antagonists or dopamine (D_2) antagonists.

85. A 4-year-old child with acute lymphoblastic leukemia is receiving high-dose methotrexate during interim maintenance. He receives ondansetron and aprepitant during his stay, which control his nausea and vomiting well. These medications work by inhibiting signaling in which part of the brain?

A. Vestibular system
B. Cerebral cortex
C. Hypothalamus
D. Vomiting center
E. Chemoreceptor trigger zone

Answer: E
Explanation
High-dose methotrexate in leukemia therapy (5 g/m^2) is considered moderately emetogenic chemotherapy. Because dexamethasone cannot be given to patients with leukemia as an antiemetic, and the patient is older than 6 months, the patient is on the correct regimen of a $5HT_3$ inhibitor (ondansetron) and a NK_1 inhibitor (aprepitant). Chemotherapy, metabolic products, drugs, and toxins stimulate nausea and vomiting through their effects on the chemoreceptor trigger zone. Blocking $5HT_3$ and NK_1 occurs at the level of the chemoreceptor trigger zone and prevents further signaling to the vomiting center (receptors in the vomiting center being histamine [H_1], m-acetylcholine, and $5HT_2$). Medications that have antidopaminergic (D_2) activity such as olanzapine, haloperidol, and promethazine also work at the chemoreceptor trigger zone. The vestibular system is mediated through histamine and m-acetylcholine. These are relevant in children with motion sickness or labyrinth disorders. Medications that work at the level of the cerebral cortex are lorazepam (anticipatory nausea) and dexamethasone (increased intracranial pressure).

86. A 16-year-old patient with a left-side pelvic osteosarcoma is taking extended release oxycodone twice daily as well as immediate release oxycodone for breakthrough pain approximately 2 or 3 times per day. She describes her pain as burning, tingling, and shooting in her left leg. Her pain worsens with hot showers. Her most recent EKG has a QTc of 495. What would be the best strategy to manage her pain?

A. Switch from long-acting oxycodone to methadone.
B. Recommend more frequent use of her immediate release oxycodone.
C. Add amitriptyline daily. Start low and titrate upward on dosage.
D. Add gabapentin three times daily. Start low and titrate upward on dose.
E. Add sertraline daily. Start low and titrate upward on dose.

Answer: D
Explanation
This patient has both nociceptive pain from her tumor/bony erosion, which is being managed with opioids, and neuropathic pain, likely due to nerve compression from her pelvic tumor. There are multiple classes of medications used to treat neuropathic pain, such as gabapentinoids (gabapentin, pregabalin), serotonin–norepinephrine reuptake inhibitor (SNRIs; venlafaxine, duloxetine), tricyclic antidepressants (TCAs; amitriptyline, nortriptyline), opioids (methadone), and other agents like lidocaine and ketamine. As her QTc is near 500, methadone and amitriptyline should be avoided because they could worsen the QTc prolongation. Sertraline is a selective serotonin reuptake inhibitor (SSRI; antidepressant/antianxiolytic). SSRIs do not treat neuropathic pain like the SNRIs (duloxetine or venlafaxine). Using more oxycodone will probably cause more opioid-induced side effects and is not the best long-term management strategy for neuropathic pain. In this setting, adding gabapentin three times daily, and titrating up slowly to a weight-based dose or adult dose is the best strategy. Gabapentin does not cause QTc prolongation.

27. Research Ethics and Quality Improvement

87. A leukemia investigator plans to obtain bone marrow under general anesthesia to measure minimal residual disease (MRD) and to see if this time point can predict early relapse. The specimen will be obtained at a time point when otherwise no bone marrow would be sampled. The results are not shared with the treating oncologist, and no therapeutic interventions are decided or based on the results. Which of the following statements is most accurate about this intervention?

A. It constitutes a minimal-risk procedure because bone marrow assessments are considered routine for patients diagnosed with acute lymphoblastic leukemia.
B. It constitutes a minimal-risk procedure because it is a single additional procedure being performed during the course of treatment.
C. It constitutes a greater than minimal-risk procedure because it is being done under general anesthesia.
D. It is justifiable because future patients may benefit from knowledge gained by the research.

Answer: C
Explanation
The regulatory definition of "minimal" risk is that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

88. What are the six dimensions of quality care according to the Institute of Medicine?

A. Safe, timely, effective, efficient, equitable, and person-centered
B. Safe, transparent, effective, efficient, equitable, and person-centered
C. Safe, timely, effective, low-cost, equitable, and person-centered
D. Safe, timely, effective, efficient, cutting-edge, and person-centered

Answer: A
Explanation
In their landmark report *Crossing the Quality Chasm*, the Institute of Medicine outlined six major domains of quality health care, which can be remembered using the mnemonic STEEP. These are a good guide for teams to use in developing organizational and project-based aims.

- First, health care must be **safe**. This means much more than the ancient maxim, "first, do no harm," which makes it the individual caregiver's responsibility to somehow try extra hard to be more careful (a requirement modern human factors theory has shown to be unproductive). Instead, the aim means that safety must be a property of the system. No one should ever be harmed by health care again.
- Second, health care must be **effective**. It should match science, with neither underuse nor overuse of the best available techniques—every elderly heart patient who would benefit from beta-blockers should get them, and no child with a simple ear infection should get advanced antibiotics.
- Third, health care should be **patient-centered**. The individual patient's culture, social context, and specific needs deserve respect, and the patient should play an active role in making decisions about his or her own care. That concept is especially vital today, as more people require chronic rather than acute care.
- Fourth, care should be **timely**. Unintended waiting that doesn't provide information or time to heal is a system defect. Prompt attention benefits both the patient and the caregiver.
- Fifth, the healthcare system should be **efficient**, constantly seeking to reduce the waste—hence the cost—of supplies, equipment, space, capital, ideas, time, and opportunities.
- Sixth, health care should be **equitable**. Race, ethnicity, gender, and income should not prevent anyone in the world from receiving high-quality care. We need advances in healthcare delivery to match the advances in medical science so the benefits of that science may reach everyone equally.

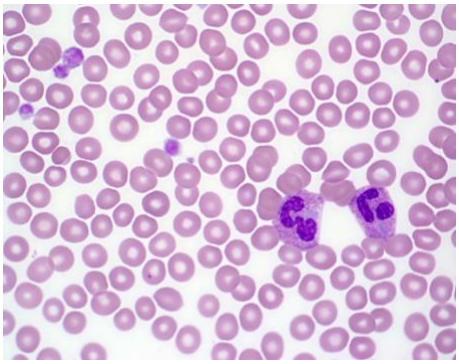
89. A pediatric fellow is planning a project intended to decrease the incidence of acute chest syndrome among patients with sickle cell disease who are already admitted to the hospital for other reasons. The fellow discussed with her mentor whether the project proposal should be submitted for review by the Institutional Review Board (IRB). The mentor explains that, at their intuition, quality improvement activities do not require IRB review but research projects must be submitted to the IRB. Which of the following is NOT a relevant consideration in determining whether the project is research or quality improvement?

A. The aim to create new knowledge for the individual institution versus discovering new and generalizable knowledge
B. The chosen methodology which will include repeated Plan-Do-Study-Act cycles
C. The intent to publish the results in a peer reviewed hematology journal
D. The efforts to hold biases/confounders stable over time, rather than control for them with, for example, randomization

Answer: C
Explanation
The distinction between quality improvement projects and traditional research projects can be a confusing one but, over time, the relevant distinctions between these two activities have become clearer. The first pertains to intent. Researchers intend to discover new knowledge that would be generalizable to others whereas quality improvement aims more to create new knowledge that would be applied to local practices and local systems of care. Second, research often involves a single experiment or trial, often done over a large amount of time, controlling for as many biases/confounders as possible. In quality improvement, the methodology involves short, repeated cycles of intervention, each time layering on something new, while keeping biases/confounders otherwise stable, even if not controlled. In research we collect as much data as possible from this single experiment while in quality improvement we collect just enough data to allow us to plan the next cycle. Individuals unsure of whether their project is best characterized as research vs. quality improvement are encouraged to seek consultation from their local IRB.

28. Review of Peripheral Blood and Bone Marrow Morphology: Non-Malignant Hematology

90. The patient is a 6-year-old boy referred to a hematologist for thrombocytopenia. He has no bleeding history or family history of bleeding. His only other past medical history is mild high-frequency hearing loss. What gene is responsible for these findings?



A. *NBEAL2*
B. *GP-1Ba*
C. *MYH9*
D. Deletions of long arm of chromosome 11
E. *GATA1*

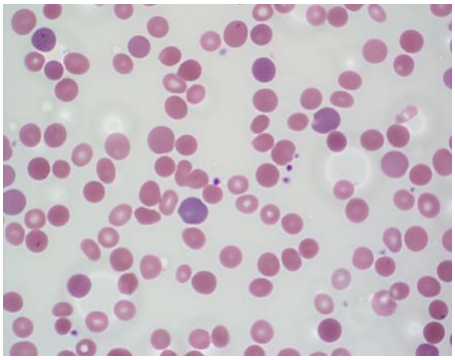
Answer: C
Explanation
The peripheral blood smear shows macrothrombocytopenia with otherwise normal platelet granulation. The neutrophils have prominent Döhle-like cytoplasmic inclusions. The smear is consistent with May-Hegglin anomaly caused by mutations in *MYH9.* MYH9-related diseases include Epstein syndrome, Fechtner syndrome, and May–Hegglin anomaly.

Other genetic syndromes associated with giant platelets include Bernard-Soulier syndrome (*GP-1Ba*), grey platelet syndrome (*NBEAL2*), some patients with von Willebrand factor type 2b, and Paris-Trousseau thrombocytopenia (deletion of 11q23-terminus).

91. A 4-year-old boy is pale with intermittent jaundice and splenomegaly.

Laboratory results are as follows: RBC 4.85 M/mcL (N); Hgb 8.6 g/dL (L); Hct 25.8% (L); MCV 81.6 (N); MCHC 38% (H); RDW 20% (H); Retic 7% (H).

What are the two best tests to distinguish autoimmune hemolytic anemia from hereditary spherocytosis?



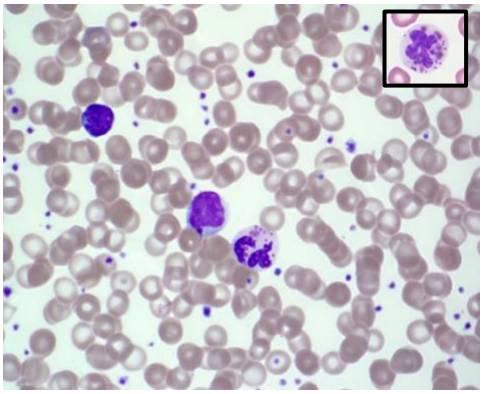
A. Free erythrocyte protoporphyrin and IgG levels
B. Hemoglobin electrophoresis and direct antiglobulin test (DAT)
C. Lactate dehydrogenase (LDH) and modified Russell viper venom test
D. Red cell distribution width (RDW) and mean corpuscular hemoglobin concentration (MCHC)
E. DAT and osmotic fragility testing

Answer: E
Explanation
The findings on the peripheral blood smear include small, dense, round microspherocytes; polychromasia; and red cells with central pallor, which are often smaller than normal. In this case, the direct antiglobulin test (DAT) was negative, and the patient was diagnosed with hereditary spherocytosis. A high mean corpuscular hemoglobin concentration (MCHC) (≥ 36 g/dL) is consistent with the presence of spherocytes.

Free erythrocyte protoporphyrin testing is useful is the evaluation of porphyrias. Hemoglobin electrophoresis is useful in the evaluation of hemoglobinopathies. The modified Russell viper venom test is useful in the evaluation of lupus anticoagulant.

Hereditary spherocytosis is caused by mutations in membrane skeletal proteins ankyrin, alpha-spectrin, beta-spectrin, band 3, or protein 4.2. Hereditary elliptocytosis is typically caused by heterozygous mutations in alpha-spectrin, beta-spectrin, or protein 4.1. Hereditary pyropoikilocytosis is typically caused by homozygous mutations in alpha-spectrin, beta-spectrin, or protein 4.1.

92. The patient is a 2-month-old boy who presented with a skin abscess and is febrile. On exam, he is noted to have silvery hair and hypopigmented skin. A CBC shows a leukocyte count of 3.4 K/mcL with 10% neutrophils. What does the abnormality on the peripheral smear suggest?



A. Abnormal lysosomal biogenesis
B. Abnormal ribosome function
C. Abnormal phagocytosis of opsonized particles
D. Abnormal mitochondrial activity
E. Impaired DNA repair activity

Answer: A
Explanation
The peripheral blood smear shows abnormally large azurophilic or grey granules in the neutrophils and lymphocytes. These abnormal coalesced lysosomes can be found in all leukocytes.

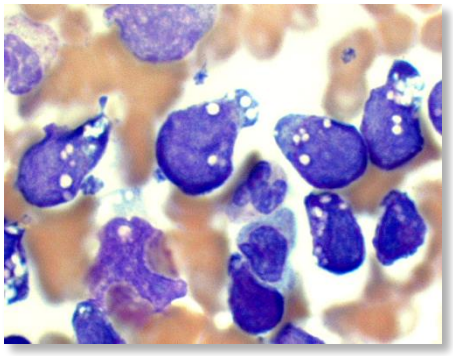
Chediak-Higashi syndrome is due to abnormal lysosomal biogenesis. Patients in the stable phase have increased susceptibility to infection and oculocutaneous albinism. An accelerated phase with hemophagocytic lymphohistiocytosis is typically fatal.

Of the other choices, the following diseases are examples that have defects in the cellular system named:

- Diamond-Blackfan anemia characterized abnormal ribosomal function
- leukocyte adhesion deficiency characterized by abnormal phagocytosis
- Pearson syndrome characterized by abnormal mitochondrial activity
- ataxia-telangiectasia characterized by abnormal DNA repair.

29. Review of Peripheral Blood and Bone Marrow Morphology: Malignant Diseases

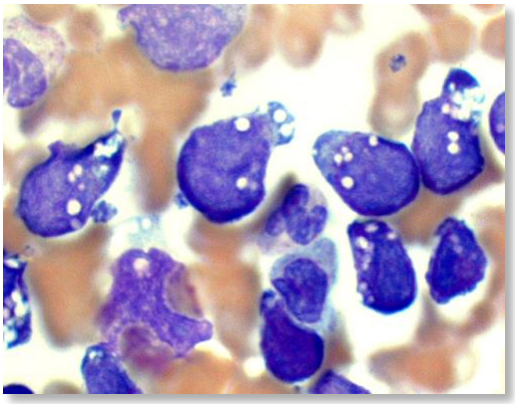
93. A 7-year-old boy presents with recent onset of vomiting and lethargy. Blood smear shows increased neutrophils with a left shift and 8% abnormal cells. Bone marrow contains 60% of the same cells. Flow cytometry shows that the cells are TdT–, CD10+, CD19+, CD20+, sIg+.



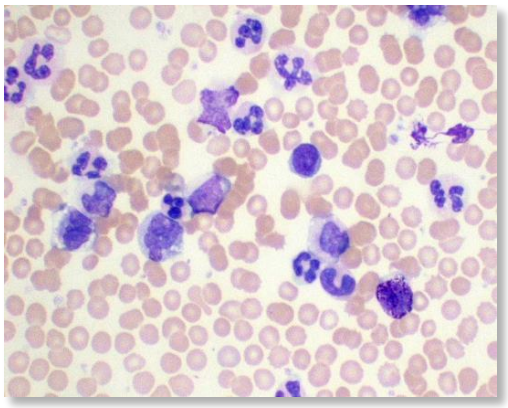
What is the most likely diagnosis?

A. Burkitt leukemia/lymphoma
B. B-cell acute lymphoblastic leukemia (ALL)
C. T-cell ALL
D. Hematogones
E. Diffuse large B-cell lymphoma (DLBCL)

Answer: A
Explanation
Flow cytometry shows mature CD10+ B-cells, and the morphology is that of Burkitt lymphoma, which occasionally can have a leukemic phase. DLBCL certainly is a consideration, but a truly leukemic phase (rather than just marrow involvement) would be unusual. An MYC rearrangement by cytogenetics/fluorescence in situ hybridization (FISH) also would be diagnostically helpful.



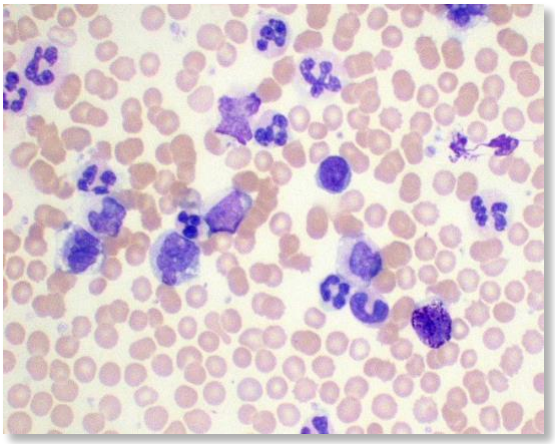
94. You are seeing a 13-year-old boy with fatigue, weight loss, night sweats, and splenomegaly. Peripheral blood shows anemia, thrombocytosis, and leukocytosis (300,000/mm3).



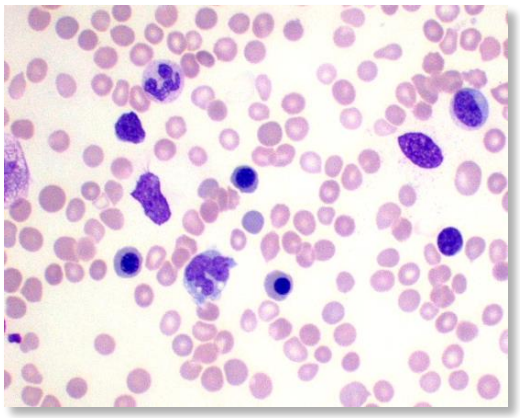
What is this patient's most likely diagnosis?

A. Leukemoid reaction
B. Acute lymphoblastic leukemia (ALL)
C. Chronic myeloid leukemia (CML)
D. Juvenile myelomonocytic leukemia (JMML)
E. Acute myeloid leukemia (AML)

Answer: C
Explanation
A neutrophilic leukocytosis and a left shift with a basophilia and thrombocytosis without increased blasts are typical of the chronic phase of CML. Cytogenetics/fluorescence in situ hybridization (FISH) showing t(9;22)(q34;q11.2) would be diagnostic. Leukemoid reaction is also in the differential, but basophilia and an absence of monocytosis would be unusual. JMML is a disease of much younger children (typically younger than 4 years and certainly younger than 8 years) and nearly always is associated with thrombocytopenia.



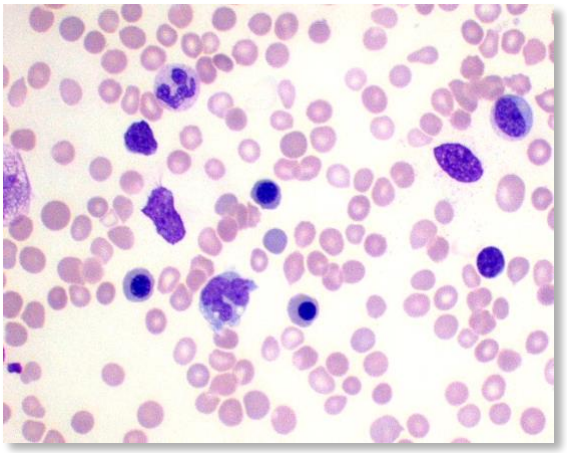
95. You are seeing a 2-year-old girl with new onset of fever and bronchitis. She has maculopapular rash and hepatosplenomegaly. Blood smear shows leukocytosis (100,000/mm3), anemia, and thrombocytopenia. Ancillary tests include fetal hemoglobin of 80% and normal blood karyotype.



What is the most likely diagnosis?

A. Leukemoid Reaction
B. Acute lymphoblastic leukemia (ALL)
C. Chronic myeloid leukemia (CML)
D. Juvenile myelomonocytic leukemia (JMML)
E. Acute myeloid leukemia (AML)

Answer: D
Explanation
Marked leukocytosis, including monocytosis without increased blasts or a basophilia, are typical of JMML, as are thrombocytopenia and anemia often accompanied by erythroblastosis. Elevation of fetal hemoglobin is characteristic of JMML. Cytogenetics typically are normal and a *BCR/ABL1* fusion is not present. Somatic mutations in the RAS signaling pathway are common.



30. Survivorship

96. A 15-year-old girl with a history of osteosarcoma presents to survivor clinic for her first evaluation. Her mother complains that she does not listen well and is wondering if she may have trouble hearing. Which of the follow is true regarding platinum-associated hearing loss?

A. Platinum chemotherapy is most often associated with conductive hearing loss.
B. Low-frequency volumes are affected first.
C. Older age at exposure increases risk.
D. Platinum-associated hearing loss is due to destruction of the cochlear hair cells.
E. Carboplatin is more ototoxic than cisplatin.

Answer: D
Explanation
Platinum-associated sensorineural hearing loss is due to the destruction of cochlear hair cells. The hair cells are arranged tonotopically; therefore, the high-frequency hair cells (>2000 Hz) are affected first. As cumulative dose increases, injury progresses toward the cochlear apex, where lower frequencies in the audible range are affected. Cisplatin is more ototoxic than carboplatin. Younger age at exposure (younger than 5 years), higher doses, receipt of multiple ototoxic agents, and combination treatment with cisplatin and cranial radiation places patients at increased risk for hearing loss. Radiation is associated with both conductive and sensorineural hearing loss; however, platinum agents are typically associated with sensorineural hearing loss only.

97. An 18-year old male patient with acute lymphoblastic leukemia recently started maintenance therapy and is complaining of increased hip pain. The pain increases during weight-bearing activity; however, it occasionally hurts at night as well. His CBCd is normal. Which of the following risk factors is most commonly associated with this process?

A. Younger age at diagnosis
B. Non-White race
C. Low body-mass index
D. Dexamethasone exposure
E. Male sex

Answer: D
Explanation
Avascular necrosis (AVN) is a well-known complication of therapy for acute lymphoblastic leukemia and can lead to significantly impaired quality of life. AVN can develop during treatment or after therapy completion and is associated with exposure to glucocorticoids. Dexamethasone has more bone toxicity compared with equivalent doses of prednisone, and continuous exposure increases this risk. Weight-bearing joints are affected in 95% of patients with AVN, with the femoral head as the most commonly involved joint, though often it is multifocal. The mechanism of injury is thought to be multifactorial, including disruption of osteoblasts, intramedullary lipocyte proliferation impacting circulation, and fat embolization to subchondral arteries. Common risk factors include female sex, radiation exposure, White race,

and obesity. Teenagers are more likely to develop AVN compared with younger patients; therefore, current treatment protocols limit the exposure to long courses of dexamethasone in adolescents.

98. A 19-year old male patient with a history of acute lymphoblastic leukemia, currently 13 years from completion of therapy, presents for a fertility consultation. He is interested in his risk for infertility. Which of the following statements is true?

A. A semen analysis at this point would provide accurate information about future fertility.
B. Males can maintain gonadal function at higher cumulative alkylator dosages compared with females.
C. He should have been offered sperm cryopreservation at diagnosis.
D. His risk for testosterone deficiency is greater than his risk for infertility.
E. Prepubertal status at diagnosis is protective from gonadal injury in males.

Answer: A
Explanation
Adolescents and young adults are often concerned about their risk for future infertility. Risk for gonadotoxicity and fertility preservation options differ for males and females. Males are more sensitive to gonadotoxic exposures and have a higher risk of infertility compared to females with equivalent treatment. The Leydig cells that secrete testosterone are fairly resistant to gonadotoxic injury; therefore, males are often able to produce normal levels of testosterone even if they have Sertoli/germ cell damage leading to infertility. In females, the stromal and germ cells are equally affected by therapy; therefore, after girls receive highly gonadotoxic therapy, they are more likely to need hormone replacement to proceed through puberty or maintain menstrual cycles. Prepubertal status is protective from gonadal injury in females; however, this is not true in males. In males, gonadal recovery after therapy can take up to 5 years. After recovery, gonadal function is stable with aging. On the other hand, females may have recovery after treatment leading to a reproductive window prior to premature menopause. A semen analysis is the best method for fertility evaluation in males and would be appropriate to pursue at this time if the patient is interested. Semen cryopreservation is only possible in postpubertal males. Prepubertal males can undergo testicular tissue cryopreservation; however, it is still considered experimental.

31. Vascular Anomalies

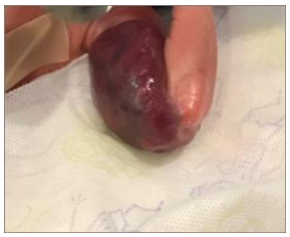
99. An infant is born with a firm mass over the chest with a central area of purpura and a "halo" around it. An ultrasound reveals a high-flow lesion. What is the most likely diagnosis?

A. Fibrosarcoma
B. Infantile hemangioma
C. Congenital hemangioma
D. Capillary malformation

Answer: C
Explanation

The mass is completely present at birth. It is firm with a central area of purpura but a halo around the central area. A fibrosarcoma is firm and violaceous with no halo surrounding the tumor. It is more mass-like on ultrasound. An infantile hemangioma is not present at birth but grows after birth. A capillary malformation is a cutaneous anomaly that is flat. A congenital hemangioma is present at birth with high flow on ultrasound and a "halo" around the lesion.

100. An infant is born with a 7 cm × 6 cm lesion over the upper extremity from the elbow to the shoulder. The lesion is indurated and purpuric, with some petechiae around the edges. No other areas of petechiae are noted on the skin. The infant is doing well without other systemic problems. i were 9 and 9. You are called by the pediatric nurse practitioner to the NICU.



What is the most appropriate next step?

A. Do nothing because the infant is doing well and had good Apgars.
B. Obtain an ultrasound for more information about the lesion.
C. Obtain an MRI to assess the extent of the lesion.
D. Obtain labs, including a CBC with platelet count and fibrinogen.

Answer: D
Explanation
This appearance is that of a possible vascular tumor, but information is still needed to better define the lesion. Some of these lesions, such as a congenital hemangioma, are benign, but others are classified as an intermediate malignancy (kaposiform hemangioendothelioma) or a high-risk malignancy (angiosarcoma or a fibrosarcoma). The infant should have some intervention because this lesion is violaceous and has some petechiae, which can be a sign of thrombocytopenia. An ultrasound may help differentiate flow and makeup of the lesion but can be done after further investigation because an MRI may be necessary to determine the extent of the tumor. For an infant, an MRI can be done without sedation at most institutions. Because this lesion is violaceous and this could be a sign of a coagulopathy in a vascular tumor, Answer D is correct. The first, easy, step would be to obtain labs to rule out a coagulopathy. This could be the most critical issue for the patient. Further investigation can then occur.